NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lu 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

Lu 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:

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

1. **Company submission** from Novartis Pharmaceuticals

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. British Nuclear Medicine Society
   b. Prostate Cancer UK
   c. TACKLE Prostate Cancer

4. **Evidence Review Group report** prepared by ScHARR

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Prof. Amit Bahl, Consultant Oncologist – clinical expert, nominated by Novartis Pharmaceuticals
   b. Dr Amarnath Challipalli, Consultant Clinical Oncologist – clinical expert, nominated by Prostate Cancer UK
   c. Dr Stephen Allen, Acting Chairman – patient expert, nominated by Tackle Prostate Cancer
   d. Mr Peter Isard – patient expert, nominated by Tackle Prostate Cancer
   e. Prof. Sabina Dizdarevic, Research Lead and Principal Lead Consultant in Imaging and Nuclear Medicine – clinical expert, nominated by the British Nuclear Medicine Society *(see item 8b)*

8. **Technical engagement responses from consultees and commentators:**
   a. Bayer
   b. British Nuclear Medicine Society
   c. Prostate Cancer UK

9. **Evidence Review Group critique of company response to technical engagement** prepared by ScHARR

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

15 March 2022

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List of Abbreviations

Abbreviation	Definition
^{177}Lu	Lutetium-177
5HT3	5-hydroxytryptamine
AAA	Advanced Accelerator Applications
ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Akaike information criterion
ARPI	Androgen receptor pathway inhibitor
ASCO	American Society of Clinical Oncology
ATC	Anatomical therapeutic chemical
BIC	Bayesian information criteria
BID	Twice daily
BNF	British National Formulary
BOR	Best overall response
BPI-SF	Brief Pain Inventory – Short Form
BRCA1/2	Breast cancer genes 1 and 2
BSA	Body surface area
BSC	Best supportive care
BSoC	Best Standard of Care
CC	Clinical coding
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID	Coronavirus disease 2019
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible intervals
CRPC	Castration resistant prostate cancer
CTCAE	Common terminology criteria for adverse events
DCR	Disease control rate
DIC	Deviance information criterion
DID	Diagnostic Imaging Dataset
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EDOR	Expected duration of response
eMIT	Drugs and pharmaceutical electronic market information tool
EQ-5D-5L	EuroQoL-5 Dimension-5 Level
ESMO	European Society for Medical Oncology

FACT-P	Functional Assessment of Cancer Therapy – Prostate
FAS	Full analysis set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GBq	Gigabecquerel
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage colony-stimulating factor
GPRD	General Practice Research Database
HCRU	Healthcare resource use
HES	Hospital Episode Statistics
HR	Hazard ratio
HRG	Health Research Group
HRQoL	Health-related quality of life
HSPC	Hormone-sensitive prostate cancer
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IPCW	Inverse probability-of-censoring weighting
IPD	Individual patient data
IRT	Interactive response technology
ITC	Indirect treatment comparison
ITT	Intent to treat
IU	International unit
IV	Intravenous
KM	Kaplan-Meier
KP	Karnofsky performance-status
LDH	Lactate dehydrogenase
LPD	Life-prolonging drug
LYG	Life years gained
MBq	Megabecquerel
mCi	Millicurie
MCMC	Markov Chain Monte Carlo
mCRPC	Metastatic castration-resistant prostate cancer
MDT	Multidisciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NAAD	Novel androgen axis drug
NCR	National Cancer Registry
NCRAS	National Cancer Registration and Analysis Service
NCT	National Clinical Trial
NE	Not evaluable
NHS	National Health Service
NICE	National Institute of Health and Care Excellence

NMA	Network meta-analysis
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PC	Prostate cancer
PCWG3	Prostate Cancer Working Group 3
PD	Progressed disease
PET	Positron emission tomography
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PHE	Public Health England
PIM	Promising Innovative Medicines
PR	Partial response
PRO	Patient-reported outcome
PSA	Prostate-specific antigen
PSI	Prostate symptom index
PSMA	Prostate-specific membrane antigen
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once daily
QTc	Corrected QT interval
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RLT	Radioligand therapies
rPFS	Radiographic progression-free survival
RTDS	Radiotherapy Dataset
RWE	Real-world evidence
SACT	Systemic Anticancer Therapy Dataset
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	Standard of Care
SPECT	Single photon emission computed tomography
SRE	Skeletal-related events
SSE	Symptomatic skeletal event
TA	Technology appraisal

TDM	Therapeutic drug monitoring
TEAE	Treatment-emergent adverse event
TOI	Trial outcome index
TSD	Technical Support Document
UK	United Kingdom

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

B.1.1 *Decision problem*

This submission covers the technology's full anticipated marketing authorisation for [^{177}Lu]Lu-PSMA 617 (hereinafter ^{177}Lu vipivotide tetraxetan) "for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive, metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibition (ARPI) and taxane-based chemotherapy or who are not medically suitable for taxanes". The decision problem addressed within this submission is broadly consistent with the NICE final scope for this appraisal with respect to the population, intervention, outcomes and comparators (with the exception of docetaxel rechallenge, radium-223, and olaparib), and the NICE reference case. The differences between the decision problem addressed within this submission and the NICE final scope are outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with prostate-specific membrane antigen (PSMA) positive, hormone-relapsed metastatic prostate cancer previously treated with an ARPI and taxane based chemotherapy.	Adult patients with prostate-specific membrane antigen (PSMA)-positive, metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibition (ARPI) and taxane-based chemotherapy or who are not medically suitable for taxanes	The patient population of relevance for this submission is in line with the full anticipated marketing authorisation for ^{177}Lu vipivotide tetraxetan in PSMA-positive mCRPC, focussing on patients who experienced disease progression despite treatment with ARPI and taxane-based chemotherapy, or who are not medically suitable for (or do not tolerate) taxanes.
Intervention	Lutetium-177 prostate-specific membrane antigen-617 (^{177}Lu-PSMA-617)	As per NICE final scope	In line with NICE final scope. ^{177}Lu vipivotide tetraxetan (^{177}Lu-PSMA-617) is intended for monotherapy use in the patient population of relevance for this submission. This is consistent with the indication and summary of product characteristics which do not require pre-medication or concomitant medication, as submitted to the MHRA for approval.
Comparator(s)	• Cabazitaxel • Docetaxel (for people who have had docetaxel in combination with ADT previously) • Radium-223 dichloride (for people with bone metastases) • Best supportive care The different positions that these comparators could be used in the treatment pathway will be considered in the appraisal.	The relevant comparators addressed in this submission include: • Cabazitaxel • SOC[a] as defined by the clinical judgement of the treating physician which may include: ○ Supportive measures (pain medications, hydration, transfusions, erythropoietin stimulation agents, etc.) ○ Ketoconazole ○ Androgen reducing agents ○ ARPIs ○ Bone-targeted agents (including zoledronic acid,	Cabazitaxel is the most relevant comparator in patients who have previously received treatment with an ARPI and docetaxel who are eligible for further taxane treatment. SOC is the most relevant comparator for all other patients eligible for ^{177}Lu vipivotide tetraxetan who would not be eligible for further treatment with taxane therapy. Patients eligible to receive ^{177}Lu vipivotide tetraxetan are expected to have either already received docetaxel or be considered not medically suitable to receive docetaxel, therefore further use of docetaxel would be in the context of a rechallenge. Docetaxel rechallenge was not considered a relevant comparator in this appraisal for the reasons provided below. • In current UK clinical practice docetaxel is

		denosumab, and bisphosphonates) ○ External beam or seeded form radiation therapy • SOC is not considered to include: ○ investigational agents ○ Cytotoxic chemotherapy ○ Immunotherapy ○ Systemic radioisotopes (e.g., radium-223) ○ Semi-body radiotherapy	generally used early in the treatment pathway, and this is reflected in the NHS clinical commissioning policy which states that NHS England will commission docetaxel for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in patients initiating ADT therapy.[1] Furthermore, NICE Guideline (NG131) states that off-label use of docetaxel in people diagnosed with mHSPC occurs in current practice.[1, 2] The increasing use of docetaxel prior to mCRPC setting can also be inferred from the National Prostate Cancer Audit which reports an increase in receipt of primary docetaxel by newly-presenting hormone-sensitive metastatic patients from 27% in 2019 to 36% in 2020.[3] There is also emerging evidence for triplet therapy (a combination of docetaxel, ADT and ARPI) in mHSPC, which may lead to further increases in the use of docetaxel earlier in the PC treatment pathway.[4] • NICE guidelines state that retreatment with docetaxel should only be considered if the patients' disease does not recur (progress) following completion of the initial planned course of chemotherapy.[2] In clinical practice docetaxel rechallenge likely occurs in as low as 2% of patients, as advised by UK clinical experts in an advisory board setting.[5, 6] • The systematic literature review (SLR) conducted as part of this appraisal did not identify any evidence to support the use of docetaxel in mCRPC after disease progression on an ARPI, which limits the ability to conduct an indirect comparison. Additionally, in the forthcoming NICE appraisal for pembrolizumab in combination with olaparib in patients with

			progressive mCRPC (ID3814), docetaxel was not considered a relevant comparator by NICE in the published draft scope.[7] Radium-223 is not considered a relevant comparator in this appraisal as it is indicated in patients with symptomatic bone metastases but without any visceral metastases, limiting comparability with ^{177}Lu vipivotide tetraxetan, which is intended for use regardless of metastasis site. Compared with ^{177}Lu vipivotide tetraxetan, which offers targeted delivery of radiotherapy to the primary tumour and PSMA-positive metastases, radium-223 mimics calcium and delivers radiotherapy preferentially at sites of bone metastses.[8] As reflected in NICE's recommendation for treating symptomatic PC bone metastases,[9] radium-223's primary action is to palliate bone pain. The SLR did not identify any evidence to support the use of radium-223 in mCRPC in heavily pre-treated (post-ARPI, post-taxane) patients, which limits the ability to conduct an indirect comparison.

Outcomes	The outcome measures to be considered include:
	• progression free survival (rPFS)
	• overall survival (OS)
	• time to a first symptomatic skeletal event (SSE)
	• adverse effects of treatment
	• health-related quality of life
		The outcome measures considered include:
		• Primary outcome measures
		  ○ rPFS
		  ○ OS
		• Key secondary outcome measures
		  ○ Time-to-first SSE
		  ○ Adverse events of treatment
		  ○ Health-related quality of life
		• Additional secondary outcome measures
		  ○ Overall response rate (ORR)
			In line with NICE final scope
			
			Whilst not specified in the NICE scope, additional secondary outcomes measures from VISION are presented in this submission to demonstrate the benefit of ^{177}Lu vipivotide tetraxetan as a treatment for mCRPC, but these outcomes do not inform indirect treatment comparisons or health economic modelling.

		○ Disease control rate (DCR) ○ Duration of response (DOR)	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	As per NICE final scope and NICE reference case	In line with the NICE final scope
Subgroups to be considered	No subgroup analyses were specified in the NICE final scope	Three patient subgroups may be considered: • Adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy and are suitable for further treatment with taxanes • Adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy and are ineligible for further treatment with taxanes • Adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and who are not medically suitable for treatment with taxanes	Limiting the use of ^{177}Lu vipivotide tetraxetan to those patients who have previously received treatment with taxane-based chemotherapy would create inequity biased against those patients who are not medically suitable for treatment with taxanes, but who would be considered medically suitable for treatment with ^{177}Lu vipivotide tetraxetan. Mechanistically, there is no reason that the efficacy and safety of ^{177}Lu vipivotide tetraxetan would be significantly different in patients who have not previously received taxanes unless they had significantly more comorbidities; patients who are not medically suitable to receive taxanes for PSMA-positive mCRPC are still likely to derive clinical benefit from ^{177}Lu vipivotide tetraxetan. Therefore, a small proportion of patients with even fewer treatment options, who have been treated with ARPI and who are not medically suitable for taxanes may be considered appropriate for treatment with ^{177}Lu vipivotide tetraxetan.

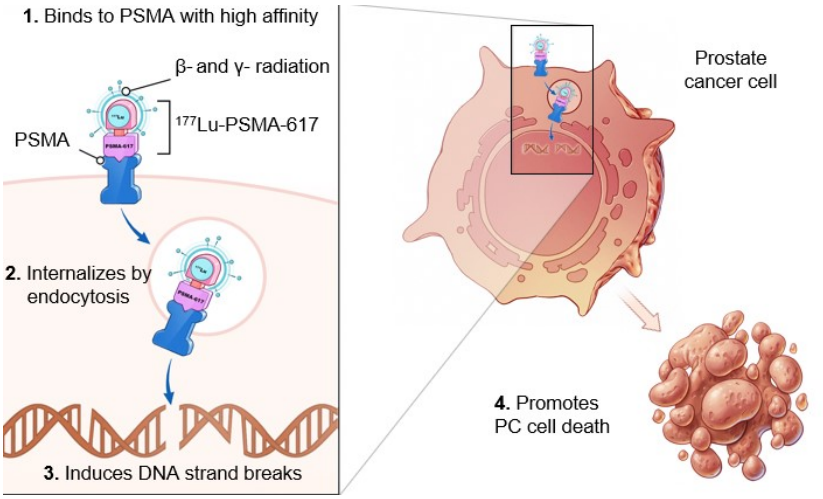
Special considerations including issues related to equity or equality	N/A	N/A	• Approximately 50% of patients with mCRPC have been identified as being ineligible for taxane-based chemotherapy.[10] This may be due to any number of reasons, including: medical unsuitability secondary to clinical frailty or pre-existing co-morbidities, unwillingness to undergo the high risk of toxicity and associated impact on their quality of life, and insufficient social support system to assist with hospital visits and potential side effects.[11] Limiting the scope of ^{177}Lu vipivotide tetraxetan to only those patients who have received a taxane-based chemotherapy would potentially create an inequality. The wording of the anticipated marketing authorisation is designed to avoid such an inequality. • There are a currently a limited number of clinical centres in the UK which would be able to conduct the required assessment for PSMA positivity patients and then subsequently deliver treatment with ^{177}Lu vipivotide tetraxetan. Unless expansion of these existing services is prioritised there may be geographical inequality due to the need for some patients to travel long distances to receive treatment.

[a]The terminology 'Standard of Care (SOC)' is used throughout this submission to align with the lexicon from the VISION trial. SOC should be considered equivalent to the other widely used terminology of 'Best Standard of Care (BSoC)'.
Abbreviations: ^{177}Lu: Lutetium-177; ARPI: androgen receptor pathway inhibitor; BRCA1/2: breast cancer genes 1 and 2; DCR: disease control rate; DOR: duration of response; HSPC: hormone-sensitive prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; MHRA: Medicines and Healthcare products Regulatory Agency; mHSPC: metastatic hormone-sensitive prostate cancer; NA: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; QALY: quality-adjusted life year; rPFS: radiographic progression-free survival; SOC: standard of care; SSE: symptomatic skeletal event.
Source: NICE final scope document [ID3840]

B.1.2 *Description of the technology being appraised*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements of ^{177}Lu vipivotide tetraxetan in the treatment of mCRPC is presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	^{177}Lu vipivotide tetraxetan
Mechanism of action	^{177}Lu vipivotide tetraxetan is a novel targeted radioligand therapy that consists of three distinct components: 1. An unstable lutetium isotope (^{177}Lu). This radioactive atom decays emitting a high energy beta particle which induces double- and single-stranded DNA breaks that result in tumour cell death. 2. A ligand that binds specifically to PSMA expressed on the surface of PC cells. 3. A binder which attaches the PSMA-specific ligand to a cage housing the ^{177}Lu atom. PSMA is an actionable therapeutic and diagnostic target, expressed primarily on prostate cancer cells at levels substantially greater than benign prostate tissues. Once bound to a prostate cancer cell, ^{177}Lu vipivotide tetraxetan is internalised through endocytosis and a sustained retention of the ligand alongside its bound radioactive cargo occurs within the cancerous cell where the ^{177}Lu isotope decays, emitting a beta particle and delivering radiotherapy directly to the harboring cell.[12, 13] Beta particles have a short path length (1.8 mm), allowing for precision delivery to the site of malignancy whilst limiting damage to surrounding tissues.[14] ^{177}Lu also has a relatively long physical half-life of 6.6 days that combines with the retention of ^{177}Lu vipivotide tetraxetan within the tumour to reduce the necessary dosing frequency. An overview of the mechanism of action for ^{177}Lu vipivotide tetraxetan is provided in Figure 1. **Figure 1: Mechanism of action for ^{177}Lu vipivotide tetraxetan**  **Abbreviations**: ^{177}Lu: lutetium-177; PSMA: prostate-specific membrane antigen.

Marketing authorisation/CE mark status	An application for a marketing authorisation for ^{177}Lu vipivotide tetraxetan in the indication of interest was submitted directly to the Medicines and Healthcare products Regulatory Agency (MHRA) on [redacted]. UK marketing authorisation approval for ^{177}Lu vipivotide tetraxetan in this indication is expected in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated UK marketing authorisation for ^{177}Lu vipivotide tetraxetan is: "for the treatment of adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy or who are not medically suitable for taxanes".
Method of administration and dosage	**Method of administration**[15] • ^{177}Lu vipivotide tetraxetan is a clear, colourless to slightly yellow solution which may be administered intravenously as an injection using a disposable syringe fitted with a syringe shield (with or without a syringe pump), as an infusion using the gravity method (with or without an infusion pump), or as an infusion using the vial (with a peristaltic infusion pump). Full instructions for the methods of administrations are provided in the draft SmPC supplied alongside this submission in Appendix C.[15] **Dosage**[15] • The recommended dose of ^{177}Lu vipivotide tetraxetan is 7,400 MBq (200 mCi) every 6 weeks (±1 week). • Treatment with ^{177}Lu vipivotide tetraxetan should be continued until disease progression, unacceptable toxicity, or a maximum of 6 doses. • ^{177}Lu vipivotide tetraxetan is administered over a total duration of 30 to 40 minutes, followed by an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution • AAA expects the vast majority of administrations to be done on an outpatient or day case basis, with guidance of keeping patients up to 4 hours post-infusion
Additional tests or investigations	Patients receiving ^{177}Lu vipivotide tetraxetan should receive the following tests/investigations prior to/during treatment:[15] • The presence of PSMA-positive lesions must be confirmed by PSMA imaging prior to receiving treatment with ^{177}Lu vipivotide tetraxetan ○ It is anticipated that commercialisation of ^{68}Ga gozetotide (a AAA product) and ^{18}F fluorinated PSMA radiotracers for use with PET/CT infrastructure will provide further options for the identification of appropriate patients. Technitium-99m imaging using single photon emission computed tomography (SPECT) scans is also a potential option for imaging within the NHS given its more widespread adoption. The anticipated approved indication for ^{177}Lu vipivotide tetraxetan will include PSMA-positivity, which can be demonstrated through the use of any radioisotope linked to an appropriate PSMA ligand, which is quickly becoming standard of care.

	○ The following laboratory tests should be performed before and during treatment with ^{177}Lu vipivotide tetraxetan. These are in line with standard monitoring requirements for existing treatments in mCRPC.[16, 17] Dosing should be modified as per the SmPC based on the results of laboratory results.[15] ▪ Haematology (haemoglobin, white blood cell count, absolute neutrophil count, platelet count). ▪ Kidney function (serum creatinine or calculated creatinine clearance). ▪ Liver function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood serum albumin, total blood bilirubin).
List price and average cost of a course of treatment	The proposed list price of one single dose vial of ^{177}Lu vipivotide tetraxetan is [redacted].
Patient access scheme (if applicable)	This submission includes the confidential simple patient access scheme (PAS) for ^{177}Lu vipivotide tetraxetan, representing a discount to the list price of [redacted]%. The proposed PAS price of one single dose vial of ^{177}Lu vipivotide tetraxetan is [redacted]. A confidential PAS is known to be in place for cabazitaxel.[10] As this information is not publicly available, it has not been included in the submission.

Abbreviations: ^{177}Lu: lutetium-177; CHMP: Committee for Medicinal Products for Human Use; DNA: deoxyribonucleic acid; MBq: megabecquerel; mCi: millicurie; mCRPC: metastatic castration-resistant prostate cancer; MHRA: Medicines and Healthcare products Regulatory Agency; NICE: National Institute for Health and Care Excellence; PAS: patient access scheme; PSMA: prostate-specific membrane antigen; UK: United Kingdom.

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

Summary of the health condition

- Prostate cancer is the most common cancer in males in the UK, with an incidence of 52,280 cases diagnosed in the UK between April 2018 and March 2019.[18] The incidence of PC in the UK has increased steadily over the past decade, and is projected to rise to 233 cases per 100,000 males by 2035 (12% increase 2014–2035).[19]
- PC is the second most common cause of cancer death amongst men in the UK[20]Due to the insidious nature of the symptoms of early stage PC, patients may often present with advanced/metastatic disease.[18]
- Metastatic PC causes a wide range of physical and psychological symptoms that significantly impact upon patients' lives,[21, 22] imposing considerable burden on patients, their families, and society.[23]
- PC is the second most common cause of cancer death amongst men in the UK.[20] The population for this submission is patients with advanced disease, that has progressed despite prior therapies.
- Clinical trials in patients with mCRPC who have progressed despite docetaxel have reported median OS in their control arms of 11.2–13.6 months.[24] Considered together, alongside the fact that patients who have progressed despite also receiving ARPI are likely to have even

shorter OS, the estimated prognosis for patients considered in this submission is under 12 months. The median OS for patients in the SOC arm of VISION, the primary source of evidence for ^{177}Lu vipivotide tetraxetan in this submission, was only 11.3 months.[25]

- PSMA-positivity is an independent poor prognostic indicator for progression-free survival and overall survival in CRPC.[26]

Summary of the treatment pathway

- Patients with mCRPC are currently treated with taxane-based chemotherapy, ARPIs, and radium-223 (if they have bone metastases but no visceral metastases), alongside SOC supportive treatments. With the advent of new therapies, as well as the diversifying use of existing therapies such as ARPIs and docetaxel, the treatment pathway for mCRPC is becoming increasingly complex and lacks definitive evidence for sequencing of specific therapies.[2]
- Physicians rely on published guidelines and clinical expertise to consider the risk-to-benefit profile of therapeutic options, as well as considering patient characteristics, prior therapies (as above), and patient preferences to make treatment decisions.[27, 28]
- Treatment options are severely limited by factors such as a patients' functional performance status, treatment-related toxicities, treatments previously received earlier in the disease course, disease resistance to ARPIs, and the presence of visceral metastases (which precludes the use of radium-223). Therefore, there remains a considerable unmet need for additional effective and well-tolerated, targeted therapeutic options for those with mCRPC who have progressed despite multiple prior non-targeted therapies.[27-30]

Position of ^{177}Lu vipivotide tetraxetan

- ^{177}Lu vipivotide tetraxetan is positioned for the treatment of adult patients with PSMA-positive, mCRPC who have been treated with an ARPI and a taxane-based chemotherapy, or who are not medically suitable for taxanes.
- As such, ^{177}Lu vipivotide tetraxetan represents a much-needed treatment option with a novel mechanism of action for patients with mCRPC. This is reflected by the Promising Innovative Medicines (PIM) designation granted by the MHRA for ^{177}Lu vipivotide tetraxetan.[31]

B.1.3.1 Disease overview and epidemiology

Prostate cancer (PC) is a type of cancer that originates in the gland cells of the prostate where excessive and aberrant cell growth leads to the formation of tumours. These tumours may remain confined to the prostate but often eventually extend beyond the prostate's capsule and spread to local or distant sites in the body as metastases.[32] The vast majority of PCs originate from the prostate's glandular cells and the most common subtype of PC is acinar adenocarcinoma, which accounts for 90–95% of PC cases.[32, 33] The majority of remaining cases of PC are generally classified as ductal adenocarcinoma (originating in cells lining the prostate gland ducts) or neuroendocrine carcinoma (originating from neuroendocrine cells in the prostate).

The cause of PC is thought to be a complex interplay of genetic factors, environmental factors and hormonal imbalances, which collectively drive chronic inflammation and abnormal proliferation of PC cells. The majority of PC cases in the UK are sporadic (non-hereditary) in nature, while approximately 5−9% of men have hereditary disease.[34] Notably, the most frequently mutated DNA repair genes in PC are BRCA1/2 and these convey more aggressive disease and earlier onset.[35] Certain environmental and lifestyle factors (such as dietary carcinogens, infectious agents and obesity) have been implicated as risk factors for PC; however, no definitive link has been established between PC and preventable risk factors.[32]

Prostate cancer may present as either localised, locally advanced, or advanced/metastatic and is the most common cancer in males in the UK, with an incidence of 52,280 cases diagnosed in England between April 2018 and March 2019.[18] As of 2018, the World Cancer Research Fund reported the UK to have the 16th highest PC rate worldwide (age-standardised incidence of 80.7

per 100,000).[36] The overall incidence of PC in the UK has increased steadily over the past decade, and is projected to rise to 233 cases per 100,000 males by 2035 (12% increase 2014–2035).[19] Age is a major risk factor in the development of PC and age-specific incidence rates rise sharply from around age 50–54 years (70 cases per 100,000), with the highest rates found at ages 75–79 years (819 cases per 100,000).[19]

In England during 2018, the proportion of patients diagnosed with stage I, II, III, and IV PC were 35.5% (n=17,670), 13.6% (n=6,758), 23.9% (n=11,889), and 17% (n=8,442); 10.1% (n=5,051) newly diagnosed patients were of unknown stage.[37] There proportions remained broadly stable from 2013–2018.[37] Of all patients diagnosed with PC in England and Wales during 2020, 14% presented with metastatic disease.[18] Furthermore, although incidence data specific to mCRPC is not widely reported for the UK, a longitudinal analysis of the UK-based General Practice Research Database (GPRD) revealed that 28% of PC patients that had undergone androgen deprivation therapy (ADT) developed CRPC between 1999–2009 (8.3 per 100 person years in all PC patients).[38] These figures are in line with an international systematic review of prevalence studies, which indicated that 10–20% of patients with PC developed CRPC over a 5-year follow-up period.[39] The same study indicated that almost all patients had bone metastases (84–95%) at the point of mCRPC diagnosis.[39]

PSMA positivity in PC

PSMA is a 750-amino-acid type II transmembrane protein encoded by the folate hydrolase 1 gene.[13] PSMA is expressed in benign prostate tissue at modest levels as well as demonstrating some limited expression in other tissues.[13] However, in prostate adenocarcinoma, PSMA expression increases substantially. Furthermore, expression of PSMA has been shown to be higher in more aggressive disease, including more advanced tumour staging, and in cases of biochemical recurrence or CRPC.[13] Due to the specificity of PSMA expression on cancerous prostate tissue, particularly in advanced or recurrent PC, imaging using PSMA-targeted radioligands has become an important modality to detect nodal or distant metastases and inform clinical decision making.[40] The vast majority of patients with mCRPC are PSMA-positive, with the VISION trial (which represents the key source of clinical evidence for ^{177}Lu vipivotide tetraxetan in this submission) reporting 86.6% of screened patients meeting criteria for PSMA-positivity. In a retrospective analysis of 1,007 consecutive patients in a single-centre who underwent assessment for PSMA-status over a 3-year period, PSMA-positivity was on average detected in 79.5% of patients with PC.[41] However, this proportion was noted to markedly increase in patients with an elevated PSA (46% in patients with PSA ≤0.2 ng/ml – 96% in patients with PSA >10.0 ng/ml).[41] Given that patients with progressive mCRPC are expected to have an elevated PSA (mean PSA of patients in VISION was 77.5 ng/ml in the treatment arm and 74.6 ng/ml in the standard of care arm), it is reasonable to expect the proportion of PSMA-positivity to be approximately 90% in the patient population covered within this submission.[25]

B.1.3.2 Disease burden

Patients with early stage, non-metastatic PC often do not experience any symptoms from their disease.[42] However, symptoms may develop when the cancer grows large enough to press against the urethra and interfere with urinary habits. Possible early symptoms of localised or locally advanced PC include difficulty in commencing urination or emptying the bladder, a weak urinary flow, urinary frequency, urinary urgency, haematuria, and nocturia.[42] The insidious nature of early PC and the non-specific symptoms which present with early disease can often result in a

delayed diagnosis, which leads to a considerable proportion of patients presenting with metastatic disease, as described in Section B.1.3.1.

Metastatic PC on the other hand causes a wide range of symptoms that can significantly impact upon patients' lives.[21, 22] In addition to the urinary symptoms experienced in early disease, patients may experience constitutional symptoms such as unexplained weight loss, generalised fatigue, sleep disturbance and anxiety.[22] Disease burden in the pelvis can lead to pelvic or back pain, as well as colorectal dysfunction in the form of constipation and/or diarrhoea.[22] Additionally, bone metastases can lead to significant skeletal morbidity (often known as "symptomatic skeletal events"), such as pain, pathological fractures, spinal cord compression, or hypercalcaemia and its associated complications (nausea and vomiting, polydipsia, myalgia, delirium, renal impairment, and cardiac arrythmias).[22] Visceral metastases can also cause a variety of symptoms, depending on the site and extent of the metastases.[43] For instance, lung metastases can lead to shortness of breath whereas liver metastases can lead to jaundice, pruritis, abdominal swelling and pain.[44]

Due to the wide range or debilitating symptoms, patients with mCRPC experience a substantial impact on their physical, mental, and social well-being, which leads to a negative impact on health-related quality of life (HRQoL) that deteriorates further in more advanced cases.[45-47] In a UK-based survey of chemotherapy naïve-patients with mCRPC (n=163), EuroQoL 5 Dimension (EQ-5D) utility scores were significantly lower in symptomatic patients (0.63; standard deviation [SD]: 0.17) than asymptomatic/mildly symptomatic patients (0.83; SD: 0.13).[47] A European observational study of patients with mCRPC (n=602), which included patients based in the UK (n=79), further demonstrated the impaired HRQoL for patients with mCRPC both pre-chemotherapy (EQ-5D utility: 0.70; SD: 0.02) and post-chemotherapy (EQ-5D utility: 0.60; SD: 0.03).[46] Mean EQ-5D utility scores for mCRPC patients ranged from 0.59 to 0.84 across six studies of patients in centres in Europe (including the UK) and Asia Pacific.[46-51] In the advanced stages of mCRPC, patients can also experience a profound psychological impact. According to a survey of patients with mCRPC, 72% highlighted the emotional impact of a metastatic diagnosis, reporting worry/anxiety/fear, low mood/depression, shock, increased burden on carers and strain on relationships.[52] As confirmed by UK clinical experts, very few patients with mCRPC receive three lines of treatment, as there is a lack of effective treatments beyond second-line, likely contributing to the emotional impact of progressive mCRPC.[5]

Bone metastases, which are commonly observed for patients with mCRPC, carry a further negative impact on HRQoL for patients.[53] Symptomatic skeletal events (SSEs), comprising of spinal cord compression, pathological fractures, radiation to bone, and surgery to bone, have been associated with poorer HRQoL. There is a lack of data concerning the utility detriment of bone metastases in PC patients in the UK. However, global studies document a significant burden of disease. A multinational study of HRQoL in PC patients (n=3,477) in five major European countries (UK, France, Germany, Spain, and Italy) found that patients with CRPC and bone metastases had significantly lower EQ-5D and FACT-P scores than CRPC patients without bone metastases but at high risk of developing bone metastases in the future. EQ-5D scores for these groups were 0.59 and 0.77, and FACT-P scores were 82.99 and 99.54, respectively. Furthermore, in a cross-sectional study of patients with mCRPC and bone metastasis (n=125) in Asia Pacific, although the incidence of skeletal-related events (SREs) was 3.0% (95% CI 2.26, 3.78), bone pain was reported by 39.2% of patients.[48] Patients experiencing bone pain faced significant burden on their lives including: hospitalisation (26.5% of patients; mean [SD] length of stay 16.0 [21.67] days), surgeries (14.3%), and emergency department attendance (18.4%). In

contrast with mCRPC patients as a whole, patients with SREs had an EQ-5D utility score of 0.34 (SD: 0.32), which is indicative of higher humanistic burden.[48]

Mortality

PC is the second most common cause of cancer death amongst men in the UK, and accounted for 13% of all cancer deaths in 2018 (11,890 deaths; age-standardised mortality of 45.9 per 100,000 males).[20] PC mortality is strongly correlated with age and almost three-quarters of deaths occur in men aged ≥75 years, with age-specific mortality rates rising steeply in patients over 55 years old.[20]

While survival rates are initially high in patients with localised to locally advanced disease (Stages 1–3), prognosis worsens when patients progress to advanced/metastatic PC (Stage 4). Among patients diagnosed between 2013 and 2017 in England, the 1-year survival rate decreased from 100% for those diagnosed at Stages 1–3, to 88% at Stage 4.[54] Five-year survival rates also decreased substantially, from 100% for Stage 1–2 disease, to 96% for Stage 3 and 49% for Stage 4 disease.[54] However, these figures are not sub-divided by hormone-sensitivity status, nor by response to initial lines of therapy, and thus are not representative of the target population of this submission who have mCRPC uncontrolled by initial lines of therapy.

A summary of recent clinical trials in mCRPC patients with recurrent disease despite ADT and docetaxel treatment identified three trials (TROPIC, NCT00417079; COU-301, NCT00638690; AFFIRM, NCT00974311).[24] These trials reported a median OS of 15.1, 15.8 and 18.4 months for intervention arms and 12.7, 11.2, and 13.6 months for their control arms, respectively. Overall, this suggests that the OS for patients with mCRPC that progress despite docetaxel is approximately 12–13 months, although is likely shorter for patients who have also experienced further disease progression despite ARPI treatment. The median OS for patients in the SOC arm of VISION, the primary source of evidence for ^{177}Lu vipivotide tetraxetan in this submission, was only 11.3 months (Section B.2.5.2).[25]

The link between high PSMA expression and mCRPC means that survival outcomes are particularly poor in patients with a high level of PSMA expression.[55, 56] According to a retrospective study of patients with mCRPC who were treated with various life-prolonging therapies and underwent baseline PSMA imaging (n=238), patients with high PSMA expression had significantly shorter OS compared with those with low PSMA expression (15.8 months [95% CI 13.0, 18.1] versus 22.7 months [95% CI 17.7, 30.7 months]; p=0.002).[57] After accounting for life-prolonging therapies and prognostic groups, high PSMA expression was identified as an independent prognostic factor for a reduction in OS (HR 1.7 [95% CI 1.2, 2.2]; p=0.003).[57]

B.1.3.3 Current treatment pathway for patients with mCRPC

Guidelines for the treatment of patients with prostate cancer in the UK are available from the National Institute for Health and Care Excellence, NG131.[2] Other key guidelines for management of prostate cancer are available from the European Association of Urology and the European Society for Medical Oncology.[58, 59] These guidelines contain largely congruent treatment recommendations.

Diagnosis

If there is clinical or radiographic suspicion of advanced/metastatic PC (e.g. concerning symptoms such as bone pain or evidence of prostatic capsular breach on magnetic resonance

imaging [MRI]), imaging procedures such as an isotope bone scan using single photon emission computed tomography (SPECT), further MRI, CT, or PET, may be recommended to diagnose, locate, and stage metastatic disease.[2, 34, 60, 61] In particular, PET scanning with choline-based radiotracers (^{11}Carbon [C]-Choline, and ^{18}Fluorine [F]-Choline) provides greater detail than conventional methods (CT or bone scans) to offer a more accurate picture of PC metastases,[62, 63] although currently available PET methods offer limited sensitivity in patients with low prostate-specific antigen (PSA) levels and/or lymph node metastases.[34, 64, 65]

PSMA testing in the UK

PSMA scanning represents a highly sensitive and accurate method for the staging of metastatic PC and is currently being used in selected NHS centres for patients who require more accurate staging of disease than can be achieved with bone scanning and MRI. Determination of PSMA-positivity should be radiotracer agnostic, meaning that healthcare professionals who wish to determine the PSMA-status of a patient with mCRPC may use any suitable gamma-emitting radiotracer linked to an appropriate PSMA ligand to do so. In general, once products with marketing authorisation are available from any manufacturer, these products should be used in preference to unlicenced products. This is in accordance with the SmPC for ^{177}Lu vipivotide tetraxetan, which does not specify the determination method for PSMA-status.[15]

There are multiple modalities for assessing PSMA-status, including PET–CT and SPECT scans. Currently ^{68}Ga PET–CT scanning is accessible in five cities in England. An MHRA marketing authorisation application for the AAA ^{68}Ga gozetotide compound was submitted in [redacted], with approval expected in [redacted]. The diagnostic molecule ^{68}Ga gozetotide will offer an additional option for imaging at these centres. Another commercial ^{68}Ga radiotracer manufactured by University of California, Los Angeles, has been approved by the Food and Drug Administration (FDA), with potential future MHRA approval. This radiotracer is for imaging of PSMA-positive lesions in patients with suspected PC metastases who are potentially curable by surgery or radiation therapy and therefore is anticipated to become the SOC for diagnosis and staging in patients with advanced prostate cancer.[66] Furthermore, a technetium-99m[^{99m}Tc]-labelled PSMA radiotracer is currently in development, with an open-label Phase I trial having commenced in April 2021 sponsored by Jonsson Comprehensive Cancer Centre, University of California, Los Angeles.[67] This radiotracer is for use with single photon emission computed tomography–computed tomography (SPECT–CT) scanning.[68, 69] It is important to note that these imaging techniques can be used at various points in the prostate cancer pathway, for instance if a patient experiences biochemical recurrence, for disease staging, or when more sensitive imaging is required compared to conventional imaging, and as such are not solely to support the treatment decision with a PSMA-targeted therapy such as ^{177}Lu vipivotide tetraxetan.

Expansion of existing services has been addressed through the NHS Levelling Up agenda and the future expansion of PET–CT facilities is eagerly anticipated by the clinical community. It is also anticipated the commercialisation of ^{18}F fluorinated PSMA radiotracers for use with PET–CT infrastructure will provide further options for the identification of PSMA-positive patients with mCRPC.

VISION, the pivotal trial providing clinical evidence for ^{177}Lu vipivotide tetraxetan, defined PSMA-positivity as ^{68}Ga gozetotide uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system.[25] Furthermore, in the context using ^{68}Ga gozetotide, PSMA-negativity may be defined as ^{68}Ga gozetotide uptake equal to or lower than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any metastatic

solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of at least 1.0 cm in the short axis.[25]

PC treatment pathway

The treatment of PC is dependent upon disease location, stage, grade, PSA level and other patient-related considerations.[2, 70] Treatment for patients with localised or locally advanced prostate cancer (Stages I–III) may have a curative intent, whereas there are no curative pharmacological treatment options for patients with metastatic PC (Stage IV), and treatment instead focuses on extending survival, as well as relieving symptoms and preserving quality of life.[2]

Localised or locally advanced PC

Patients with newly diagnosed localised or locally advanced PC undergo risk stratification and discussion by a urological cancer multidisciplinary team (MDT).[2] Patients are categorised into either low-, intermediate-, or high-risk disease based upon their PSA level, Gleason score, and clinical disease stage.[2] Patients with high-risk or locally-advanced disease are offered radical treatment if it is likely their disease can be controlled in the long term.[2] Otherwise, docetaxel chemotherapy alongside long-term ADT is offered to patients who have no significant co-morbidities.

ADT is a standard treatment that can be used to lower androgen levels (such as testosterone) to slow growth or even shrink PC tumours.[71, 72] ADT can be performed with drugs in the form of luteinising hormone-releasing hormone agonists/antagonists, anti-androgen therapies such as bicalutamide and flutamide, or alternatively by surgery to remove the testicles (orchidectomy).[71] Patients with localised or locally-advanced PC may be eligible for ADT in combination with radiotherapy when they have an intermediate to high risk of disease recurrence, or ADT alone when surgery or radiotherapy are not appropriate.[71] In cases of non-metastatic CRPC, one of two ARPIs (darolutamide or apalutamide) may be offered alongside ADT.[73, 74]

Metastatic hormone-sensitive PC

For patients with metastatic PC (stage IV), the cancer has spread to distant sites beyond the prostate and no curative treatment options remain and the aim of therapy should be to prolong life and to maintain patients' HRQoL for as long as possible.[75]

Patients diagnosed with hormone-sensitive metastatic PC may undergo ADT to prolong survival, palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (such as spinal cord compression, pathological fractures and ureteral obstruction).[76] Patients with advanced/metastatic PC may receive ADT monotherapy, ADT and ARPI therapies together, or a combination of ADT plus chemotherapy (docetaxel).[72]

First-line therapy for metastatic PC is docetaxel chemotherapy (alongside ADT).[2] Docetaxel chemotherapy may be offered to patients who do not have significant comorbidities and should be commenced within 12 weeks of starting ADT. Docetaxel may be used for six 3-weekly cycles at a dose of 75 mg/m^2, with or without daily prednisolone. Docetaxel is frequently used whilst a patient's disease is hormone-sensitive, rather than following confirmation of CRPC. During 2019, the National Prostate Cancer Audit found that 36% of UK patients with newly diagnosed hormone-sensitive metastatic PC received docetaxel (alongside ADT) as upfront therapy.[18] However, during 2020 there was a marked fall by 74% in mHSPC patients receiving docetaxel

with a concomitant rise in the use of enzalutamide, in line with NICE's interim guidance on systemic anti-cancer therapies during the COVID-19 pandemic to reduce potential patient exposure to coronavirus.[77] Furthermore, work by Prostate Cancer UK highlighted that the proportion of patients with newly diagnosed metastatic PC who received first-line docetaxel significantly varied by age.[11] For men aged under 70, 63.6% received docetaxel first-line. This proportion fell significantly to 21.9% of those men aged over 70 and declined further still to 5.7% in men aged 80 and older. Given that docetaxel was only added to the NICE guidelines as a treatment option for newly diagnosed hormone-sensitive PC in 2019, it is possible that the proportion of patients in this setting receiving docetaxel will increase over time, especially with emerging evidence for triplet therapy (a combination of docetaxel, ADT and ARPI).[4]

A further option for treatment of metastatic hormone-sensitive PC is ARPI therapy in combination with ADT. Both enzalutamide and apalutamide have recently each been individually recommended by NICE as options for treatment alongside ADT in this setting.[74, 78] However, despite available therapies, after some months or years, patients usually develop hormone-relapse, at which point patients are classified as having mCRPC.[79]

Metastatic castration-resistant PC

Hormone-relapse (otherwise known as 'castration-resistance') is broadly defined as the point of failure of primary ADT in the treatment of a patient's PC,[2] or specifically defined as a patient with a testosterone level of <50 ng/dL (<1.7 nM/L) plus either biochemical progression (three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir and a PSA >2 ng/ml) or radiological progression (the appearance of new lesions: either ≥2 bone lesions or a soft tissue lesion using Response Evaluation Criteria in Solid Tumours).[28] mCRPC is sometimes referred to as 'hormone-relapsed' disease, however throughout this submission mCRPC is used to align with the most commonly used terminology in medical literature and other Health Technology Assessment (HTA) appraisals.

If chemotherapy is not yet felt to be clinically indicated, then a patient may initially be treated with corticosteroids (e.g. dexamethasone 0.5 mg daily) or an ARPI (abiraterone or enzalutamide) in combination with prednisone or prednisolone in patients who have no or mild symptoms after primary failure of ADT. It is important to note that ARPIs may not be used in sequence under NICE guidelines and should only be used once within the entire PC treatment pathway due to limited evidence of the efficacy of re-challenge with ARPIs.[80] Thus, the expanding use of ARPIs in earlier stages of PC management (e.g. in hormone-sensitive disease) will preclude their use in mCRPC.[73, 74, 78, 81] This changing landscape has been particularly noted during the COVID-19 pandemic in 2020, with a marked rise in ARPI (enzalutamide) use (3 patients in 2019 vs. 1,011 patients in 2020), in line with NICE's interim systemic anticancer therapy guidance.[77]

In patients where chemotherapy is clinically indicated, the NICE guidelines state that mCRPC patients' first-line treatment option is docetaxel.[2] Docetaxel is recommended, within its licensed indications, as a treatment option for people with mCRPC only if their Karnofsky performance-status score is 60% or more. Docetaxel treatment should be discontinued after a maximum of 10 cycles, if a severe adverse event occurs, or if the patient shows evidence of disease progression. Repeat treatment with docetaxel is not recommended if the patient experiences disease recurrence following completion of previously completed docetaxel treatment. Patients who receive docetaxel in earlier hormone-sensitive disease are highly unlikely to receive repeat treatment with docetaxel in the mCRPC setting. This has been confirmed by UK clinical experts within an advisory board setting.[5]

For patients with mCRPC who progress despite docetaxel, those who are not medically suitable for docetaxel, or those who have previously been treated with docetaxel earlier in the treatment pathway, remaining options are limited:

- Cabazitaxel, another taxane chemotherapy, is recommended in patients who maintain an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and have previously received 225 mg/m^2 or more of docetaxel. Treatment with cabazitaxel should be continued for a maximum of 10 cycles or until disease progression.[10]
- An ARPI, either abiraterone or enzalutamide, may be used following failure of docetaxel or in patients in whom docetaxel was not suitable.[82, 83] However, if any ARPI has been used previously at any stage in the treatment pathway, further use of ARPIs is not commissioned.
- Radium-223 is recommended in patients with mCRPC who have already received docetaxel and who have symptomatic bone metastases. Its use is precluded in patients with visceral metastases.[84]

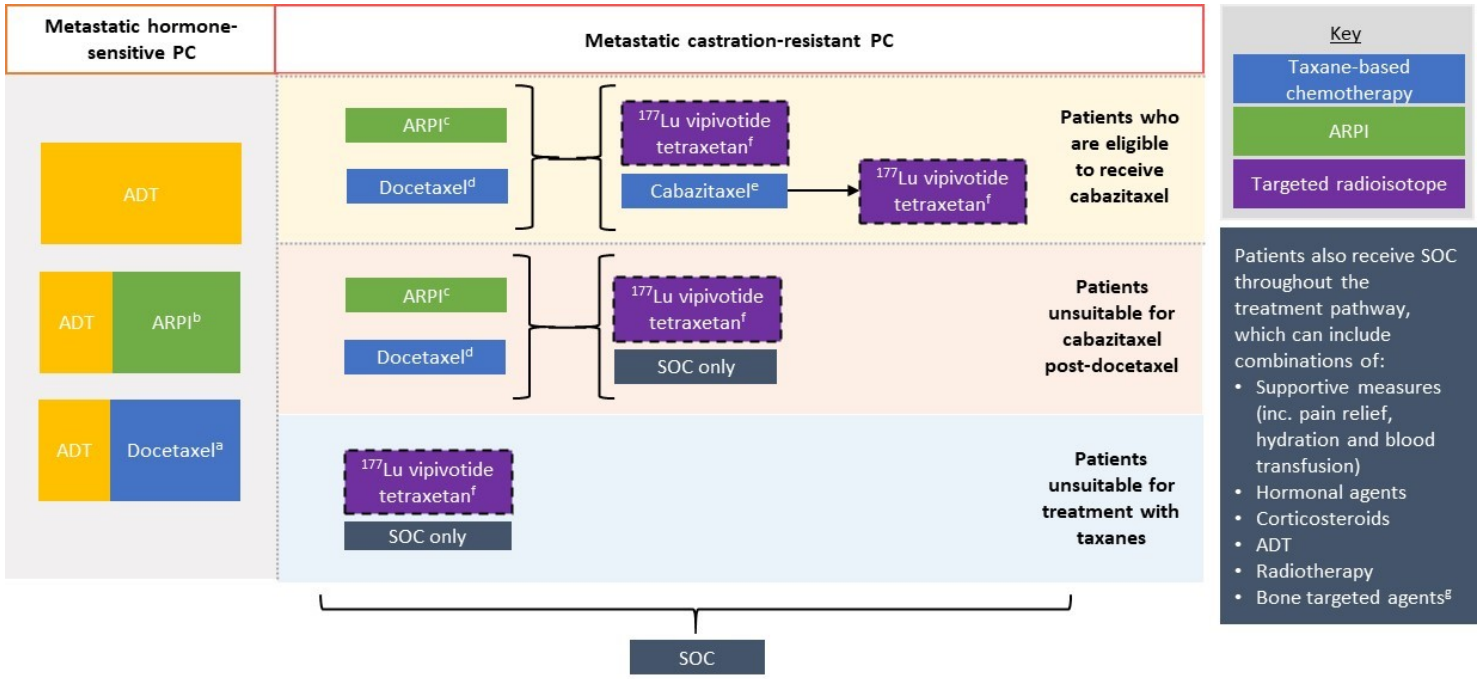
Importantly, some patients are medically unsuitable for taxane-based chemotherapy. It has been acknowledged in previous NICE appraisals that creating an exhaustive list of reasons for a patient being medically unsuitable for taxanes is particularly challenging,[81] reasons for medical unsuitability may include but are not limited to: hypersensitivity to active substance or excipients, neutropenia <1,500 cells/mm^3, severe hepatic impairment, poor performance status (ECOG ≥3, ECOG ≥2 with substantial comorbidities, and lack of social support or impaired cognitive understanding sufficient to impact upon treatment compliance or toxicity monitoring.[84] These ineligibility criteria may apply to patients after they have received treatment with ARPI and prior to a first taxane, or after ARPI treatment and subsequent treatment with a taxane, at the point of treatment decision for a second taxane (e.g., cabazitaxel).

In UK clinical practice, it has been estimated that of the patients with mCRPC who receive first-line treatment with docetaxel, approximately 55% are eligible to receive second-line chemotherapy.[10] As discussed previously, UK clinical experts have advised that retreatment with docetaxel is highly unusual in UK clinical practice, occurring in as low as 2% of patients,[5] and thus the vast majority of patients who do receive further chemotherapy currently receive cabazitaxel and not retreatment with docetaxel.

Additional palliative interventions can be used at any point during the treatment pathway and are considered SOC. These may include supportive measures (pain medication, hydration, blood product transfusion, etc), ADT, corticosteroids, 5-alpha reductases (finasteride or dutasteride), targeted radiotherapy for SREs (e.g. malignant spinal cord compression or painful bone metastases), bone-targeted therapies aimed at providing symptomatic relief (zoledronic acid, bisphosphonates), or surgical intervention (e.g. ureteric stenting for obstructive nephropathy), as well as emotional and psychological support.

An overview of the clinical pathway for mCRPC in UK clinical practice including the proposed positioning of ^{177}Lu vipivotide tetraxetan is provided in Figure 2.

Figure 2: Treatment pathways for patients with mCRPC and the proposed positioning of ^{177}Lu vipivotide tetraxetan



ARPIs may only be used a single time during a patient's PC treatment pathway. In addition to the places in therapy shown here, ARPIs may also be used earlier in the PC treatment pathway in cases of non-metastatic CRPC.

[a]For patients who do not have significant comorbidities. Commenced within 12 weeks of starting ADT. Six 3-weekly cycles at a dose of 75 mg/m^2 (with or without daily prednisolone). [b]Either enzalutamide or apalutamide are recommended for use in this hormone-sensitive, metastatic setting alongside ADT. [c]Either enzalutamide or abiraterone are recommended for use in this castration-resistant, metastatic setting. ARPIs may only be used once during a patient's PC treatment pathway. [d]Recommended as an option for patients with a Karnofsky performance-status score of 60% or more. Treatment should be stopped at a maximum of 10 cycles, if a severe adverse event occurs, or if disease progression occurs. Repeat cycles are not advised in the case of disease recurrence following prior docetaxel. [e]Recommended as an option for patients with an ECOG performance score of 0 or 1 who have received 225 mg/m^2 or more of docetaxel. Retreatment with docetaxel is permitted according to NICE guidelines but is not typical, occurring in as low as 2% of patients,[6] and thus is not represented in this pathway. [f]Positioned as a treatment for patients with PSMA-positive mCRPC who have progressed on previous ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes. [g]Bone targeted agents include zolendronic acid (recommended as an options for patients with bone metastases to reduce the risk of skeletal-related events), bisphosphonates (recommended as an option for pain relief in patient with bone metastases when other analgesics and palliative radiotherapy have not been sufficient), and radium-223 (recommended as an option for patients with symptomatic bone metastases who do not have visceral metastases and who have already received docetaxel or in who docetaxel is contraindicated or not suitable).

Abbreviations: ^{177}Lu: lutetium-177; ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitor; ECOG: Eastern Cooperative Oncology Group; KP: Karnofsky performance-status; mCRPC: metastatic castration-resistant prostate cancer; PSMA: prostate-specific membrane antigen; SOC: standard of care.

Source: NICE Prostate Cancer, Diagnosis and Management[2]

B.1.3.4 Unmet need in mCRPC

Limited therapeutic options available

Treating patients with mCRPC presents a clinical challenge, with a considerable unmet need in terms of treatment options beyond palliative care for patients with symptomatic mCRPC that has progressed despite multiple prior therapies.[29, 30] Cabazitaxel represents an additional treatment option for patients who are able to tolerate further chemotherapy. However, a proportion of patients who have progressed despite multiple prior therapies would not be suitable for further chemotherapy due to these patients being elderly and/or frail with significant disease, prior treatment-related comorbidities and a higher tumour burden.[85] Furthermore, with the expanding indications for docetaxel and ARPIs, multiple lines of treatment may be exhausted in the metastatic hormone-sensitive setting, prior to developing mCRPC, even if patients maintain a good performance score.[2] Thus, for many patients with mCRPC who have progressed on ARPIs and taxane treatment, palliative care is often the only available treatment option.[30] This results in patients with mCRPC facing very poor prognoses while suffering from a significant quality of life deterioration caused by rapid disease progression, highlighting a significant unmet need for new treatments that prolong life and preserve HRQoL.

Furthermore, only one in three men with newly diagnosed metastatic prostate cancer were prescribed docetaxel therapy in the UK, despite NICE recommendations that this be offered to all men at this stage, with this proportion falling by 74% during 2020 due to the COVID-19 pandemic.[18, 77] Furthermore, the majority of these patients are likely to have hormone-sensitive PC and will not yet have developed mCRPC. Although it is unclear why docetaxel uptake is this low, clinical leads for this audit suggested patient choice may play a part.[86] In addition, there was widespread variability across NHS providers in England for those who received docetaxel, ranging from 0% to 39%.[18] The National Cancer Registration and Analysis Service (NCRAS) have addressed the disparities in prescription of chemotherapy across the UK, and the reasons for this are complex, but there are some factors which were been established such as age and comorbidity.[87] Therefore, with a shift of recommended non-taxane based therapies to earlier in the prostate cancer pathway, and the detrimental effect of multiple lines of treatment, by the time patients progress to mCRPC, if taxanes are not suitable patients are left with little or potentially no further options (i.e., if ARPIs have already been utilised).

Patients with visceral metastases

Currently available treatments are limited in their ability to treat visceral metastases, which are found in 22–33% of patients with mCRPC.[88-90] Patients with visceral metastases are well-established to have a worse prognosis than those with non-visceral metastases.[91] According to a prognostic model based on Phase 3 data (N=1,050), patients with mCRPC that received first-line chemotherapy are at increased risk of death when they have visceral disease compared to those with lymph node metastases (hazard ratio [HR] 1.27; 95% confidence interval [CI] 0.96–1.51).[92] In a separate Phase 3 study, men treated with chemotherapy (docetaxel or mitoxantrone [a chemotherapy that is no longer a treatment option in the UK][2]) who had visceral liver metastases had a significantly shorter OS (10.0 months; 95% CI 5.4–11.5) than those with bone metastases only (19.0 months; 95% CI 14.4–17.2) and those with lymph node metastases only (26.7 months; 95% CI 22.3–34.2).[93] Moreover, a dual-centre retrospective observational study showed that patients treated with cabazitaxel for mCRPC had a significantly shorter OS when they had visceral disease (8.7 months; 95% CI 5.9–11.5) compared to those who had bone or lymph node metastases only (11.7 months; 95% CI 7.5–15.9; p=0.042).[94]

Visceral metastases are a similarly important prognostic factor for patients treated with an ARPI. In a small study of patients treated with abiraterone (N=265), a significantly shorter median OS was associated with liver metastases than other sites of metastasis (10.5 months vs 18.5 months, respectively; p=0.006).[95] Similar findings have been found in a Phase 3 study of enzalutamide, whereby patients with mCRPC visceral metastases had a substantially shorter median OS (13.4 months; 95% CI 10.4–16.5) than those with non-visceral metastases (median OS not reached; 95% CI 18.3–not reached).[91] Furthermore, radium-223 is only recommended for mCRPC patients with bone metastases and no known visceral metastases, further reducing available treatment options.[84] mCRPC patients with visceral metastases represent a substantial subgroup of unmet need in the current treatment landscape.

Safety and tolerability of current treatment options

Both safety and tolerability of treatments become increasingly important in patients with PC who have progressed despite prior treatments. The majority of patients with mCRPC, especially those who are medically unsuitable for taxane-based chemotherapy, are elderly and frail, rendering them less able to tolerate treatment-related toxicities.[85] Advanced age and a higher comorbidity burden are associated with increased risk of death in patients with PC.[96] In this advanced disease stage, patients need options that improve OS, PFS, and HRQoL without serious AEs.

Taxanes are cytotoxic agents and are associated with higher rates of toxicity and higher-grade AEs than other treatments.[30] Across Phase 3 randomised controlled trials (RCTs), the incidence of all-grade AEs is over 90% in mCRPC patients treated with taxanes, while the incidence of Grade 3–4 AEs ranges from 66% to 75% (summarised in Table 3).[89, 97-100] In particular, high rates of Grade 3–4 haematological AEs have been reported for taxane-based chemotherapies, including leukopenia (docetaxel: 17.1%;[97] cabazitaxel: 68.2%[90]) and neutropenia (docetaxel: 57.7%;[97] cabazitaxel: 81.7%[90]), predisposing vulnerable patients to severe and life-threatening infections.

Table 3: Incidence of AEs (any Grade and Grade 3–4) according to Phase 3 RCTs

Study	Any grade AE	Grade 3–4 AE
Taxane-based chemotherapies		
Docetaxel[97]	94.6%	74.8%
Cabazitaxel[98]	95.2%	66.4%
Androgen receptor pathway inhibitors		
Enzalutamide[89]	98.1%	45.3%
Abiraterone[99]	95.1%	32.2%
IV radiotherapy		
Radium-223[100]	95.1%	47.3%

Abbreviations: AE: adverse event; IV: intravenous; RCT: randomised controlled trial.

Though ARPI is generally better-tolerated than taxanes, it is not without risk: enzalutamide has been associated with both falls and fractures,[101] and abiraterone acetate has a warning for hepatotoxicity.[102] In a clinical study of enzalutamide, higher incidence of fatigue, diarrhoea, hot flashes, musculoskeletal pain, and headache were reported in the enzalutamide group compared with placebo.[89] In a clinical study evaluating abiraterone acetate plus prednisolone, AEs including oedema, hypokalaemia, and cardiac disorders were more common in the group that received abiraterone acetate plus prednisone compared to the prednisone-only arm.[103]

A recent trial of radium-223 plus abiraterone acetate and prednisolone versus placebo plus abiraterone acetate and prednisolone was unblinded due to increased fractures and deaths in the intervention arm, and thus due to safety concerns these two therapies are contraindicated for concurrent usage.[8, 104]

Overall, the significant toxicity associated with successive lines of therapy for patients with mCRPC limits their routine use, both through progressive comorbidities (secondary to advancing age and prior treatment) and through patient choice when considering the benefits of treatment against potential adverse events. As such, there is a significant unmet need for patients who have progressed through or are medically unsuitable for currently available therapies and who would be otherwise only eligible for SOC. Accordingly, compared with mCRPC patients more broadly, prognosis is particularly poor for patients who have progressed through or are medically unsuitable for currently available therapies; patients receiving standard of care (SOC) in the VISION trial (which provides the key clinical evidence for ^{177}Lu vipivotide tetraxetan in this indication) included patients previously treated with ARPI and one or more taxane-based chemotherapies. The patients in VISION receiving SOC alone had a median OS of only 11.3 months (see Section B.2.5), emphasising the significant unmet need for patients with mCRPC who have progressed despite currently available life-prolonging therapies.

Need for novel targeted therapies

Additional treatment options with novel targeted mechanisms of action able to improve survival and preserve HRQoL in patients with mCRPC are urgently needed, given the currently poor prognosis experienced by mCRPC patients who have progressed through available treatment options. Despite NICE appraising several technologies in the mCRPC and advanced prostate cancer setting during the previous few years, these compounds all fall within the ARPI drug class (which can only be commissioned once in the pathway), or the taxane drug class (cabazitaxel – for use after docetaxel). In part, limitations in efficacy and safety for currently available therapies may be due to their non-targeted mode of action. In recent years, major steps have been taken to develop radioligand therapies (RLT) which offer the possibility to treat the cancer lesions in a specific and tumour-selective manner by exploiting cell surface receptors mainly expressed on malignant cells.[34, 105] In particular, PSMA is a potential target for RLT due to high expression on the surface of PC cells and limited expression on normal tissues,[55, 106-109] allowing PSMA-targeted radiotherapeutics to bind with high-affinity to PSMA[107] and deliver radiation locally to tumour cells while minimising radioactivity-related side effects.[110] Whilst radium-223 targets bone metastases through mimicking calcium, there are no currently available PC treatments that specifically target primary tumour cells This approach offers a key advantage in patient selection over conventional therapies. As such, ^{177}Lu vipivotide tetraxetan represents a much-needed treatment option with a novel mechanism of action for patients with mCRPC. This is reflected by the Promising Innovative Medicines (PIM) designation granted by the MHRA for ^{177}Lu vipivotide tetraxetan.[31]

Using PSMA scanning (PET/CT or SPECT), PSMA-positive patients can be identified, allowing clinicians to identify those patients which may benefit from the PSMA-targeted RLT.[34] Patients who are not PSMA-positive and may not benefit from PSMA-targeted RLT can also avoid unnecessary exposure to a treatment without significant benefit, an approach not currently available for more conventional treatment strategies such as taxane-based chemotherapy. In particular, the European Association of Urology highlights ^{177}Lu vipivotide tetraxetan as the PSMA therapeutic radiopharmaceutical with the most robust supporting data and compassionate usage is already widespread.[34, 111] ^{177}Lu vipivotide tetraxetan therefore represents an important

development in the treatment of patients with mCRPC, providing a more selective and targeted approach with a superior risk-to-benefit ratio, compared to currently available treatments. ^{177}Lu vipivotide tetraxetan has the potential to improve survival outcomes alongside a more tolerable side-effect profile for patients with mCRPC, a disease which currently carries a very poor prognosis.

B.1.4 *Equality considerations*

There are a currently a limited number of clinical centres in the UK which would be able to conduct the required assessment for PSMA positivity and then subsequently deliver treatment with ^{177}Lu vipivotide tetraxetan. The limited number of centres may have an impact on equal access for patients across the country, based on ability to travel. At present, due to the substantial disease burden of mCRPC, patients are currently actively seeking treatment with ^{177}Lu vipivotide tetraxetan through private healthcare in the UK, thus emphasising the current unmet need in this patient cohort and potentially exacerbating socioeconomic health inequalities.[112]

In addition, there is a need for additional therapeutic options for prostate cancer progression in patients who are not medically suitable to receive taxanes. It has been reported that approximately 50% of mCRPC patients do not receive treatment with a taxane, mostly due to specific safety concerns, frailty, and/or patient refusal (due to the side effect profile of taxanes).[10] Thus, limiting the eligibility of ^{177}Lu vipivotide tetraxetan to only those patients who have received taxanes would create significant inequality in the management of patients with mCRPC. Both safety concerns and side effects are data-driven and largely non-overlapping with ^{177}Lu vipivotide tetraxetan (i.e., patients not medically suitable for taxanes can benefit from ^{177}Lu vipivotide tetraxetan). The phase III VISION study was designed to specifically select patients who had previously received taxanes to demonstrate that ^{177}Lu vipivotide tetraxetan provides clinical benefit in patients that have tried all available treatments known to influence OS.[25] However, mechanistically, there is no reason that the efficacy and safety of ^{177}Lu vipivotide tetraxetan would be significantly different in patients who have not previously received taxanes compared to patients who have previously received taxanes. Thus, patients who are not medically suitable to receive taxanes for PSMA-positive mCRPC are still likely to derive clinical benefit from ^{177}Lu vipivotide tetraxetan. Therefore, the clinical effectiveness and safety demonstrated in the phase III VISION study could be clinically and mechanistically extrapolated to encompass the unmet medical need in patients who would not be medically suitable to receive taxanes.

B.2 Clinical effectiveness

- The efficacy and safety of ^{177}Lu vipivotide tetraxetan has been demonstrated in VISION, an international, prospective, open-label, randomised Phase III trial investigating the ^{177}Lu vipivotide tetraxetan + SOC vs SOC only in patients with mCRPC previously treated with ARPI and taxane-based chemotherapy.
- As VISION did not include a direct comparison of ^{177}Lu vipivotide tetraxetan to cabazitaxel, the clinical effectiveness of ^{177}Lu vipivotide tetraxetan has been compared against cabazitaxel using real-world database analyses, with further supporting information from an indirect treatment comparison (ITC), and data from the head-to-head TheraP Phase 2 study. This robust and comprehensive set of data support the benefit of ^{177}Lu vipivotide tetraxetan compared to cabazitaxel, and was gathered to reduce uncertainty and inform decision-making

Efficacy

- VISION trial compared ^{177}Lu vipivotide tetraxetan + SOC, (n=551) to SOC only (n=280). The data-cut for the final analyses of VISION was 27th January 2021.
- In VISION patients receiving treatment with ^{177}Lu vipivotide tetraxetan + SOC demonstrated a significant extension in both of primary endpoints (OS and rPFS) compared to patients receiving SOC (p<0.001).
  - ^{177}Lu vipivotide tetraxetan + SOC reduced the risk of death by 38% vs SOC alone (p<0.001).
    - Median OS was significantly improved with ^{177}Lu vipivotide tetraxetan + SOC compared with SOC alone (15.3 vs 11.3 months).
  - ^{177}Lu vipivotide tetraxetan + SOC reduced the risk of radiographic disease progression or death (rPFS) by 60% versus SOC alone (p<0.001).
    - Median rPFS was significantly improved with ^{177}Lu vipivotide tetraxetan + SOC versus SOC alone (8.7 vs 3.4 months).
- In VISION patients receiving treatment with ^{177}Lu vipivotide tetraxetan + SOC demonstrated significant improvement across all key secondary outcomes compared with SOC.
  - ^{177}Lu vipivotide tetraxetan + SOC significantly reduced the risk of SSEs or death by 50% relative to SOC alone (p<0.001).
  - ^{177}Lu vipivotide tetraxetan + SOC significantly prolonged the median time to first SSE versus SOC alone (11.5 vs 6.8 months).
  - ^{177}Lu vipivotide tetraxetan + SOC improved patients' QoL vs. SOC alone by delaying the time to FACT-P, BPI-SF (pain intensity) and EQ-5D-5L score deterioration by 3.5, 3.7 and 0.5 months, respectively (all p<0.001).
- VISION demonstrated significant improvements for ^{177}Lu vipivotide tetraxetan + SOC across multiple secondary endpoints including an increased rate of ORR (p<0.001) and DCR (p<0.001)
- Subgroup analysis, although limited by low patient numbers in certain subgroups, demonstrated that the benefit of ^{177}Lu vipivotide tetraxetan extended across multiple key subgroups such as patients aged ≥65 and those with liver metastases, which represent some of the frailer cohorts of patients with mCRPC.
- Similar efficacy was demonstrated for patients receiving ^{177}Lu vipivotide tetraxetan + SOC regardless of whether ARPI was included as part of SOC. This emphasises the applicability of the VISION results to UK clinical practice in which multiple courses of ARPI treatment are not permitted.
  - The VISION study was a global trial, with SOC varying between countries according to physician discretion and local guidelines. The consistency of treatment effect across subgroups such as those receiving or not receiving ARPI as a component of SOC provides confidence in the generalisability of VISION to UK clinical practice, and this generalisability has been confirmed by UK clinicians in an advisory board setting.[5]

Real-world evidence

- In order to further understand the mCRPC patient population within the UK healthcare system, a retrospective real-world evidence (RWE) study of patients with mCRPC was carried out using linked healthcare datasets from Public Health England (PHE) and NHS Digital, including records from 1st January 2009 to 31st December 2018.
    - This data was collected in an effort to provide the most relevant data possible for cabazitaxel in UK clinical practice, and to address the paucity of UK RWE available in the mCRPC setting
- Baseline characteristics for mCRPC patients in VISION closely align with those in UK clinical practice in terms of age, ethnicity, and ECOG status, highlighting the generalisability of VISION trial results to UK clinical practice.
- Patients receiving cabazitaxel in UK clinical practice are expected to most closely resemble the VISION trial population in that in the UK, cabazitaxel can only be prescribed post-docetaxel, and is highly likely to be given in the post-ARPI setting.[10] The median OS for patients receiving cabazitaxel in the UK RWE analysis was [redacted] months.

Indirect treatment comparison

- The only head-to-head evidence comparing ^{177}Lu vipivotide tetraxetan to cabazitaxel is the TheraP trial. TheraP demonstrated a benefit for ^{177}Lu vipivotide tetraxetan versus cabazitaxel in terms of rPFS (1.59 [95% CI: 1.16–2.17]).
- However, TheraP was not powered to robustly investigate overall survival and has not yet published any results for this endpoint. The trial utilised an on-site, non-official synthesised version of ^{177}Lu vipivotide tetraxetan (not provided by the company) and differed in inclusion criteria due to the requirement for a fluorodeoxyglucose (FDG) PET-CT scan in addition to gallium PET-CT imaging. For these reasons, TheraP does not provide an appropriate head-to-head comparison to inform efficacy in the economic model.
- Given the lack of suitable head-to-head efficacy data to compare ^{177}Lu vipivotide tetraxetan and cabazitaxel, an indirect treatment comparison was explored to generate relative efficacy estimates for these two treatment options.
- The NMA demonstrated a significant benefit in terms of OS ([redacted]) and rPFS ([redacted]) for ^{177}Lu vipivotide tetraxetan compared to cabazitaxel. The rPFS result from the NMA was validated by close alignment to the rPFS HR reported in TheraP.

Adverse reactions

- ^{177}Lu vipivotide tetraxetan demonstrated a very manageable safety profile compared to protocol-permitted SOC alone with the most common grade 3+ TEAEs experienced by >5% of patients treated with ^{177}Lu vipivotide tetraxetan relating to bone marrow suppression - lymphopenia (7.8% vs 0.5%), anemia (12.9% vs 4.9%), and thrombocytopenia (7.9% vs 1.0%) - and fatigue (7.0% vs 2.4); these adverse events did not severely impact patient QoL and less than 12% of patients randomised to ^{177}Lu vipivotide tetraxetan discontinued treatment due to TEAEs.
- Although rates of AEs were higher across multiple categories in the ^{177}Lu vipivotide tetraxetan + SOC arm compared with the SOC arm, these AEs were likely at least in part contributed to be a longer mean exposure to treatment in the intervention arm ([redacted] vs. [redacted]), due to extended OS.
- The rate of AEs leading to death were similar between intervention and control arms (3.6% vs. 2.9%).
- The most common category of AEs leading to dose reduction or interruption of ^{177}Lu vipivotide tetraxetan was myelosuppression, representing a category of AEs that can be addressed prophylactic measures. Despite the lack of required G-CSF prophylaxis in VISION, rates of grade ≥3 leukopenia and neutropenia were 2.3% and 3.2% respectively. In contrast, CARD, the pivotal trial that investigated the efficacy of cabazitaxel in mCRPC patients having progressed despite docetaxel and ARPI, required all patients receiving cabazitaxel to receive primary prophylaxis G-CSF. Despite this, CARD still high reported rates of grade ≥3 leukopenia and

neutropenia with cabazitaxel treatment, 32.0% and 44.7% respectively.[113]

End of life criteria

- Given the short life-expectancy for patients with mCRPC previously treated with ARPI and taxane-based chemotherapy, and the extension to life compared to current treatment (cabazitaxel or SOC) that is offered by ^{177}Lu vipivotide tetraxetan treatment, ^{177}Lu vipivotide tetraxetan should be considered to meet the end of life criteria for this patient population.

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted December 2019, with subsequent updates conducted in April 2021 and November 2021, to identify relevant clinical evidence on the efficacy and safety data of treatment for patients with mCRPC, and to specifically identify evidence related to efficacy and safety of ^{177}Lu vipivotide tetraxetan in the patient population relevant to this submission. The searches identified 9,099 records that were considered relevant for the review, of these, 26 publications reporting on 18 unique clinical trials were included in the SLR. Full details of the SLR search strategy, methodology and results can be found in Appendix D. Of the included studies, one study, VISION, presented relevant data to inform the direct evidence for ^{177}Lu vipivotide tetraxetan + SOC versus SOC in the patient population considered in this submission.

B.2.2 *List of relevant clinical effectiveness evidence*

The clinical evidence to support the efficacy and safety of ^{177}Lu vipivotide tetraxetan in this submission derives from VISION, the pivotal trial comparing ^{177}Lu vipivotide tetraxetan + SOC against SOC only. VISION is a Phase III, international, prospective, open-label, randomised controlled trial. VISION was designed from a global perspective and as such, the study may not capture all country-specific comparators or components of SOC. However, subgroup analyses were performed to ensure generalisability of results (Section B.2.6). Data from VISION has been published in the New England Journal of Medicine by Sartor *et al.* (2021).[25] The patient populations in VISION is aligned with the population of relevance for this submission. A summary of VISION is presented below in Table 4.

A summary of the clinical evidence for the efficacy and safety of currently available treatments in UK clinical practice, namely cabazitaxel, the relevant active comparator for ^{177}Lu vipivotide tetraxetan, is presented in Section B.2.8. This includes a real-world evidence (RWE) analysis, which was undertaken to understand the mCRPC patient population within the UK healthcare system.

A further source of supportive clinical effectiveness evidence for ^{177}Lu vipivotide tetraxetan is Thera-P, a multicentre, unblinded, randomised (1:1), phase II trial that compared ^{177}Lu vipivotide tetraxetan monotherapy (n=99) to cabazitaxel (n=101) in patients with mCRPC who had progressed despite prior treatments with docetaxel and ARPI.[114] The TheraP trial was not captured by SLR criteria as it is Phase II, hence falling outside the inclusion requirement of Phase III. Despite not offering sufficiently robust head-to-head evidence between ^{177}Lu vipivotide tetraxetan and cabazitaxel to inform the economic analysis in this submission, TheraP is described in further detail in Section B.2.8.

A summary of the clinical evidence for the efficacy and safety of currently available treatments in UK clinical practice, namely cabazitaxel, the relevant active comparator for ^{177}Lu vipivotide

tetraxetan, is presented in Section B.2.8. This includes a real-world evidence (RWE) analysis, which was undertaken to understand the mCRPC patient population within the UK healthcare system.

Table 4: Clinical effectiveness evidence

Study	**VISION (NCT03511664)**		
Study design	Phase III, international, prospective, open-label RCT		
Population	Patients with mCRPC who had progressed after receipt of previous treatment both with one or more ARPIs and with either one or two taxane chemotherapy regimens		
Intervention(s)	^{177}Lu vipivotide tetraxetan + SOC		
Comparator(s)	SOC only		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	VISION was included in the economic model as it is the only Phase III RCT assessing ^{177}Lu vipivotide tetraxetan in the relevant indication, and therefore represents the primary source of clinical effectiveness data. This trial informed the marketing authorisation application and considers a population directly relevant to the decision problem addressed in this submission.		
Reported outcomes specified in the decision problem	Primary outcome measures: • **Overall survival (OS)** • **Radiographic progression-free survival (rPFS)** Key secondary outcome measures: • **Time-to-first symptomatic skeletal event (SSE)** • **Adverse events of treatment** • **Health-related quality of life**		
All other reported outcomes	Additional secondary outcome measures reported in this submission: • Overall response rate (ORR) • Disease control rate (DCR) • Duration of response (DOR)		

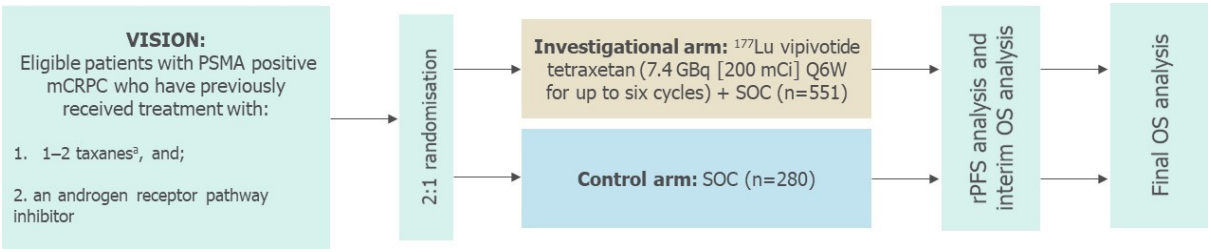
Outcomes in **bold** indicate those used in the economic model.
Abbreviations: ^{177}Lu: lutetium-177; ARPI: androgen receptor pathway inhibitor; DCR: disease control rate; DOR: duration of response; mCRPC: metastatic castration-resistant controlled trial; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PSMA: prostate-specific membrane antigen; RCT: randomised controlled trial; rPFS: radiographic progression-free survival; SOC: standard of care; SSE: symptomatic skeletal event.
Source: Sartor *et al.* (2021).[25]

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

B.2.3.1 Trial design

An overview of the study design of VISION is presented in Figure 3.

Figure 3: Overview of the study design for VISION



[a]Patients who had received only 1 prior taxane treatment were eligible only if they were unwilling to receive a further taxane treatment or their physician deemed the patient medically unsuitable to receive a second regimen. VISION OS data were mature by the time of the first rPFS data analysis.
Abbreviations: ^{177}Lu: lutetium-177; ARPI: androgen receptor pathway inhibitor; mCRPC: metastatic castration-resistant controlled trial; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Sartor *et al.* (2021).[25]

Patients were initially selected based on the eligibility criteria described below (Section B.2.3.2).[25] Eligible patients were assigned in a 2:1 ratio to receive either the interventional arm (^{177}Lu vipivotide tetraxetan + SOC) or the control arm (SOC only). Randomisation was stratified by baseline lactate dehydrogenase (LDH) [≤260 U/mL or >260 U/mL], presence of liver metastases (yes or no), ECOG performance status (0–1 or 2), and inclusion of an ARPI in protocol-permitted standard care at the time of randomisation (yes or no).[25] Patients continued treatment in either arm of the trial until either disease progression based upon radiological assessment as measured by PCWG3 criteria, the investigator feels there was a lack of clinical benefit or unacceptable toxicity, a prohibited treatment is clinically required, patient is non-adherent to the trial regimen, consent to continue with treatment is withdrawn, or at the sponsor's or investigator's discretion.[25] A summary of the full trial design is presented in Table 5.

Table 5: Summary of the trial design for VISION

Overview	• Prospective, open-label, randomised, controlled, international, Phase III trial.
Eligibility criteria for participants	• Patients were initially assessed against predefined eligibility criteria, as described in Table 6 • Patients who were eligible for inclusion were assessed for PSMA-positivity with following criteria upon PET/CT scan: ○ PSMA positivity was defined as ^{68}Ga gozetotide uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system. ○ PSMA-negativity was defined as ^{68}Ga gozetotide uptake equal to or lower than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any metastatic solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of at least 1.0 cm in the short axis ○ Patients were eligible for inclusion if they had at least one PSMA-positive lesion and no PSMA-negative lesions
Randomisation	• Patients were randomly allocated on a 2:1 basis using an interactive response system. Randomisation was stratified by: ○ Baseline LDH (≤260 U/mL or >260 U/mL) ○ Presence of liver metastases (yes or no) ○ ECOG Performance Status (0–1 or 2)

	○ Inclusion of an ARPI in protocol-permitted standard care at the time of randomisation (yes or no)
Blinding	• VISION was an open-label trial. Access to patient treatment allocation was limited to those individuals whose roles required access to perform their study responsibilities. Statistical analysis was performed in a blinded manner prior to database lock, and unblinded thereafter.
Assessments	• Baseline PSMA PET–CT scans were performed 1–6 weeks before the start of treatment • Patients were re-imaged every 8 weeks for 24 weeks after starting treatment, then every 12 weeks until end of treatment, and every 3 months during the subsequent follow-up period (for patients who discontinued treatment for reasons other than imaging-based progression and consented to further assessment). This follow-up imaging was performed with either CT or MRI and technetium-99m (^{99}mTc)–labelled methylene diphosphonate bone scans • Additional assessments included: ○ ECOG performance status ○ HRQoL (EQ-5D, FACT-P, BPI-SF) ○ Physical examinations ○ Measurements of weight and vital signs ○ Blood monitoring (Testosterone, PSA, Haematology, and Biochemistry)

Abbreviations: ^{177}Lu: lutetium-177; ^{68}Ga: gallium-68; ARPI: androgen receptor pathway inhibitor; BPI-SF: Brief Pain Inventory – Short Form; CT: computerised tomography; ECOG: Eastern Cooperative Oncology Group; EQ-5D-5L: EuroQoL-5 Dimension-5 Level; FACT-P: Functional Assessment of Cancer Therapy – Prostate; ITT: intention to treat; LDH: lactate dehydrogenase; OS: overall survival; PET–CT: positron emission tomography – computerised tomography; PFS: progression-free survival; PFS-FAS: progression-free survival full analysis set; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; rPFS: radiographic progression-free survival; SOC: standard of care.
Source: Sartor *et al.* (2021).[25]

B.2.3.2 Trial methodology

A summary of the methodology of VISION is presented in Table 6.

Table 6: Summary of the VISION trial methodology

Location	International multicentre trial conducted across 88 sites in nine countries: Belgium, Canada, Denmark, France, Germany, Netherlands, Sweden, **United Kingdom**, and United States.
Trial design	Prospective, open-label, randomised, controlled, international, Phase III trial.
Eligibility criteria[a]	**Inclusion criteria** • Patients must be ≥18 years of age. • Patients must have an ECOG performance status of 0–2. • Patients must have progressive mCRPC. • Patients must have a positive ^{68}Ga gozetotide PET–CT scan, as determined by the sponsor's central reader. • Patients must have received the following prior treatment: ○ ADT ○ At least 1 ARPI ○ At least 1, but not more than 2, taxane regimens[b] • Patients must have adequate organ function:

	○ Bone marrow ○ Hepatic ○ Renal **Exclusion criteria** • Patients must not have received previous treatment with Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223 or hemi-body irradiation within 6 months prior to randomisation. • Patients must not have received previous PSMA-targeted radioligand therapy. • Patients must not be receiving concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy. • Patients must not currently have symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression. • Patients must not have any concurrent, serious (as determined by the investigator) medical conditions that in the opinion of the investigator would impair study participation or cooperation. • Patients must not be diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment.
Method of study drug administration	• Patients randomised to the ^{177}Lu vipivotide tetraxetan arm received protocol-permitted SOC plus a maximum of six cycles of ^{177}Lu vipivotide tetraxetan 7.4 GBq (200 mCi) every six weeks. At the discretion of the investigator, ^{177}Lu vipivotide tetraxetan doses could be delayed by up to 4 weeks or reduced by 20% (without further reduction or re-escalation) to manage toxicity or adverse events. • 7.4 GBq (200mCi) of ^{177}Lu vipivotide tetraxetan administered once every 6 weeks for a maximum of 6 cycles has been used, for a maximum cumulative dose of 44.4 GBq. • ^{177}Lu vipivotide tetraxetan was administered via a slow intravenous injection by a qualified healthcare/authorised healthcare professional. • Following ^{177}Lu vipivotide tetraxetan administration, a saline infusion of 500 mL was recommended. • At the investigator's discretion, for patients with high tumour burden or gout, allopurinol could be started within 7 days and up to 10 days following ^{177}Lu vipivotide tetraxetan therapy.
Permitted and disallowed concomitant medication	**Permitted concomitant medications** **SOC:** • SOC treatments were administered based upon the clinical judgement of the treating physician and were optimised for all patients regardless of randomisation arm and disease status. • SOC treatments could be modified over time to suit a patient's evolving clinical needs. • SOC options were predefined in the study protocol and included any, and all, of the following: ○ Supportive measures (pain medications, hydration, transfusions, etc). ○ Ketoconazole. ○ Androgen reducing agents (including any corticosteroid and 5-alpha reductases).

	○ ARPIs: abiraterone, enzalutamide, apalutamide or any other ARPI. ○ Radiation in any external beam or seeded form (systemic radioisotopes [e.g. radium-223], or hemi-body radiotherapy treatment were not permitted on study). ○ Bone targeted agents including zoledronic acid, denosumab, and any bisphosphonates. ○ Blood transfusion or erythropoietin stimulation agents were allowed throughout the study after randomisation. ○ Routine prophylaxis with G-CSF/GM-CSF and erythropoietin was not recommended. Nevertheless, use was permitted at the investigator's discretion. ○ Patients had to maintain castrate levels of serum/plasma testosterone either by chemical castration or by previous orchiectomy. **Disallowed concomitant medication** • Investigational agents • Cytotoxic chemotherapy • Immunotherapy • Other systemic radioisotopes (e.g. radium-223) • Hemi-body radiotherapy
Duration of study and follow-up	The data-cut for the final analyses was on 27th January 2021. The median follow-up at this time was 20.9 months.

[a]The inclusion and exclusion criteria presented here represent a summary of the full eligibility criteria, which is presented in Appendix M.
[b]If a patient had only received one taxane regimen, the patient was only eligible if they were not willing to receive a second taxane regimen or the patient's physician deemed him unsuitable to receive a second taxane regimen.
Abbreviations: ^{177}Lu: lutetium-177; ^{68}Ga: gallium-68; ARPI: androgen receptor pathway inhibitor; BPI-SF: Brief Pain Inventory – Short Form; CT: computerised tomography; DCR: disease control rate; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EQ-5D-5L: EuroQoL-5 Dimension-5 Level; FACT-P: Functional Assessment of Cancer Therapy – Prostate; GBq: gigabecquerel; G-CSF: granulocyte colony stimulating-factor; GM-CSF: granulocyte macrophage colony-stimulating factor; HRQoL: health-related quality of life; ITT: intention to treat; LDH: lactate dehydrogenase; mCi: millicurie; MRI: magnetic resonance imaging; ORR: overall response rate; OS: overall survival; PET–CT: positron emission tomography – computerised tomography; PFS: progression-free survival; PFS-FAS: progression-free survival full analysis set; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; rPFS: radiographic progression-free survival; SOC: standard of care; SSE: symptomatic skeletal event.
Source: Sartor *et al.* (2021).[25]

Definitions for efficacy outcome measures used in VISION are presented in Table 7.

Table 7: Definitions for outcome measures used in VISION

Outcome measure	Definition
Primary outcomes	
OS	OS was defined as the time from randomisation to the date of death from any cause.
rPFS	rPFS was defined as the time from the date of randomisation to the date of radiographic disease progression (as outlined in PCWG3 Guidelines [Scher *et al* (2016)]) or death from any cause.[115]
Key secondary outcomes	
Time-to-first SSE	Time to first SSE was defined as the time (in months) from the date of randomisation to the date of the SSE (first new symptomatic pathological bone fracture, spinal cord compression, tumour-related

	orthopaedic surgical intervention, requirement for radiation therapy to relieve bone pain) or death from any cause.
HRQoL	For HRQoL analyses, patient-reported outcomes (PROs) were assessed using the questionnaires: **EQ-5D-5L** • EQ-5D-5L is a 5-item, self-reported questionnaire comprised of 5 domains of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. Patients may indicate impairment in each domain according to five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. **FACT-P** • FACT-P is a 39-item, self-reported questionnaire intended for people with prostate cancer aged 18 years and older. It is composed of 5 subscale domains: physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate cancer subscale. The total score ranges 0–156. **BPI-SF** • BPI-SF is a 9-item, self-reported questionnaire intended to evaluate the severity of a patient's pain and the impact that pain has upon their daily functioning.
Other secondary outcomes	
ORR	ORR was defined as the proportion of patients with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 response per central review assessment.
DCR	DCR was defined as the proportion of patients with BOR of CR, PR, or Stable disease according to RECIST v1.1 response per central review assessment.
DOR	DOR was defined as the duration between the date of first documented BOR of CR or PR and the date of first documented radiographic progression or death due to any cause.

The following rules were taken into account to define the BOR: CR = at least 2 determinations of CR at least 4 weeks apart; PR = at least 2 determinations of PR or better (i.e. CR) at least 4 weeks apart (and not qualifying for CR); Stable disease = at least 1 Stable disease assessment or better (i.e. CR or PR) > 6 weeks after first dose of randomised treatment (and not qualifying for CR or PR); PD = PD at first evaluable scan after first dose of randomised treatment (and not qualifying for CR, PR or Stable disease).
Abbreviations: AE: adverse event; BOR: best overall response; BPI-SF: Brief Pain Inventory – Short Form; CR: complete response; CT: computerised tomography; EQ-5D-5L: EuroQol 5-dimensions 5-level; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HRQoL: health-related quality of life; MRI: magnetic resonance imaging; ORR: overall response rate; OS: overall survival; PCWG3: Prostate Cancer Working Group 3; PD: progressed disease; PR: partial response; PRO: patient reported outcome; PSA: prostate specific antigen; RECIST: Response Evaluation Criteria in Solid Tumours; rPFS: radiographic progression-free survival; SAE: serious adverse event; SSE: symptomatic skeletal event.
Source: Sartor *et al.* (2021),[25] Scher *et al* (2016).[115]

B.2.3.3 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Trial Populations

The trial was originally designed to randomise 750 patients. However, shortly after commencement of the trial, a high, early dropout rate amongst those randomised to SOC became evident (47 of 84; 56%) with the majority of these dropouts withdrawing consent to follow-up.[25] The root cause of this was identified as disappointment among those not randomly

assigned to receive ^{177}Lu vipivotide tetraxetan. This dropout meant that rPFS data could not be collected for these patients, unlike for OS data that could become available through mCRPC registries, which consequently could result in bias in the analysis of rPFS. To address this, remedial measures were put in place on 5th March 2019 following discussions with the FDA, including:

- Regular contact with sites to discuss management of patients in the control arm
- Production of a patient information tool to guide pre-screening discussions of expectations
- Limiting reimbursement for patients to discourage long-distance travel

To address potential bias created by the initial high dropout rate disproportionately affecting the SOC arm, the primary analysis of rPFS was altered to focus on patients prospectively randomised on or after 5th March 2019. This patient cohort comprises the progression-free survival full analysis set (PFS-FAS).

Furthermore, at time of the rPFS primary analysis, a planned interim analysis of OS was performed on an ITT basis and included all randomised patients (i.e., including those randomised before 5th March 2019). This planned interim analysis became the final OS analysis, as sufficient events had accrued by this time point for the data to be mature. To achieve these analyses, the total number of patients randomised into the trial was increased from N=750 to N=814.

Table 8: Analysis sets used in the analysis of outcomes in VISION

Analysis set	Definition
Full Analysis Set (FAS)	• All randomised patients (n=831). • Patients were included in the treatment arm to which they were randomised regardless of actual treatment received. This is an intent to treat (ITT) analysis set. • This analysis set is used for the analysis of OS.
PFS Full Analysis Set (PFS-FAS)	• All patients randomised on or after 5th March 2019 (n=581). • Patients were included in the treatment arm to which they were randomised regardless of actual treatment received. • This analysis set is used for the primary analyses of rPFS and all secondary endpoints except ORR and DCR.
Response Evaluable Analysis Set	• The subset of patients in the PFS-FAS with evaluable disease by RECIST at baseline (i.e. at least one target and/or non-target lesion per independent central review radiologist assessment used as the final radiology assessment) (n=439). • Patients were included in the treatment arm to which they were randomised. • Soft tissue response as measured by RECIST was assessed in this dataset. • This analysis set was used for the primary analyses of ORR and DCR.
FAS Safety Analysis Set (FAS-SAS)	• The subset of patients in the FAS who received at least one dose of randomised treatment (n=734). • Patients were included in the treatment arm corresponding to the actual treatment received.

Abbreviations: DCR: disease control rate; FAS: full analysis set; ITT: intention to treat; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; rPFS: radiographic progression-free survival.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Summary of clinical data cut-off dates

The analyses presented in this assessment submission are based on cumulative data generated in VISION up to the data cut-off date of 27th January 2021, at which time 530 OS events were reached in the main study, triggering the primary OS analysis and the primary analysis of rPFS.[25]

Primary efficacy analysis

The primary objectives of VISION were to evaluate if ^{177}Lu vipivotide tetraxetan + SOC improved rPFS and/or OS versus SOC in patients with mCRPC who had progressed after receipt of previous treatment with one or more ARPIs and with either one or two taxane chemotherapy regimens.[25] Full details of the statistical analyses used for the primary endpoints in VISION are presented in Table 9.

Table 9: Statistical methods for the primary analysis of VISION

	OS	rPFS
Hypothesis objective	• The null hypothesis for overall survival, assumed median OS was 10 months on active treatment for a HR of 1.00. • Under the alternative hypothesis, median OS on active treatment was assumed to be 13.7 months for a HR of 0.7306.	• The null hypothesis for rPFS, assumed the median rPFS was 4 months on active treatment for a HR of 1.00. • Under the alternative hypothesis, median rPFS on active treatment was assumed to be 6 months for a HR of 0.67.

Statistical analysis	• The null hypothesis was tested at a one-sided level of significance.
	• The primary analysis was to test the null hypothesis and compare the two treatment arms using a stratified log-rank test stratifying for the randomisation stratification factors:
	  ○ Baseline LDH (≤260 U/mL or >260 U/mL).
	  ○ Presence of liver metastases (yes or no).
	  ○ ECOG Performance Status (0–1 or 2).
	  ○ Inclusion of an ARPI in protocol-permitted standard care at the time of randomisation (yes or no).
	• The primary analysis of OS was based on the FAS population.
	• The OS distribution was estimated using the Kaplan–Meier method, and Kaplan–Meier curves (including numbers at risk and confidence limits), median and associated 95% CIs are presented for each treatment arm.
	• A supportive analysis was performed in terms of a stratified Cox regression model with a single covariate for randomised treatment arm, stratifying again for the randomisation stratification factors.
	• The HR for OS was calculated, along with its 95% CI from the stratified Cox model.
	• The HR and CI from this model was used as an adjunct to the primary stratified log-rank test p-value to provide the quantification of the treatment effect on OS.
		• The null hypothesis was tested at a one-sided level of significance.
		• The primary analysis was to test the null hypothesis and compare the two treatment arms using a stratified log-rank test stratifying for the randomisation stratification factors.
		• The primary analysis of rPFS was based on the PFS-FAS population.
		• The rPFS distribution was estimated using the Kaplan–Meier method, and Kaplan–Meier curves (including number at risk and confidence limits), median and associated 99.2% confidence intervals (CIs) are presented for each treatment arm.
		• A supportive analysis was performed in terms of a stratified Cox regression model with a single covariate for randomised treatment arm, stratifying again for the randomisation stratification factors.
		• The HR for rPFS was calculated, along with its 99.2% CI, from the stratified Cox model.
		• The HR and CI from this model was used as an adjunct to the primary stratified log-rank test p-value to provide the quantification of the treatment effect on rPFS.

Sample size, power, calculation	The sample size was determined based on the alternate primary endpoints of OS and rPFS. Based on a non-linear patient accrual profile over 14 months, a total of 814 patients randomised and followed on an ITT basis for a minimum of 13 months was expected to yield 508 deaths.	
	• 508 deaths was calculated to provide at least 90% power to test the hypothesis that the HR for OS is 0.7306 or better with a 1-	• A total of approximately 557/814 patients were expected to be randomised on or after 5th March 2019, these being the

	sided alpha level of at least 0.020.	patients of the primary analysis of rPFS. • With a minimum of approximately 6 months follow-up, these patients were expected to yield 364 rPFS events which was sufficient to provide 84% power to test the hypothesis that the HR of rPFS is 0.67 or better with a 1-sided alpha level of 0.004.
Data management, patient withdrawals	• For time to event and duration endpoints (e.g. OS, rPFS), if a patient had no assessment after the first dose, censoring was at date of randomisation. • Patients who were lost to follow-up at the time of analysis were censored for rPFS at the time of their last evaluable radiographic assessment. • Patients who were lost to follow-up at the time of the OS analysis were censored at the time they were last known to be alive for the OS analysis. • Patients with missing data were excluded from the denominator of percentage calculations in any frequency tables.	

Abbreviations: FAS: full analysis set; CI: confidence interval; HR: hazard ratio; ITT: intention to treat; OS: overall survival; PFS-FAS: progression free survival full analysis set; rPFS: radiographic progression free survival;
Source: Sartor *et al.* (2021).[25]

B.2.3.4 Baseline characteristics

The baseline characteristics of the VISION study population are presented in Table 10. Patient demographic characteristics were well balanced between analysis sets and between treatment arms. Patients exhibited high levels of bone (>90%) and lymph node (~50%) metastases, with lower levels of visceral metastases: lung (~10%) and liver (~12%). Over half of all patients had received only a single line of ARPI therapy, reflecting current UK practice guidelines. Notably, the vast majority of patients had received docetaxel (~97%), which aligns with current UK guidelines where docetaxel is recommended in hormone-sensitive PC as well as mCRPC and thus patients can receive docetaxel prior to developing hormone-relapse. The baseline characteristics for patients in VISION are closely aligned to those of mCRPC patients in UK clinical practice (Section B.2.8), which provides assurance that VISION results are generalisable to UK clinical practice.

Table 10: Baseline characteristics for PFS-FAS and FAS in VISION

Characteristic	PFS-FAS (N = 581)		FAS (N = 831)	
	^{177}Lu vipivotide tetraxetan + SOC (N=385)	SOC (N=196)	^{177}Lu vipivotide tetraxetan + SOC (N=551)	SOC (N=280)
Median age (range), years	71.0 (52–94)	72.0 (51–89)	70.0 (48–94)	71.5 (40–89)
ECOG ≤1, n (%)	352 (91.4)	179 (91.3)	510 (92.6)	258 (92.1)
Site of disease, n (%)				
Lung	35 (9.1)	20 (10.2)	49 (8.9)	28 (10.0)
Liver	47 (12.2)	26 (13.3)	63 (11.4)	38 (13.6)
Lymph node	193 (50.1)	99 (50.5)	274 (49.7)	141 (50.4)
Bone	351 (91.2)	179 (91.3)	504 (91.5)	256 (91.4)
Median PSA level (range), ng/ml	93.2 (0–6,988)	90.7 (0–6,600)	77.5 (0–6,988)	74.6 (0–8,995)
Median alkaline phosphatase level (range), IU/litre	108.0 (26–2,524)	96.0 (34–1,355)	105.0 (17–2,524)	94.5 (28–1,355)
Median LDH (range), IU/litre	230.5 (119–5,387)	232.0 (105 – 2,693)	221.0 (88 – 5,387)	224.0 (105 – 2,693)
Median time since diagnosis (range), years	7.3 (0.9–28.9)	7.0 (0.7–26.2)	7.4 (0.9–28.9)	7.4 (0.7–26.2)
Previous prostatectomy, n (%)	159 (41.3)	82 (41.8)	240 (43.6)	130 (46.4)
Previous ARPI, n (%)				
One regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
Two regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
More than two regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Previous taxane therapy, n (%)				
One regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)

Two regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
Docetaxel	377 (97.9)	191 (97.4)	534 (96.9)	273 (97.5)
Cabazitaxel	161 (41.8)	84 (42.9)	209 (37.9)	107 (38.2)

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.
Source: Sartor *et al.* (2021).[25]

B.2.3.5 Concomitant medications

Concomitant medications that were indicated as SOC and taken by ≥10% of patients in either treatment arm are presented in Table 11. Medications used in SOC were predominantly used for symptom control at the discretion of treating physicians, as they would be used in UK clinical practice, and are not expected to impact on OS. The exception to this is ARPIs, which are not expected to be used concurrently with ^{177}Lu vipivotide tetraxetan in UK clinical practice. This is because multiple uses of ARPI treatments at different stages of disease (sequencing) is not commissioned in the UK. However, as VISION was a global study and sequencing of ARPIs is permitted in other countries, ARPIs were included as part of SOC at the treating physician's discretion. To account for this difference in SOC a subgroup analysis was performed on the VISION data based on whether ARPIs were included as part of SOC, with results presented in Section B.2.6.

Table 11: Concomitant medications indicated as SOC that were taken by ≥10% of patients in either treatment arm (FAS SAS)

Concomitant medications[a,b], n (%)	^{177}Lu vipivotide tetraxetan + SOC N=529	SOC N=205
Alpha-adrenoreceptor antagonists	74 (14.0)	41 (20.0)
Anilides	213 (40.3)	92 (44.9)
Paracetamol	201 (38.0)	88 (42.9)
ARPIs	182 (34.4)	97 (47.3)
Enzalutamide	157 (29.7)	87 (42.4)
Abiraterone	87 (16.4)	49 (23.9)
Abiraterone acetate	47 (8.9)	23 (11.2)
Bisphosphonates	45 (8.5)	28 (13.7)
Zoledronic acid	37 (7.0)	23 (11.2)
Electrolyte solutions	66 (12.5)	12 (5.9)
Sodium chloride	60 (11.3)	9 (4.4)
Glucocorticoids	335 (63.3)	134 (65.4)
Prednisone	180 (34.0)	77 (37.6)
Dexamethasone	160 (30.2)	34 (16.6)
Prednisolone	43 (8.1)	24 (11.7)
Gonadotrophin releasing hormone analogues	468 (88.5)	172 (83.9)
Leuprorelin acetate	309 (58.4)	96 (46.8)

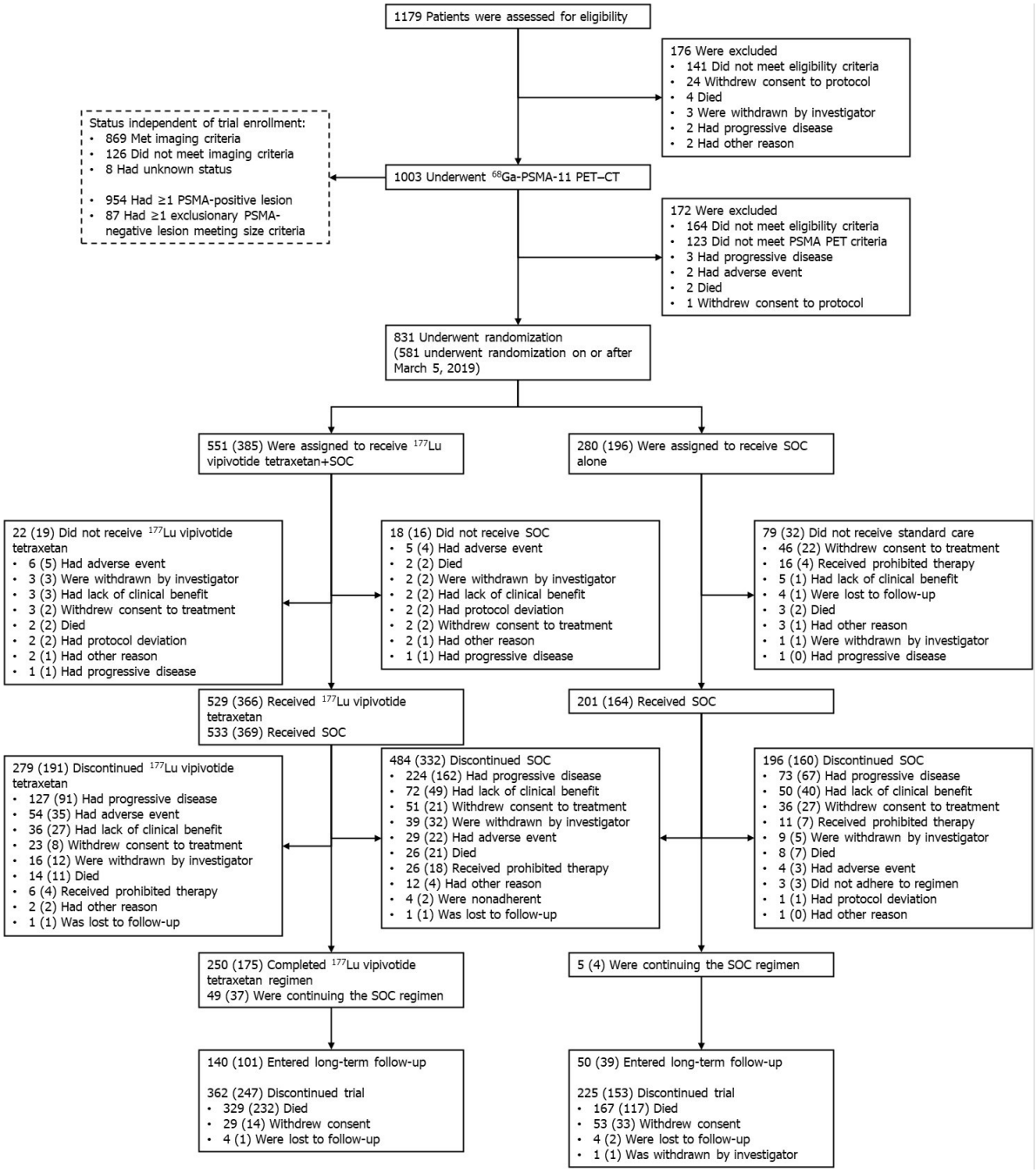
Leuprorelin	74 (14.0)	33 (16.1)
Goserelin	53 (10.0)	24 (11.7)
Iron bivalent, oral solutions	29 (5.5)	21 (10.2)
Natural opium alkaloids	177 (33.5)	75 (36.6)
Oxycodone	64 (12.1)	19 (9.3)
Oxycodone hydrochloride	62 (11.7)	24 (11.7)
Opioids in combination with non-opioid analgesics	95 (18.0)	40 (19.5)
Other analgesics and antipyretics	28 (5.3)	21 (10.2)
Other antiemetics	83 (15.7)	17 (8.3)
Other blood products	80 (15.1)	11 (5.4)
Other drugs affecting bone structure and mineralisation	184 (34.8)	80 (39.0)
Denosumab	184 (34.8)	80 (39.0)
Other opioids	58 (11.0)	20 (9.8)
Tramadol	54 (10.2)	16 (7.8)
Propionic acid derivatives	144 (27.2)	56 (27.3)
Ibuprofen	97 (18.3)	42 (20.5)
Propulsives	74 (14.0)	13 (6.3)
Serotonin (5HT3) antagonists	270 (51.0)	35 (17.1)
Ondansetron	261 (49.3)	32 (15.6)
Vitamin B12	40 (7.6)	24 (11.7)
Cyanocobalamin	34 (6.4)	21 (10.2)

[a]ATC levels are presented alphabetically; preferred terms within ATC level are sorted by descending frequency, as reported in the 'Lu vipivotide tetraxetan + SOC' column. A medication/therapy can appear in more than one ATC level. Every patient is counted a single time for each applicable specific medication category.
[b]Concomitant medications indicated as SOC are all medications indicated as SOC (per sponsor pre-specified list) starting on or after the start of randomised treatment or starting prior to and continuing after the start of randomised treatment but not more than 30 days after end of randomised treatment
Abbreviations: ^{177}Lu: Lutetium-177; 5HT3: 5-hydroxytryptamine; ARPI: androgen receptor pathway inhibitor; ATC: anatomical therapeutic chemical; FAS: full analysis set; PSMA: prostate-specific membrane antigen; SAS: safety analysis set; SOC: standard of care.
Source: Sartor *et al.* (2021),[25] Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

B.2.3.6 Participant flow

1,179 patients were initially screened for eligibility for VISION and 1,003 (85.1%) went on to receive a ^{68}Ga gozetotide PET-CT scan.[25] Of those scanned, 869 (86.6%) of patients met the eligibility criteria based on PSMA-status (one or more PSMA-positive lesion and no PSMA-negative lesions).[25] A total of 831 (82.9%) met all eligibility criteria for VISION and were included in the trial. Patients were randomised in a 2:1 ratio between 4th June 2018 and 23rd October 2019. 551 patients were assigned to the intervention arm (^{177}Lu vipivotide tetraxetan + SOC) whilst 280 were assigned to the control arm (SOC).[25] The data-cut for the final analyses of VISION was 27th January 2021.[25] A full CONSORT diagram of participant flow in VISION is presented below in Figure 4.

Figure 4: CONSORT diagram showing participant flow in VISION



The numbers in parentheses indicate the numbers of patients who underwent randomisation on or after March 5, 2019, which was the date on which trial-site education measures were implemented to reduce the incidence of withdrawal from the trial in the control group (see Document B, Section B.2.3.3 for further details).
Abbreviations: 177Lu: Lutetium-177; PET: positron emission tomography; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Sartor *et al.* (2021).[25]

B.2.4 *Quality assessment of the relevant clinical effectiveness evidence*

Full details of the SLR, including methods and results of the quality assessment can be found in Appendix D.

A quality assessment of VISION was performed using the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs (as per recommendations in the NICE user guide), and is presented in Appendix D.[117] Overall, VISION is considered to be of high quality with low risk of bias.

B.2.5 *Clinical effectiveness results of the relevant trials*

B.2.5.1 Overview of results

The following section of the submission presents results for patients receiving ^{177}Lu vipivotide tetraxetan + SOC or SOC only from the 27th January 2021 data-cut of the VISION trial. At this time, the median follow-up was 20.9 months.[25] This section details results for VISION's alternative primary endpoints (OS and rPFS) and secondary endpoints (time to first SSE, HRQoL, overall response rate [ORR], duration of response [DOR], and disease control rate [DCR]).

VISION met its alternative primary endpoints of demonstrating significant improvements in OS and in rPFS with ^{177}Lu vipivotide tetraxetan + SOC compared with SOC.[25] Treatment with ^{177}Lu vipivotide tetraxetan+ SOC was also associated with significant improvements in ORR, DOR, time to first SSE, as well as significantly delaying time to deterioration across multiple HRQoL measures compared with treatment with SOC alone.[25, 116]

B.2.5.2 Overall survival (OS)

At the 27th January 2021 data-cut, VISION met both of its alternative primary objectives. Firstly, VISION demonstrated a statistically significant improvement in OS for patients receiving ^{177}Lu vipivotide tetraxetan + SOC compared with patients receiving SOC only (p<0.001, Table 12).[25] There was an estimated 38% reduction in the risk of death in the ^{177}Lu vipivotide tetraxetan + SOC arm compared with the SOC only arm (HR=0.62; 95% CI: 0.52, 0.74) and patients receiving ^{177}Lu vipivotide tetraxetan + SOC benefited from a median extension to OS of 4 months (15.3 versus 11.3 months).[25] Highly similar results were obtained through an alternative analysis of OS using PFS-FAS, presented in Appendix M, with ^{177}Lu vipivotide tetraxetan + SOC extending OS by [redacted] compared with SOC only. The benefit to OS became rapidly apparent and was found to be significant within six months of commencing ^{177}Lu vipivotide tetraxetan (Figure 5), furthermore, this benefit was maintained throughout the follow-up duration of approximately 20 months.[25] Additionally, the number and types of post-treatment cancer-related therapies were generally well-balanced between the two randomised arms (^{177}Lu vipivotide tetraxetan + SOC, 28.1%; SOC, 34.6%) with proportions remaining similar across the most common cancer-related therapies. Therefore, receipt of post-treatment cancer-related therapies were not considered to have a substantial influence on the OS of trial participants.

In summary, considering the poor prognosis and lack of effective treatment options for patients with mCRPC following treatment with ARPI and taxane-based chemotherapy, extension of OS of greater than 4 months represents an important improvement for these patients (Section B.2.12).

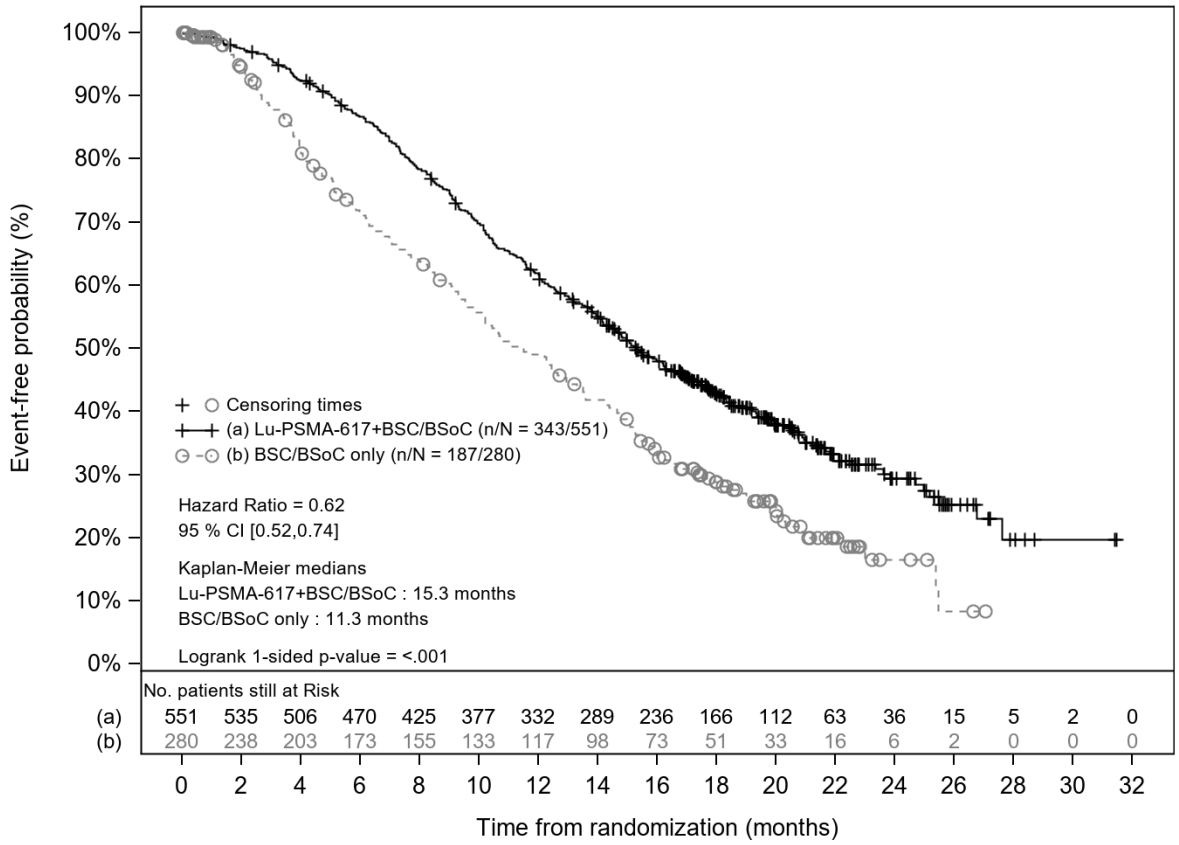
Table 12: OS in VISION (FAS)

	^{177}Lu vipivotide tetraxetan + SOC (N=551)	**SOC (N=280)**

Events	343 (62.3)	187 (66.8)
Median OS [95% CI]	15.3 [redacted]	11.3 [redacted]
OS rates (%)		
6 months (SE) [95% CI]	[redacted]	[redacted]
12 months (SE) [95% CI]	[redacted]	[redacted]
18 months (SE) [95% CI]	[redacted]	[redacted]
Log-Rank test and Cox regression model		
HR (95% CI)[a,c]	0.62 (0.52, 0.74)	
p-value[b,c]	<0.001	
Follow-up time (months)[d]		
Median [95% CI]	20.3 [19.8, 21.0]	19.8 [18.3, 20.8]
Minimum, Maximum	[redacted]	[redacted]

[a]Hazard Ratio of ^{177}Lu vipivotide tetraxetan + SOC vs. SOC from stratified Cox PH model. [b]Stratified Log-rank Test one-sided p-value. [c]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. [d]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.
Source: Sartor *et al.* (2021),[25] Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Figure 5: Kaplan–Meier plot of OS (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.
Source: Sartor *et al.* (2021).[25]

B.2.5.3 Radiographic progression-free survival (rPFS)

At the 27th January 2021 data-cut, VISION also met its other alternative primary objective of demonstrating a statistically significant improvement in PFS for patients receiving ^{177}Lu vipivotide tetraxetan + SOC compared with patients receiving SOC only (p<0.001,

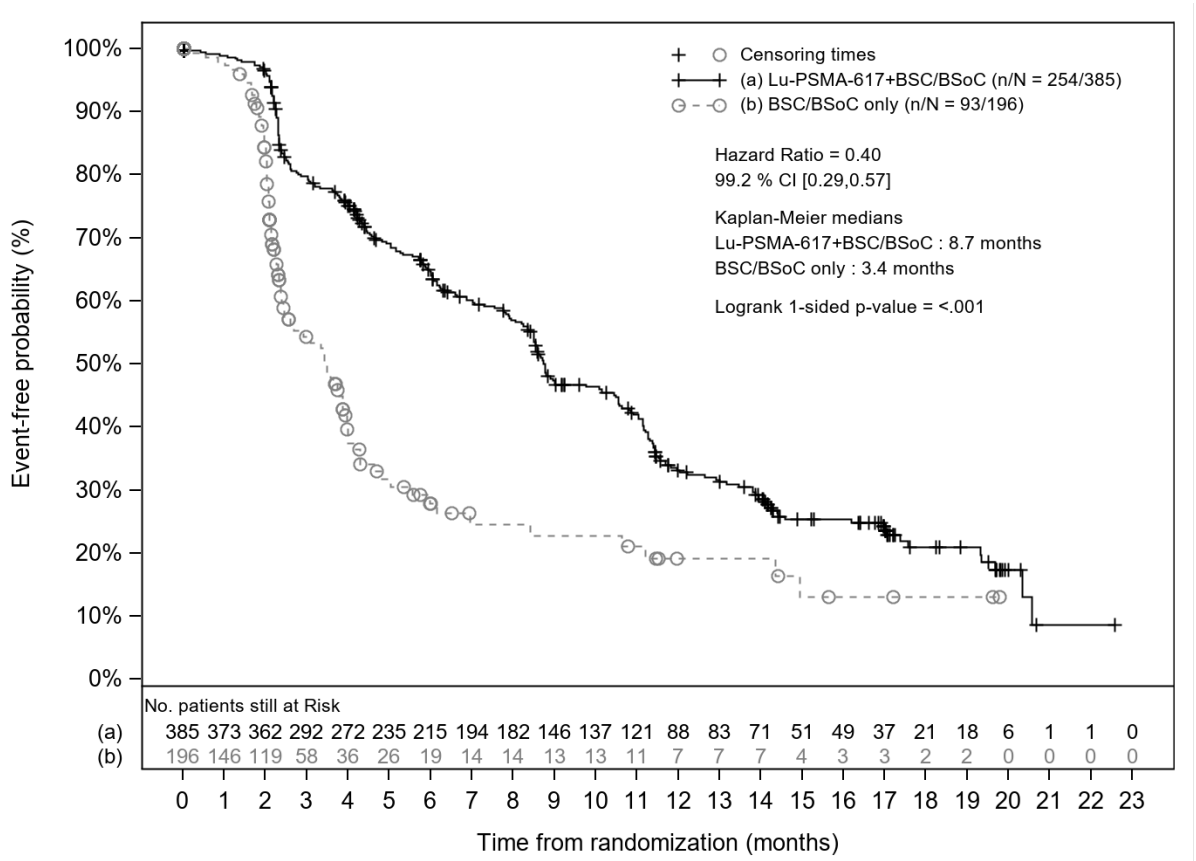
Table 13).[25] There was an estimated 60% reduction in the risk of radiographic progression in the ^{177}Lu vipivotide tetraxetan + SOC arm compared with the SOC only arm (HR=0.40; 95% CI: 0.29, 0.57). Patients receiving ^{177}Lu vipivotide tetraxetan + SOC benefited from a median extension to rPFS of 5.3 months, equivalent to an approximately 2.5-fold extension to radiographic progression-free survival.[25] As with OS, the benefit to rPFS became rapidly apparent and was found to be significant within three months of commencing ^{177}Lu vipivotide tetraxetan (Figure 6). This result is of importance as it translates into patients receiving ^{177}Lu vipivotide tetraxetan + SOC delaying the considerable reduction in HRQoL associated with disease progression.[45-47]

Table 13: rPFS in VISION per independent central review (PFS-FAS)

	^{177}Lu vipivotide tetraxetan + SOC N=385	SOC N=196
Events (progression or death)	254 (66.0)	93 (47.4)
Radiographic progressions	171 (44.4)	59 (30.1)
Deaths	83 (21.6)	34 (17.3)
Censored	131 (34.0)	103 (52.6)
Ongoing without event	90 (23.4)	24 (12.2)
Event documented after 2 or more missed tumour assessments	36 (9.4)	44 (22.4)
Adequate assessment not available[c]	5 (1.3)	35 (17.9)
Median rPFS [99.2% CI]	8.7 [redacted]	3.4 [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]	0.40 (0.29, 0.57)	
Stratified Log-rank Test one-sided p-value	<0.001	
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.
Source: Sartor *et al.* (2021),[25] Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Figure 6: Kaplan–Meier plot of rPFS 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.
Source: Sartor *et al.* (2021).[25]

B.2.5.4 Time to first symptomatic skeletal event (SSE)

At the 27th January 2021 data-cut, VISION demonstrated a statistically significantly prolonged time to first SSE for patients receiving ^{177}Lu vipivotide tetraxetan + SOC compared with patients receiving SOC only, with an estimated 50% reduction in the risk of experiencing an SSE (p<0.001, Figure 7).[25] As with the alternate primary endpoints, the effect on time to first SSE became rapidly apparent following just three months of treatment (equivalent to two doses). The median time to first SSE was extended by 4.7 months (

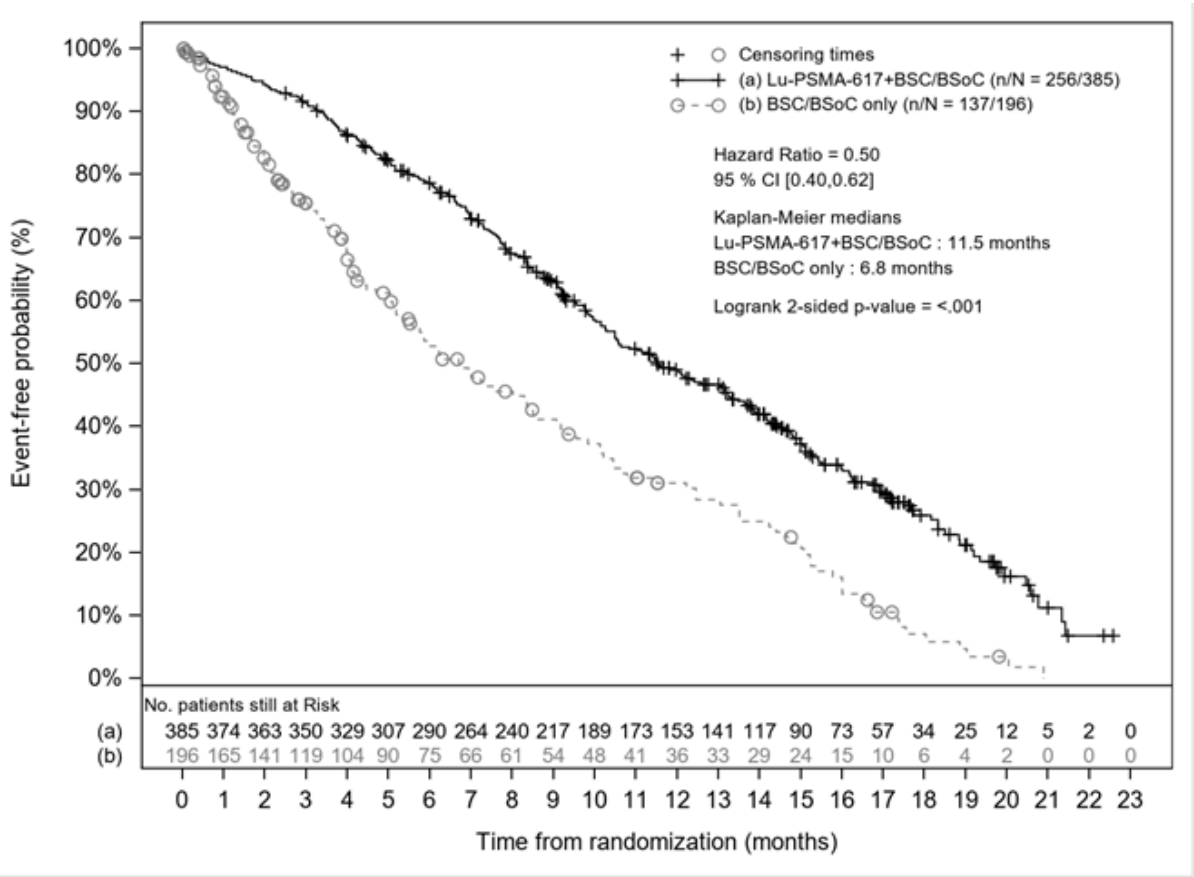
Table 14). Given the significant morbidity associated with SSEs (pain, radiation therapy, surgical intervention, spinal cord compression and associated functional disability),[49] a prolonged time to first SSE is a meaningful result for patients with mCRPC of whom the vast majority already have established bone metastasis.[25]

Table 14: Time to first SSE (PFS-FAS)

	^{177}Lu vipivotide tetraxetan + SOC N=385	SOC only N=196
Kaplan–Meier estimates (months)		
Median time to first SSE [95% CI]	11.5 [redacted]	6.8 [redacted]
25th percentile [95% CI]	[redacted]	[redacted]
75th percentile [95% CI]	[redacted]	[redacted]
Log-Rank test and Cox regression model		
Hazard Ratio (95% CI)[a,b]	0.50 (0.40, 0.62)	
Stratified Log-rank Test two-sided p-value	<0.001	
Time to first symptomatic skeletal event (SSE), n (%)		
Events (SSE or Death)	[redacted]	[redacted]
SSEs	[redacted]	[redacted]
Deaths	[redacted]	[redacted]
First SSE rates (%)		
3 months (SE) [95% CI]	[redacted]	[redacted]
6 months (SE) [95% CI]	[redacted]	[redacted]
12 months (SE) [95% CI]	[redacted]	[redacted]
Follow-up time (months)[c]		
Median [95% CI]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]

[a]Hazard Ratio of 177Lu vipivotide tetraxetan + BSC/BSoC vs. BSC/BSoC.
[b]Cox PH model is 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 NAAD 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 censoring for death or SSE.
Abbreviations: ^{177}Lu: Lutetium-177; CI: confidence interval; IRT: interactive response technology; NAAD: novel androgen axis drug; NE: not evaluable; PFS-FAS: progression-free survival full analysis set; PH: proportional hazards; PSMA: prostate-specific membrane antigen; SE: standard error; SSE: symptomatic skeletal event.
Source: Sartor *et al.* (2021),[25] Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Figure 7: Kaplan–Meier plot of time to first SSE (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: Easter Cooperative Oncology Group; IRT: interactive response technology; LDH: lactate dehydrogenase; PFS-FAS: progression-free survival full analysis set; PSMA: prostate-specific membrane antigen; SSE: symptomatic skeletal event.
Source: Sartor *et al.* (2021).[25]

B.2.5.5 Health-related quality of life (HRQoL)

VISION measured HRQoL using three validated questionnaires: BPI-SF, FACT-P, and EQ-5D-5L. The results of each of these analyses at the 27th January 2021 data-cut are discussed below. Kaplan Meier curves for time-to-deterioration in these HRQoL outcomes are presented in Appendix M.

Time to worsening in Brief Pain Inventory – Short Form (BPI-SF)

Time to worsening in BPI-SF was defined as the earliest occurrence of a ≥30% increase or ≥2 point increase relative to baseline, clinical progressive disease or death. VISION demonstrated a statistically significantly prolonged time to worsening in BPI-SF for patients receiving ^{177}Lu vipivotide tetraxetan + SOC compared with patients receiving SOC only [redacted].[25] [redacted] Patients in the intervention arm experienced an increase in median time to worsening in BPI-SF of 3.7, [redacted] months for pain intensity, pain interference, and worst pain intensity, respectively.[116]

Functional Assessment of Cancer Therapy – Prostate (FACT-P)

Time to worsening in FACT-P was defined as the earliest occurrence of a ≥10 point decrease relative to baseline, clinical progressive disease or death. VISION demonstrated a statistically significantly prolonged time to worsening in FACT-P for patients receiving ^{177}Lu vipivotide tetraxetan + SOC compared with patients receiving SOC only [redacted].[25] This benefit was demonstrated across FACT-P total score, [redacted]. Patients in the intervention arm experienced an increase in median time to worsening of 3.5, [redacted] months for FACT-P total score, PSI-8 score, and TOI score, respectively.[116]

EuroQoL-5 Dimension-5 Level (EQ-5D-5L)

Time to worsening in EQ-5D-5L was defined as the earliest occurrence of no change or any decrease relative to baseline. VISION demonstrated [redacted] for patients receiving ^{177}Lu vipivotide tetraxetan + SOC compared with patients receiving SOC only [redacted].[116] Patients in the intervention arm experienced an increase in median time to worsening in EQ-5D-5L utility scores of [redacted], equivalent to a [redacted] in time to worsening compared with SOC only.[116]

B.2.5.6 ORR, DCR and DOR

The ORR and DCR were analysed using the response evaluable analysis set, as described in Section B.2.3.3 (Table 8). At the 27th January 2021 data-cut, VISION demonstrated a statistically significant improvements in ORR and DCR with ^{177}Lu vipivotide tetraxetan + SOC compared with SOC only (Table 15).[25] ORR was [redacted] in the ^{177}Lu vipivotide tetraxetan + SOC arm vs. [redacted] SOC only arm, with an odds ratio of [redacted] (95% CI: [redacted]).

The DCR was also statistically significant in favour of the ^{177}Lu vipivotide tetraxetan + SOC arm (stratified, two-sided Wald's Chi-square test p<0.001).[25] DCR was 89.0% in the ^{177}Lu vipivotide tetraxetan + SOC arm vs. [redacted] in the SOC only arm, with and odds ratio of [redacted] (95% CI: [redacted]).

These results are significant for patients with mCRPC as they indicate that ^{177}Lu vipivotide tetraxetan + SOC significantly increases the chance of an individual remaining free from disease progression compared with SOC only.

Table 15: Analyses of ORR, DCR and DOR per independent central review (Response evaluable analysis set)

	^{177}Lu vipivotide tetraxetan + SOC N=319	SOC N=120
BOR, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Non-CR/Non-PD	[redacted]	[redacted]
PD	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
ORR (CR + PR), n (%)	[redacted]	[redacted]
Odds Ratio (95% CI)[a]	[redacted]	

Two-sided p-value[a]	[redacted]	
DCR (CR + PR + Stable disease + Non-CR/Non-PD > 6 weeks)	[redacted]	[redacted]
Odds Ratio (95% CI)[a]	[redacted]	
Two-sided p-value[a]	[redacted]	
DOR (months), n (%)		
n	[redacted]	[redacted]
Events (Progression or Death)	[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[b]	[redacted]	[redacted]
Median DOR (95% CI)	[redacted]	[redacted]

[a]Odds Ratio of ^{177}Lu vipivotide tetraxetan + SOC vs. SOC based on logistic regression model stratifying for the randomisation stratification factors, 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 an ARPI in SOC at time of randomisation (yes vs no). IRT data for stratification are used. P-value based on Wald's Chi-Square test. [b]Patient censored without adequate post-baseline evaluations or adequate baseline assessment per RECIST 1.1.
Abbreviations: ^{177}Lu: Lutetium-177; BOR: best overall response; CI: confidence interval; CR: complete response; DCR: disease control rate; DOR: duration of response in responding patients (months); EDOR: expected duration of response (months) (=mean DOR multiplied by ORR); IRT: interactive response technology; ORR: overall response rate; PR: partial response; PSMA: prostate-specific membrane antigen; SE: standard error.
Source: Sartor *et al.* (2021).[25]

B.2.6 *Subgroup analysis*

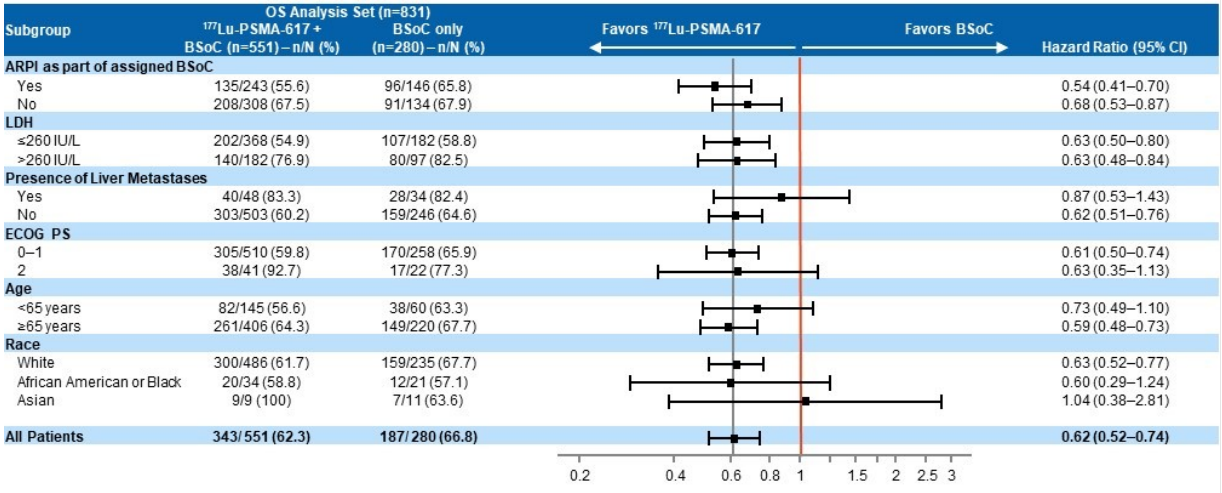
Pre-specified subgroup analyses were conducted for OS and rPFS, the primary outcomes accessed in VISION, to assess the efficacy of ^{177}Lu vipivotide tetraxetan + SOC in key patient sub-populations.[25] These pre-specified subgroups are listed in Table 6 and include: ARPI as part of assigned SOC at the start of the study, presence of liver metastasis at baseline, baseline LDH level, baseline ECOG score, age, and race. It should be noted that across these categories a number of subgroups had low sample sizes (Asian, African American or Black; ECOG score of 2; presence of liver metastases; and patients aged below 65 years), leading to wide confidence intervals. Results should be interpreted with caution for these subgroups. However, overall, the results of subgroup analyses were consistent with, and supportive of, the results from the primary analysis of OS and rPFS.[25]

Post-hoc analysis of VISION results demonstrated that patients who had received one line of taxane chemotherapy prior to entry into VISION had [redacted] advantage compared with patients who had received two prior lines of taxane chemotherapy (Appendix M). This further supports the generalisability of VISION's results to UK clinical practice in which docetaxel re-treatment is highly uncommon and patients would only be expected to receive a single line of taxane-based chemotherapy prior to cabazitaxel.[118]

Subgroup analyses of OS per independent central review

For all subgroups, with the exception of Asian patients which had a very low patient numbers and thus had extremely wide confidence intervals, the analyses showed a favourable trend for the ^{177}Lu vipivotide tetraxetan + SOC arm vs. the SOC only arm with HRs centred near the study's overall OS HR of 0.6.[25] Notably, OS for the greater than 65 years of age subgroup showed a marked improvement with narrow confidence intervals for ^{177}Lu vipivotide tetraxetan + SOC.[25] This subgroup is important as patients older than 65 years of age are more likely to be unsuitable for taxane treatment or may refuse treatment due to expected adverse events. Furthermore, the inclusion of ARPI as part of SOC did not significantly alter the benefit to OS, with both arms of this subgroup favouring ^{177}Lu vipivotide tetraxetan + SOC. A forest plot of HRs for the subgroup analyses on OS is presented in Figure 8.

Figure 8: Subgroup analyses of OS – Forest plot of HR with 95% CI (FAS)



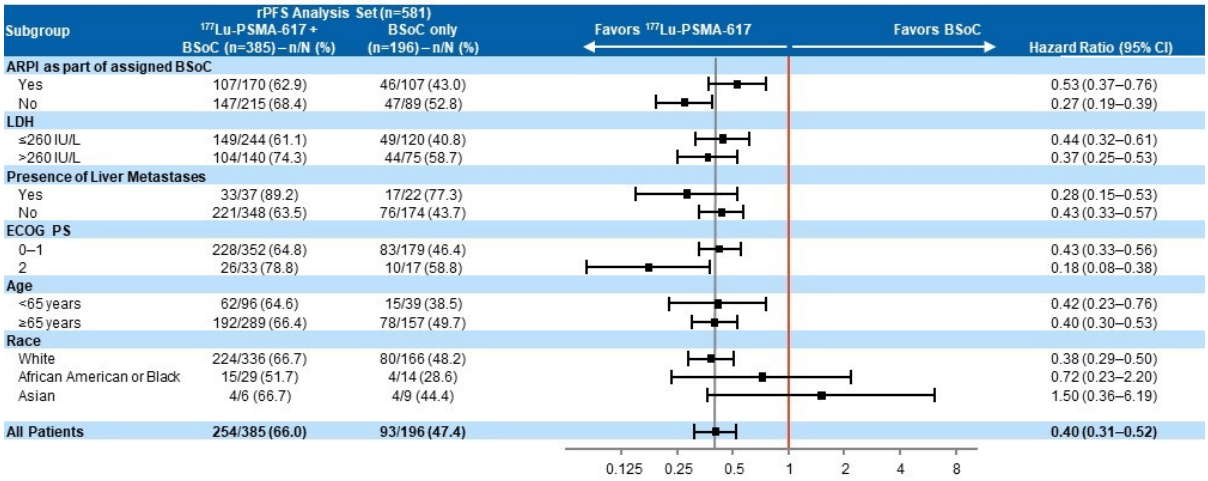
n/N: number of events/number of patients in treatment arm.
Vertical line shows HR for the overall population.
Abbreviations: ^{177}Lu: Lutetium-177; ARPI: androgen receptor pathway inhibition; CI: confidence interval; ECOG: Easter Cooperative Oncology Group; HR: hazard ratio; LDH: lactate dehydrogenase; PFS-FAS: progression-free survival full analysis set; PS: performance score; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Sartor *et al.* (2021).[25]

Subgroup analyses of rPFS per independent central review

As with OS subgroup analyses, all subgroups, with the exception of Asian patients, showed a favourable trend for the ^{177}Lu vipivotide tetraxetan + SOC arm vs. the SOC only arm with HRs centred near the study's overall rPFS HR of 0.4.[25] Consistent with results for OS, rPFS for the greater than 65 years of age subgroup showed a marked improvement with narrow confidence intervals for ^{177}Lu vipivotide tetraxetan + SOC.[25] Furthermore, the inclusion of ARPI as part of SOC did not significantly alter the benefit to rPFS, with both of these subgroups favouring ^{177}Lu vipivotide tetraxetan + SOC. A forest plot of HRs for the subgroup analyses on rPFS is presented in

Figure 9.

Figure 9: Subgroup analyses of rPFS per independent central review – forest plot of HR with 95% CI (PFS-FAS)



n/N: number of events/number of patients in treatment arm.
Vertical line shows HR for the overall population.
Abbreviations: ^{177}Lu: Lutetium-177; ARPI: androgen receptor pathway inhibition; CI: confidence interval; ECOG: Easter Cooperative Oncology Group; HR: hazard ratio; LDH: lactate dehydrogenase; PFS-FAS: progression-free survival full analysis set; PS: performance score; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Sartor *et al.* (2021).[25]

B.2.7 *Meta-analysis*

As VISION represents the only Phase III study evaluating the safety and efficacy of ^{177}Lu vipivotide tetraxetan for the treatment of adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy (see Section B.2.2), no meta-analysis was performed.

B.2.8 *Indirect and mixed treatment comparisons*

Direct evidence for the comparison of ^{177}Lu vipivotide tetraxetan to SOC is available from VISION. However, for cabazitaxel there is no direct, Phase III RCT data available. As described in Section B.1.1, based on clinical guidelines cabazitaxel is the appropriate comparator to assess cost-effectiveness. Therefore, to assess the relative efficacy of ^{177}Lu vipivotide tetraxetan and cabazitaxel, three separate sources of data have been considered: a real-world database analysis, TheraP, and a network meta-analysis (NMA).

B.2.8.1 Supportive evidence for 177Lu vipivotide tetraxetan comparators

Real-World Evidence from UK clinical practice

In order to further understand the relevant mCRPC patient population within the UK healthcare system, a retrospective RWE study of patients with mCRPC was carried out using linked healthcare datasets from Public Health England (PHE) and NHS Digital. The analysis included records from 1st January 2009 to 31st December 2018, and used combined data from major UK databases including the National Cancer Regsitry (NCR), Systemic Anticancer Therapy Dataset

(SACT), Hospital Episode Statistics (HES), Diagnostic Imaging Dataset (DID), and Radiotherapy Dataset (RTDS).

The objective of this real-world database analysis was to assess the clinical characteristics, current standard of care, clinical outcomes, and healthcare resource usage and associated costs of patients with mCRPC in England. This data was generated in order to understand the survival of patients in UK clinical practice (focusing on cabazitaxel), as well as to assess the similarity of the VISION patient population to mCRPC patients captured in the dataset.

Challenges were encountered in identifying which patients had received and progressed despite ADT within the available data, and as such, clearly defining the population as containing only mCRPC and not also including mHSPC. However, patients who have received cabazitaxel are expected to be most closely aligned with the population of relevance to this submission (post-ARPI, post-taxane) and would be expected to be composed of exclusively patients with mCRPC. Therefore, particular focus was placed upon this cohort of patients (n=[redacted]). [redacted] patients in the RWE cabazitaxel cohort had no recorded follow-up and hence were censored from further survival analysis. Further details of the RWE study methodology provided in Appendix N.

Baseline characteristics of patients identified in the RWE analysis are presented in Table 16. The baseline characteristics from this real-world database analysis are closely aligned to VISION, and as such this analysis provides highly relevant real-word data on the current outcomes for patients in the UK who would be considered eligible for treatment with ^{177}Lu vipivotide tetraxetan (Section B.2.3.4). As such, matching of VISION patients to RWE baseline characteristics is not expected to substantially impact results. As the main clinical comparator is cabazitaxel, the characteristics of this subset of patients is reported in order to demonstrate the overall similarity with the VISION population.

Table 16: Baseline characteristics for RWE analysis

Characteristic	RWE cabazitaxel cohort (n=[redacted])[a]	VISION (FAS) (n=831)
Median age (range), years	[redacted]	[redacted]
Ethnicity, White British %	[redacted]	[redacted]
ECOG ≤1, n (%)	[redacted]	[redacted]
Presence of bone metastases, n (%)	[redacted]	[redacted]

[a][redacted] patients in the RWE cabazitaxel cohort had no recorded follow-up and hence were censored from subsequent survival analysis. [b]Age in the RWE cohort was reported as age at mCRPC diagnosis, not age at cabazitaxel initiation, and thus is not directly comparable to age reported for VISION. [c]Ethnicity in VISION was specified as 'White', not 'White British,[116] [d]ECOG status as reported at the point of cabazitaxel initiation. This data were available for [redacted] patients in total, with [redacted] patients of unknown ECOG status.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; RWE: real-world evidence.
Source: Sartor et al. 2021[25]

The RWE database analysis reviewed the OS of patients with mCRPC. Of particular relevance to the comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel, data are available for the OS of patients following receipt of cabazitaxel (Table 17; Figure 10). Median OS for patients receiving cabazitaxel was [redacted], with a restricted mean OS of [redacted]. Disease progression, rPFS or PFS, is challenging to capture in database analyses, and often relies on the commencement of a new treatment to act as a proxy for progression. However, in mCRPC that has already progressed despite multiple prior therapies, this proxy becomes inconsistent,

especially when patients do not go on to receive another therapy leading to high levels of censored data. Thus, this RWE analysis was not able to capture data on rPFS, only OS.

It was noted that the OS for cabazitaxel in the RWE analysis was shorter than the median OS for the SOC arm of VISION (months vs. 11.3 months). However, patients in clinical trials receive enhanced monitoring through more frequent visits to physicians and imaging. Therefore, patients in clinical trials may have longer OS compared to what would be anticipated in real-world practice. This effect is likely greater for patients in the control arms of trials, who are expected to receive less regular oncological follow-up and imaging in real-world practice than patients receiving active oncological therapy. Therefore, it is expected that patients in real-world practice receiving SOC would experience shorter OS than that observed in VISION.

Table 17: Patients receiving cabazitaxel in the RWE analysis

Metric	RWE cabazitaxel cohort (n=)
Number of censored observations, N (%)	
Number of events, N (%)	
Kaplan Meier median OS, months	
Kaplan Meier restricted mean OS, months	

Abbreviations: OS: overall survival; RWE: real-world evidence.

Figure 10: OS for patients in the RWE analysis following receipt of cabazitaxel

patients in the total RWE cabazitaxel cohort (n=) had no recorded follow-up and hence were censored from subsequent survival analysis. This survival analysis was performed on the remaining patients.
Abbreviations: OS: overall survival; RWE: real-world evidence

TheraP

TheraP is a Phase II, multicentre, unblinded, randomised trial conducted at 11 centres in Australia which directly compared ^{177}Lu vipivotide tetraxetan to cabazitaxel in patients with mCRPC for whom cabazitaxel was considered the next appropriate standard of treatment.[110] In TheraP, 200/291 men met screening criteria for inclusion into the trial with 98 receiving ^{177}Lu vipivotide tetraxetan monotherapy, and 85 receiving cabazitaxel.[110]

TheraP was primarily designed to evaluate PSA response (defined as a reduction of PSA ≥50% from baseline). The study observed significantly higher rates of PSA response in the ^{177}Lu vipivotide tetraxetan arm compared with the cabazitaxel arm by intention to treat (66% vs. 37%, corresponding to a difference of 29% [95% CI: 16%, 42%, p<0.0001]). Secondary objectives measured in TheraP are also supportive of superior efficacy for ^{177}Lu vipivotide tetraxetan compared with cabazitaxel. For example, patients receiving ^{177}Lu vipivotide tetraxetan had significantly longer rPFS than patients receiving cabazitaxel (HR: 0.64 [95% CI 0.44, 0.83, P=0.007]).[110] The results for rPFS are consistent in terms of point estimate and confidence intervals with the results from the network meta-analysis (Section B.2.8.6), providing further certainty in the benefit of ^{177}Lu vipivotide tetraxetan in comparison to cabazitaxel.

Furthermore, Grade 3–4 AEs occurred in only 33% of men in the ^{177}Lu vipivotide tetraxetan arm compared with 53% of the cabazitaxel arm. In particular, grade 3–4 neutropenia was less common with ^{177}Lu vipivotide tetraxetan (4% vs 13%), with no episodes of febrile neutropenia (0% vs 8%). Dose reductions due to AEs were reported in fewer men receiving ^{177}Lu vipivotide tetraxetan compared with cabazitaxel (12% vs. 25%). No deaths were attributed to ^{177}Lu vipivotide tetraxetan.[110] Overall, the safety profile of ^{177}Lu vipivotide tetraxetan was notably superior to that of cabazitaxel.

Despite representing the only direct head-to-head study comparing ^{177}Lu vipivotide tetraxetan to cabazitaxel, a number of factors mean that TheraP is not suitable to inform efficacy in the economic model. Firstly, as TheraP is a Phase II trial, it did not meet eligibility criteria for inclusion in the ITC (Section B.2.8.3). Additional aspects of the trial that limit its role as a source of direct comparison include:

- The version of ^{177}Lu vipivotide tetraxetan used in the trial was ‘hospital compounded’ (i.e., not company-manufactured) and thus the molecule is potentially subject to variability from company-specific production
- Randomisation was stratified by disease burden (>20 sites vs. ≤20 sites), previous ARPI treatment, and study site. All of these differ from the stratification factors applied to randomisation in VISION
- Patients in the experimental arm of TheraP received a starting dose of 8.5 GBq of ^{177}Lu vipivotide tetraxetan, which reduced by 0.5 GBq per cycle. This differs from the recommended dose of ^{177}Lu vipivotide tetraxetan, which was used in VISION, of 7.4 GBq per cycle
- Patients in the TheraP study received ^{18}F-FDG PET/CT imaging at baseline (in addition to ^{68}Ga PET/CT) in order to exclude patients with FDG-positive disease sites with minimal PSMA expression

Therefore, TheraP does not provide sufficiently robust evidence to support a direct head-to-head comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel for the indication of relevance to

this submission. Although not suitable for direct comparison, evidence from TheraP may be considered alongside the main body of evidence in this submission as a source of supporting evidence for patients medically suitable for taxane-based chemotherapy.

B.2.8.2 Identification and selection of relevant studies from the clinical SLR

As discussed in Section B.2.1, an interventional SLR was conducted to identify all relevant clinical evidence on the efficacy and safety of ^{177}Lu vipivotide tetraxetan and any potential comparators for the treatment of adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy. The SLR was originally conducted on 28th June 2019, with subsequent updates conducted on 6th April 2021 (Update 1) and 3rd November 2021 (update 2). In the original SLR 18 records were identified, with seven, and one additional records being subsequently identified at Update 1 and Update 2 respectively. Thus, a total of 26 records were included in the Interventional SLR, representing 20 Phase III RCTs. As the SLR was conducted from a global perspective, not all identified treatments are expected to align with NICE-specific guidance on management of mCRPC. Full details of the methodology and results of the SLR are presented in Appendix D.

For UK patients with mCRPC who have already received treatment with ARPI and taxane-based chemotherapy there are currently very limited viable options for further treatment. As previously discussed in Section B.1.1, cabazitaxel (for eligible patients) represents the only treatment option besides SOC. Patients may also have already received cabazitaxel prior to ^{177}Lu vipivotide tetraxetan under current positioning.

B.2.8.3 Eligibility criteria for the NMA

In the absence of suitable head-to-head studies, a Bayesian NMA was performed to determine the relative efficacy of ^{177}Lu vipivotide tetraxetan versus currently available mCRPC treatment options. To meet this objective, all RCTs identified as part of the SLR were reviewed against pre-defined eligibility criteria for the NMA. Any study that assessed the efficacy or safety of at least one intervention considered relevant and used in UK clinical practice was included in the NMA, including: ARPIs (abiraterone or enzalutamide), radium-223, and cabazitaxel. Of the 20 Phase III RCTs that were identified in the SLR, nine studies were ultimately included in the NMA (Table 18). Details of all 20 studies identified by the SLR, and the rationale for including or excluding these studies from the NMA are presented in Appendix D.

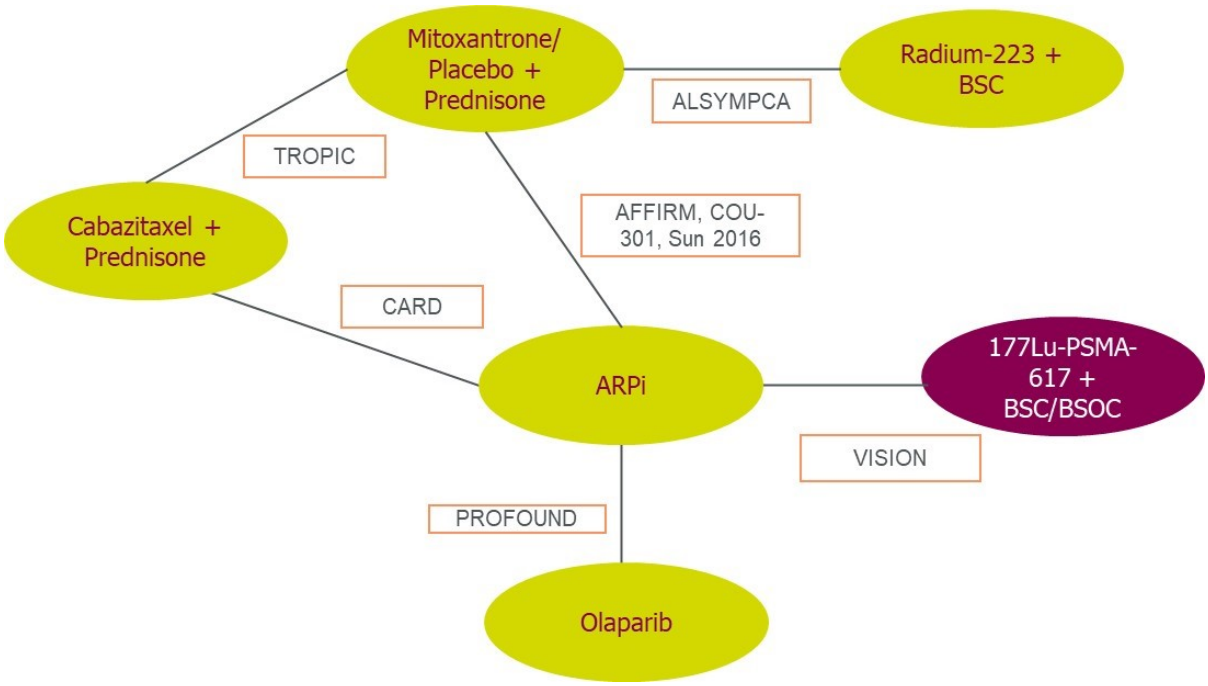
Table 18: Summary of studies included in the NMA

Trial Identifier	Study Population	Intervention (per arm)	Study N (per arm)	Study N (overall)
TROPIC NCT00417079	Patients with mCRPC that are refractory to hormone therapy and previously treated with a docetaxel-containing regimen.	Mitoxantrone + Prednisone	377	755
		Cabazitaxel + Prednisone	378	
COU-AA-301 NCT00638690	Patients with mCRPC who had previous treatment with docetaxel	Abiraterone + Prednisone/prednisolone	797	1195
		Placebo + Prednisone/prednisolone	398	
AFFIRM NCT00974311	Patients with mCRPC who had previous treatment with docetaxel	Enzalutamide	800	1199
		Placebo	399	
NR (Sun et al 2016)	Patients ≥ 18 years old with mCRPC	Abiraterone + Prednisone	143	214
		Placebo + Prednisone	71	
ALSYMPCA NCT00699751	Patients ≥ 18 years old with progressive mCRPC	Radium 223 + BSC	352	526
		Placebo + BSC	174	
PROfound NCT02987543 (short-term follow-up)	Patients with mCRPC who have progressed on prior hormonal agent	Olaparib	256	387
		Enzalutamide or abiraterone	131	
PROfound NCT02987543 (long-term follow-up)	Patients with mCRPC who have progressed on prior hormonal agent	Olaparib	256	387
		Enzalutamide or abiraterone	131	
CARD NCT02485691	Patients with progressive mCRPC who had been treated with three or more cycles of docetaxel	Cabazitaxel	129	255
		Enzalutamide or abiraterone + prednisone	126	
VISION NCT03511664	Patients with mCRPC who are pre-treated with taxane regimens	^{177}Lu vipivotide tetraxetan + SOC	551	831
		SOC	280	

Note: Progression on prior docetaxel was not a restriction in PROfound.
Abbreviations: BSC: best supportive care; mCRPC: metastatic castration-resistant prostate cancer; SOC: standard of care.

Including VISION, the NMA consisted of a total of eight RCTs that were connected through a common comparator arm of ARPI and mitoxantrone/placebo plus prednisone (Figure 11). To include VISION in the NMA, a distinct subpopulation of patients was analysed post-hoc. This subpopulation included those patients in the SOC arm who received an ARPI as a component of SOC at the time of initial randomisation. This cohort will henceforth be referred to as 'SOC-ARPI'.

Figure 11: OS network (based on HR)



Abbreviations: ARPI: androgen receptor pathway inhibitor; BSC: best supportive care; HR: hazard ratio; SOC: standard of care

B.2.8.4 Heterogeneity across studies included in the NMA

As per the best practice in evidence synthesis and NMA, studies included in the evidence network were assessed for imbalances in the distribution of treatment effect modifiers.[119] Various baseline parameters were evaluated to assess the clinical heterogeneity between the studies included in the NMA. These parameters included age, Gleason score, PSA values, prior treatment status, and ECOG performance status scores (Appendix D). Baseline characteristics were relatively similar between trials for median age and ECOG PS 0–1, with reported median PSA levels in PROfound, CARD, and VISION all being relatively similar and other trials generally reporting higher median PSAs in both intervention and placebo arms.

Furthermore, patient disease characteristics (e.g., PSMA-positivity, genetic characteristics), prior therapies, and trial duration differed substantially between trials. These differences across studies may include differences in stratification factors which could be effect modifiers. The absence of stratification at the time of randomisation could have generated some imbalances across the experimental arm and the comparator arm, which could confound the output of treatment effect in an NMA.

B.2.8.5 NMA methods

The NMA was conducted using the summary results reported in study publications and included the HRs of OS and PFS. In this analysis, a linear model with normal likelihood distribution was used for these time-to-event outcomes (log HR and standard error [SE]). The NMA was performed using the Markov Chain Monte Carlo (MCMC) software (Rücker, 2012; Rücker and Schwarzer, 2014).[120, 121] This method includes the synthesis of all included data (direct and indirect comparisons), resulting in a single set of effective sizes.

The NMA model inputs included natural log of HR (logHR) and SE of logHR. The results of the NMA were based on a sufficient number of iterations (e.g., 80,000 iterations) on at least three chains, with a burn-in of 20,000 iterations. Convergence was assessed by visual inspection of trace plots (Presented in Appendix D). The accuracy of the posterior estimates was assessed using the Monte Carlo error for each parameter (Monte Carlo error <1% of the posterior standard deviation or Monte Carlo error divided by posterior standard deviations should be ≤0.05).

For each outcome, fixed and random effects models were evaluated based on the Deviance Information Criterion (DIC) value (Table 19 and Table 20). Although random effect modelling yielded a lower DIC, given the small size of the network and low total number of studies available for inclusion, there is limited information to estimate the heterogeneity standard deviation and the prior distribution may be too heavy-tailed. The heterogeneity parameter is therefore difficult to estimate, necessitating the use of the fixed effects model in the base case. The results based on random effects models are presented in Appendix D, but should be interpreted with caution.

Table 19: DIC and residual deviance values for OS using fixed effects and random effects models

Value	Fixed Effects Model	Random Effects Model
DIC	[redacted]	[redacted]
Dbar	[redacted]	[redacted]
pD	[redacted]	[redacted]
gelman.diag	[redacted]	[redacted]

Abbreviations: DIC: Deviance information criteria; Dbar: Posterior mean of the deviance; pD: Effective number of parameters.

Table 20: DIC and residual deviance values for rPFS using fixed effects and random effects models

Value	Fixed Effects Model	Random Effects Model
DIC	[redacted]	[redacted]
Dbar	[redacted]	[redacted]
pD	[redacted]	[redacted]
gelman.diag	[redacted]	[redacted]

Abbreviations: DIC: Deviance information criteria; Dbar: Posterior mean of the deviance; pD: Effective number of parameters.

B.2.8.6 NMA results

The results of the NMA are presented in terms of 'point estimates' (median of posterior) for the comparative treatment effects, along with the 95% credible intervals (95% CrI). ^{177}Lu vipivotide tetraxetan demonstrated significant benefit in OS compared against cabazitaxel plus prednisone (Figure 12). Similarly, ^{177}Lu vipivotide tetraxetan showed significantly greater rPFS benefits compared against cabazitaxel plus prednisone (Figure 13).

The NMA results show a higher survival benefit as assessed by OS and rPFS with ^{177}Lu vipivotide tetraxetan + SOC compared with olaparib. However, statistical significance was not reached. PROfound, the trail investigating olaparib, enrolled patients with mCRPC who had progressed on prior ARPI and had variants in 1 of 15 homologous recombination repair genes. VISION included patients irrespective of any gene alterations. Progression on prior docetaxel was not a restriction in PROfound, as this study enrolled ~34% docetaxel-naïve patients in the experimental arm. VISION included patients with progressive PSMA-positive mCRPC. The PROfound study did not report PSMA positivity as the inclusion criteria and likely included patients irrespective of PSMA positivity. Median PSA level in the experimental group was lower in PROfound when compared to VISION (PROfound: 68 ng/mL [range, 24–294 ng/mL]; VISION: 77.5 [range, 0–6,988]). These differences across the studies could confound the output of an NMA and thus results are uncertain. Furthermore, Olaparib is only indicated in a minority subgroup of mCRPC patients and is not recommended by NICE at the time of this submission.

Figure 12: Base-case NMA results – OS (fixed-effects model)

Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; HR: hazard ratio; SoC: standard of care (protocol permitted)

Figure 13: Base-case NMA results – rPFS (fixed-effects model)

Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; HR: hazard ratio; SoC: standard of care (protocol permitted)

B.2.8.7 Limitations of the NMA

There are several important limitations to keep in mind when interpreting the results of the NMA:

- The key limitation of this NMA was inter-trial heterogeneity between ^{177}Lu vipivotide tetraxetan and comparator populations in terms of disease severity. Patients included in VISION had more severe disease as indicated by a higher prior treatment count and at least 40% of patients in VISION previously receiving treatment with cabazitaxel. Due to limited available data, adjusting for these differences was not possible using meta-regression techniques.

- There were differences across the included studies in terms of trial design and patient characteristics. In these trials, the assessment of reference arms may help eliminate potential unidentified confounders as the differences in reference can be adjusted using a baseline risk regression. However, limited studies and minimal statistical heterogeneity across the reference arms preclude any adjustment using baseline risk

- The small sample size and data immaturity of comparator trials limits the interpretation of the results

B.2.8.8 Conclusions of the NMA

In order to understand the relative efficacy of ^{177}Lu vipivotide tetraxetan compared to cabazitaxel, the most relevant comparator at this place in the treatment pathway, in adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy, three key sources of data are available: a real world UK database analysis, TheraP, and NMA results. Although each source of evidence individually has specific limitations, they all support the conclusion that ^{177}Lu vipivotide tetraxetan has superior efficacy compared with cabazitaxel, with TheraP indicating a favourable safety profile. The RWE analysis of patients receiving cabazitaxel, considered the most similar cohort to patients in VISION, shows a median OS of [redacted]. The median survival for patients in VISION receiving ^{177}Lu vipivotide tetraxetan was 15.3 months, emphasising the benefit that treatment with ^{177}Lu vipivotide tetraxetan brings compared with cabazitaxel.

Although rPFS data was not available from RWE, the rPFS results from TheraP demonstrate the significant superiority of ^{177}Lu vipivotide tetraxetan compared with cabazitaxel. Despite the inter-trial heterogeneity noted in the NMA, the NMA rPFS results are closely aligned with the rPFS data from TheraP. In TheraP, the HR for the comparison of ^{177}Lu vipivotide tetraxetan compared with cabazitaxel was 0.64 (95% CI: 0.44, 0.83), which is noted to be very similar to the estimated HR from the NMA for this comparison: [redacted].[110] Thus, considered together, the results of the RWE, TheraP, and NMA provide substantial evidence for the superiority of ^{177}Lu vipivotide tetraxetan over cabazitaxel for both OS and rPFS.

Given the limitations of TheraP and the NMA, the OS data from the RWE analysis were considered to be most reflective of the efficacy of cabazitaxel in the population of relevance to this submission (post-ARPI, post-taxane), as they were reported directly from patients receiving cabazitaxel in UK clinical practice, where its positioning is in line with the intended positioning of ^{177}Lu vipivotide tetraxetan. These data were therefore selected to inform OS for cabazitaxel in the economic model; given the similarity in baseline characteristics between VISION and the RWE cohort, these data were included without adjustment.

B.2.9 *Adverse reactions*

The following sections present treatment exposure and adverse event data from the FAS safety analysis set in VISION. AEs were graded according to common terminology criteria for adverse events (CTCAE) v5.0. All AE monitoring and SAE recording and reporting began at the time of patient consent and continued up to and including 30 days after the last dose of ^{177}Lu vipivotide tetraxetan or the date of deciding to end SOC, whichever was later. All AEs and abnormal test findings were recorded, regardless of suspected causal relationship to treatment. The assessment of AE causality was performed by individual investigators on a case-by-case basis.[25]

Treatment exposure

In VISION, patients randomised to the ^{177}Lu vipivotide tetraxetan + SOC arm received a minimum of 4 planned cycles of ^{177}Lu vipivotide tetraxetan 7.4 GBq (200 mCi), one cycle every six weeks, up to a maximum of six cycles. Mean duration of treatment exposure in the ^{177}Lu vipivotide tetraxetan + SOC arm was [redacted] months, [redacted] months and [redacted] months for any randomised treatment (Table 21), for ^{177}Lu vipivotide tetraxetan (Table 22), and for SOC respectively.[116] Only [redacted] of patients experienced a delay to one of their treatment cycles due to an AE.[116] On average, patients received [redacted] cycles of treatment with each cycle lasting [redacted] months, leading to a relative dose intensity of [redacted] of the planned cycles of treatment.[25]

Table 21: Duration of exposure to randomised treatment based upon trial arm (FAS safety analysis set)

	^{177}Lu vipivotide tetraxetan + SOC N=529	**SOC N=205**
Duration of exposure to randomised treatment (months), mean (SD)	[redacted]	[redacted]
Duration of exposure to ^{177}Lu vipivotide tetraxetan (months), mean (SD)	6.3 (2.4)	[redacted]

Duration of exposure to SOC (months), mean (SD)	[redacted]	[redacted]

This table presents mean duration of exposure to all treatment included in the allocated treatment arm, not just exposure to ^{177}Lu vipivotide tetraxetan in the intervention arm.
Abbreviations: ^{177}Lu: Lutetium-177; FAS: full analysis set; Max: maximum; Min: minimum; NA: not applicable; PSMA: prostate-specific membrane antigen; SD: standard deviation; SOC: standard of care.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Table 22: Duration of exposure to ^{177}Lu vipivotide tetraxetan and summary of cycles (FAS safety analysis set)

	^{177}Lu vipivotide tetraxetan + SOC N=529
Duration of exposure (months), mean (SD)	6.3 (2.4)
Number of cycles started by patient, mean (SD)	[redacted]
Average duration of treatment cycles (months), mean (SD)	1.4 (0.1)
Patients with at least one cycle delayed, n (%)	93 (17.6)
Delayed due to scheduling purposes	[redacted]
Delayed due to AE	[redacted]
Relative dose intensity (%), mean (SD)	[redacted]

A patient may be counted in more than one row for reason for delay of cycle.
Abbreviations: ^{177}Lu: Lutetium-177; FAS: full analysis set; Max: maximum Min: minimum; PSMA: prostate-specific membrane antigen; SD: standard deviation; SOC: standard of care.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Overview of adverse events (AEs)

In VISION, most patients experienced an AE, regardless of treatment arm (Table 23). For all categories except AEs leading to reduction of dose of SOC, AEs were more frequent in the ^{177}Lu vipivotide tetraxetan + SOC arm.[25] Post-hoc exposure-adjusted safety analyses showed that the higher incidence of AEs in the ^{177}Lu vipivotide tetraxetan + SOC arm was in part related to the longer exposure in this arm,[122] as emphasised by the observation that patients in the ^{177}Lu vipivotide tetraxetan + SOC arm experienced higher rates of AEs secondary to their primary SOC than those patients in the SOC only arm (Table 24).[25] Furthermore, the imbalance of drug-related AEs should be interpreted with caution as the study was open label. Moreover, patients were already receiving SOC before randomisation and as such, SOC may have not been systematically considered as a Study Drug by investigators.[25]

Table 23: Overview of AEs during randomised treatment (FAS safety analysis set)

Type of AE, n (%)	**^{177}Lu vipivotide tetraxetan + SOC N=529**	**SOC N=205**
All AE	519 (98.1)	170 (82.9)
Serious AE	192 (36.3)	57 (27.8)
Grade ≥ 3 AE	[redacted]	[redacted]
Drug-related AE	451 (85.3)	59 (28.8)
Serious drug-related AE	49 (9.3)	5 (2.4)
Drug-related grade ≥ 3 AE	[redacted]	[redacted]

AE leading to reduction of ^{177}Lu vipivotide tetraxetan	30 (5.7)	0
AE leading to reduction of SOC	[redacted]	[redacted]
AE leading to interruption of ^{177}Lu vipivotide tetraxetan	85 (16.1)	2 (1.0)[a]
AE leading to interruption of SOC	[redacted]	[redacted]
AE leading to discontinuation of ^{177}Lu vipivotide tetraxetan	63 (11.9)	1 (0.5)[a]
AE leading to discontinuation of SOC	[redacted]	[redacted]
Fatal AE	19 (3.6)	6 (2.9)

Drug-related is related to any study drug (^{177}Lu vipivotide tetraxetan or SOC), as assessed by the investigator.
[a]Four patients randomised to ^{177}Lu vipivotide tetraxetan + SOC arm received only SOC and therefore contribute to the FAS safety analysis set of the SOC arm
Abbreviations: ^{177}Lu: Lutetium-177; AE: adverse event; FAS: full analysis set; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Sartor *et al.* (2021),[25] Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Table 24: AEs by primary SOC and maximum grade during randomised treatment occurring it at least 5% of patients in either arm during randomised treatment (FAS safety analysis set)

System organ class	^{177}Lu vipivotide tetraxetan + SOC N=529		SOC N=205	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Patients with at least one event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ^{177}Lu: Lutetium-177; AE: adverse event; FAS: full analysis set; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Sartor *et al.* (2021),[25] Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Adverse events occurring in at least 5% of patients

AEs occurring is at least 5% of patients in either arm during randomised treatment that were suspected by the investigator to be related to study treatment are presented in Table 25.[25] Overall, treatment-related AEs were more frequent in the ^{177}Lu vipivotide tetraxetan + SOC arm compared with the SOC only arm. The grade ≥ 3 events that were reported with highest incidences in the intervention arm were anaemia (9.6%), thrombocytopenia and lymphopenia (6.8% each), all other grade ≥ 3 AEs were reported in less than 5% of patients in this arm.

Table 25: AEs occurring in at least 5% of patients in either arm during randomised treatment with suspected relationship by preferred term and maximum grade (FAS-SAS)

Preferred term	^{177}Lu vipivotide tetraxetan + SOC N=529		SOC N=205	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Patients with at least one event	451 (85.3)	150 (28.4)	59 (28.8)	8 (3.9)
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ^{177}Lu: Lutetium-177; AE: adverse event; FAS: full analysis set; PSMA: prostate-specific membrane antigen; SAS: safety analysis set; SOC: standard of care.
Source: Sartor *et al.* (2021).[25]

Serious adverse events occurring in at least 1% of patients

SAEs occurring in at least three patients in either arm are presented in Table 26. In either arm, [redacted][116]

Table 26: SAEs occurring in at least 1% of patients in either arm during randomised treatment (FAS-SAS)

Preferred term	^{177}Lu vipivotide tetraxetan + SOC N=529	SOC N=205

	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Patients with at least one event	**192 (36.3)**	**169 (31.9)**	**57 (27.8)**	**52 (25.4)**
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
Spinal cord compression	[redacted]	[redacted]	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]	[redacted]	[redacted]
Subdural haematoma	[redacted]	[redacted]	[redacted]	[redacted]
Infection	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ^{177}Lu: Lutetium-177; AE: adverse event; FAS: full analysis set; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Deaths occurring during randomised treatment

SAEs leading to fatal outcome during randomised treatment are presented in Table 27.[116] Per protocol, disease progression was not to be reported as an AE leading to fatal outcome, however this had not been fully clarified before [redacted] such SAEs were reported by the investigators ([redacted] in each arm).[116] [redacted].[116] No apparent patterns in the nature SAEs with fatal outcomes were observed.[116]

Table 27: On-treatment deaths during randomised treatment (FAS-SAS)

	^{177}Lu vipivotide tetraxetan + SOC N=529 n (%)	SOC N=205 n (%)
Deaths[a]	[redacted]	[redacted]
Primary cause of death		
Disease progression	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
Unknown	[redacted]	[redacted]

Other	[redacted]	[redacted]
Due to COVID-19	[redacted]	[redacted]
Reported in patients with primary reason for death = Adverse event	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]
Acute hepatic failure	[redacted]	[redacted]
Bone marrow failure	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Escherichia sepsis	[redacted]	[redacted]
Euthanasia	[redacted]	[redacted]
Haemorrhage intracranial	[redacted]	[redacted]
Hepatic failure	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]
Metastases to central nervous system	[redacted]	[redacted]
Multiple organ dysfunction syndrome	[redacted]	[redacted]
Pneumonia aspiration	[redacted]	[redacted]
Subdural haematoma	[redacted]	[redacted]
Arteriosclerosis	[redacted]	[redacted]
Cardio-respiratory arrest	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

[a]On-treatment deaths are deaths that occurred during randomised treatment or within 30 days of randomised treatment discontinuation.
Abbreviations: ^{177}Lu: Lutetium-177; COVID-19: coronavirus disease 2019; FAS: full analysis set; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

AEs leading to permanent discontinuation of ^{177}Lu vipivotide tetraxetan treatment

AEs leading to permanent discontinuation of ^{177}Lu vipivotide tetraxetan are presented in

Table 28. The most frequent events were related to cytopenias (ranging from 2.8% for thrombocytopenia and anaemia to 0.6% for pancytopenia). All other events were reported in less than 0.5% of the patients each.

Table 28: AEs leading to permanent discontinuation of ^{177}Lu vipivotide tetraxetan during randomised treatment (FAS-SAS)

Preferred term	^{177}Lu vipivotide tetraxetan + SOC N=529	
	All grades n (%)	Grade ≥ 3 n (%)

Patients with at least one event	63 (11.9)	37 (7.0)
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Thrombotic thrombocytopenic purpura	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Acute hepatic failure	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Ascites	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Eye swelling	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Metastases to central nervous system	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Skin ulcer	[redacted]	[redacted]
Spinal cord compression	[redacted]	[redacted]
Subdural haematoma	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

Abbreviations: ^{177}Lu: Lutetium-177; COVID-19: coronavirus disease 2019; FAS: full analysis set; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

AEs leading to interruption or dose reduction of ^{177}Lu vipivotide tetraxetan treatment

AEs leading to dose interruption or dose reduction of ^{177}Lu vipivotide tetraxetan are presented in Table 29. [116] The most frequent events that led to dose interruption or reduction of ^{177}Lu

vipivotide tetraxetan were anaemia (interruption: [redacted], reduction: [redacted]) and thrombocytopenia (interruption: [redacted] and reduction: [redacted]). All other events that led to dose interruption or reduction were reported for less than [redacted] of the patients.[116]

Table 29: AEs leading to interruption or dose reduction of ^{177}Lu vipivotide tetraxetan occurring in at least 0.5% of the patients during randomised treatment (FAS-SAS)

Preferred term	^{177}Lu vipivotide tetraxetan + SOC N=529	
	All grades n (%)	Grade ≥ 3 n (%)
Interruption		
Patients with at least one event	85 (16.1)	42 (7.9)
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
Dose reduction		
Patients with at least one event	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]

Abbreviations: ^{177}Lu: Lutetium-177; COVID-19: coronavirus disease 2019; FAS: full analysis set; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Treatment-emergent adverse events of interest

An overview of treatment-emergent adverse events of interest during randomised treatment is presented in Table 30.[25]

- Fatigue was selected due to its high likelihood of being associated with active cancer treatment. Higher rates of fatigue in the ^{177}Lu vipivotide tetraxetan + SOC arm compared to the SOC arm were noted. However, this effect may in part be accounted for by the longer duration of treatment exposure in the ^{177}Lu vipivotide tetraxetan + SOC arm. Furthermore, fatigue-related events leading to discontinuation of ^{177}Lu vipivotide tetraxetan were rare and only occurred in 2 patients (0.4%).
- Myelosuppression, considering the suppression of all blood cell lines, was selected due to its high likelihood of being associated with active cancer treatment, especially in the context of treatments involving radiation. Myelosuppression was commonly observed in the ^{177}Lu vipivotide tetraxetan arm (47.4%), with under half of these events being grade ≥3 (23.4%). As described previously, myelosuppressive events were the most common reasons for dose reduction, interruption, and discontinuation of ^{177}Lu vipivotide tetraxetan.

- Dry mouth was selected due to the known distribution of PSMA in the salivary glands. Dry mouth in the ^{177}Lu vipivotide tetraxetan + SOC arm was higher than that observed in the SOC arm, as expected, given the known distribution of PSMA in the salivary glands. However, no grade ≥3 events were observed.
- Nausea and vomiting were selected due to their high likelihood of being associated with active cancer treatment. Nausea and vomiting were reported approximately twice as often in the ^{177}Lu vipivotide tetraxetan + SOC arm (39.3% of patients) as compared to the SOC only arm (17.1%), but grade ≥3 events were infrequent in either arm. Only one patient (0.2%) was withdrawn from ^{177}Lu vipivotide tetraxetan due to this category of events.
- Renal effects were selected due to the known distribution of PSMA in the proximal tubule and known renal route of excretion of ^{177}Lu vipivotide tetraxetan. Renal effects were similar in frequency for grade ≥3 AEs between arms (3.4% vs. 2.9%). SAEs were reported more frequently in the SOC only arm (3.4%) than in the ^{177}Lu vipivotide tetraxetan + SOC arm (1.7%). None of the events in this category were grade 4 in severity or above (no events had a fatal outcome) and only a single patient (0.2%) was withdrawn from ^{177}Lu vipivotide tetraxetan due to this category of events
- Review of the standard safety topics of hepatotoxicity and QTc prolongation did not reveal concern for any relationship with ^{177}Lu vipivotide tetraxetan.

Table 30: Overview of treatment-emergent adverse events of interest during randomised treatment (FAS-SAS)

Safety topic	^{177}Lu vipivotide tetraxetan + SOC N=529		SOC N=205	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Fatigue	260 (49.1)	37 (7.0)	60 (29.3)	5 (2.4)
Myelosuppression	251 (47.4)	124 (23.4)	36 (17.6)	14 (6.8)
Dry mouth	208 (39.3)	0	2 (1.0)	0
Nausea and Vomiting	208 (39.3)	8 (1.5)	35 (17.1)	1 (0.5)
Hepatotoxicity	54 (10.2)	15 (2.8)	16 (7.8)	5 (2.4)
Renal effects	46 (8.7)	18 (3.4)	12 (5.9)	6 (2.9)
QT prolongation	9 (1.7)	7 (1.3)	1 (0.5)	1 (0.5)

Abbreviations: ^{177}Lu: Lutetium-177; COVID-19: coronavirus disease 2019; FAS: full analysis set; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Sartor *et al.* (2021).[25]

B.2.10 *Ongoing studies*

No additional studies are expected to reach completion within 12 months of the submission date that would offer additional evidence for ^{177}Lu vipivotide tetraxetan in addition to the evidence presented here.

B.2.11 *Innovation*

In contrast to early localised PC where patients can be well managed with available treatment options,[2] therapeutic options available to mCRPC patients following progression despite ARPI

and taxane-based chemotherapy are severely limited. Furthermore, those patients deemed medically unsuitable for taxanes who have also received an ARPI prior to developing mCRPC will be limited to supportive care alone. These patients experience significant unmet need, as discussed in Section B.1.3.4. Current real-world therapeutic options for the majority of patients are limited beyond palliative care with available therapies having significant toxicities limiting tolerability.[29, 30] Furthermore, patients who have progressed despite multiple prior therapies tend to be frail with significant disease, prior treatment-related comorbidities and a higher tumour burden.[85] Treatment options for patients with visceral metastases are limited even further, with radium-223 not being licensed for use in this subpopulation.[84] Furthermore, rates of AEs while receiving taxane-based chemotherapy are high, with correspondingly frequent dose reductions, interruptions, and discontinuation of therapy. Therefore, to meet this unmet need, new, tolerable, targeted therapies are required in this patient population, which have the potential to produce meaningful improvements in survival and preserve HRQoL.

^{177}Lu vipivotide tetraxetan is a novel radioligand therapy with a unique, targeted mechanism of action that distinguishes it from other available therapies, targeting an unexploited biomarker (PSMA) to overcome disease resistance and drive predictable response. The innovative potential of ^{177}Lu vipivotide tetraxetan, as demonstrated though the VISION trial, is summarised as follows:

- **^{177}Lu vipivotide tetraxetan offers a targeted approach to treating mCRPC**.[25] The PSMA receptor is highly expressed in prostate cancer cells and is tested for prior to initiation of therapy. Patients who are PSMA-positive can benefit from a treatment that localises to their disease, minimising off-target effects of potent radiotherapy (Section B.2.9). Whilst patients who are PSMA-negative can avoid undergoing an unnecessary therapy, which is unlikely to offer them any benefit, as may occur with untargeted chemotherapy. This approach offers a key advantage in patient selection over conventional therapies. Furthermore, despite patients with PSMA-positive PC having poorer outcomes with SOC, quantitative analysis of VISION demonstrated that patients with greater PSMA expression had statistically superior outcomes for both rPFS and OS when treated with ^{177}Lu vipivotide tetraxetan.[123]
    - ^{177}Lu vipivotide tetraxetan selectively targets the primary prostate tumour, as well as any PSMA-positive metastatic lesions, unlike radium-223, which acts through mimicking calcium, localising to bone metastases but not the primary tumour or visceral metastases.
- **^{177}Lu vipivotide tetraxetan is the first radioligand therapy in the treatment of prostate cancer**.[2] For this reason, ^{177}Lu vipivotide tetraxetan offers a new treatment paradigm via its novel mechanism of action and biomarker-targeted approach (Section B.1.2), drawing experience from other disease areas that have benefitted from targeted radioligand therapies. As ^{177}Lu vipivotide tetraxetan does not act through modifying a hormonal pathway or through systemic cytotoxic effects, it offers patients who have progressed despite these therapies a new mechanism to combat their disease alongside an advantageous safety profile.
    - Radioligand therapy (RLT) represents an important future pillar of oncology treatment with life-enhancing potential. Currently, RLT is only available on the NHS for a small number of patients with rare neuroendocrine cancers.[124] However there are roughly 30 RLT molecules in phase II/III trials globally to treat a variety of cancer types, meaning the therapy platform will soon be able to improve the lives of thousands more patients with different cancers. Investing in capacity to deliver RLT

treatments will generate value for the NHS through improved infrastructure, shared learnings, and logistical efficiencies for patients and clinicians.

- **^{177}Lu vipivotide tetraxetan provides a significant extension to both OS and rPFS for patients currently eligible for cabazitaxel, as well as those with no other options besides SOC**.[25] As such, ^{177}Lu vipivotide tetraxetan offers not only meaningful outcomes for patients but also offers new hope for patients, as evidenced by the high initial dropout rate in VISION for patients randomised not to receive ^{177}Lu vipivotide tetraxetan (Sections B.2.5.2 and B.2.5.3). The superiority of ^{177}Lu vipivotide tetraxetan compared with cabazitaxel is supported by the combined evidence of the RWE analysis, TheraP, and the NMA.
- **^{177}Lu vipivotide tetraxetan leads to a delayed time to SSE**.[25] Given the known significant morbidity and HRQoL burden of symptomatic bone metastases in mCRPC, delaying time to SSE represents a significant benefit for improving patients' HRQoL over their disease course (Section B.2.5.4).
- **^{177}Lu vipivotide tetraxetan improved patient HRQoL compared to SOC.**[98] The benefit to patients' HRQoL was reflected in the delayed time to score deterioration for patients receiving ^{177}Lu vipivotide tetraxetan compared with SOC, which was observed across all three HRQoL questionnaires completed by patients (BPI-SF, FACT-P, and EQ-5D-5L; Section B.2.5.5).
- **The beneficial effects of ^{177}Lu vipivotide tetraxetan become rapidly apparent after therapy initiation**.[25, 116] Across all primary and key secondary outcomes, the [redacted] (Section B.2.5).
- **^{177}Lu vipivotide tetraxetan is effective regardless of whether an ARPI is included as part of concurrent SOC.[25]** Given the evolving roles of ARPIs earlier in PC treatment pathways alongside the scope of their role being constrained to single-use anywhere in the UK PC treatment pathway, it is key that ^{177}Lu vipivotide tetraxetan's clinical benefits are not significantly altered by concurrent receipt of an ARPI, as patients may have received an ARPI earlier in their treatment and no longer be eligible for ARPI as part of SOC (Document B.2.6). Overall, components of SOC in VISION were designed to be used at treating physicians' discretion, to help manage disease-related symptoms not to extend OS, in the same manner that SOC would be expected to be used in UK clinical practice.
- **^{177}Lu vipivotide tetraxetan demonstrates good clinical efficacy in patients aged ≥65**.[25] Although oncological management should not be based upon age alone,[85] as the central risk factor for developing PC is advancing age, it is paramount that any treatments for PC, especially those for mCRPC, are effective and applicable for an elderly population where there is an increased risk of clinical frailty (Section B.2.6).[125]
- **^{177}Lu vipivotide tetraxetan addresses an unmet clinical need in mCRPC patients with liver metastases**.[25] Although the sample size of this subgroup was low, leading to wide confidence intervals in subgroup analysis, both OS and rPFS were extended in this vulnerable group of patients. As patients with visceral metastases are known to experience poorer HRQoL (as discussed in Section B.1.3.4) and have limited treatment options (they are unable to receive radium-223), the benefit ^{177}Lu vipivotide tetraxetan brings to both OS and rPFS has the potential to address a key area of unmet need for these patients (Section B.2.6).

The potential value of ^{177}Lu vipivotide tetraxetan in clinical practice has also been recognised by the MHRA, with a Promising Innovative Medicine (PIM) designation having been granted in August 2021. This recognises the i) life-threatening nature of mCPRC; ii) high unmet need where

there is no method of treatment available or existing methods have serious limitations; iii) the medicinal product is likely to offer major advantage over methods currently used in the UK and iv) the potential side effects are likely to be outweighed by the reasonable expectation of a positive risk balance.[126] AAA is awaiting a final decision on the Scientific Opinion that would allow for patients to enroll in the Early Access to Medicines Scheme until marketing authorisation.

In summary, ^{177}Lu vipivotide tetraxetan offers an innovative approach to treating patients with mCRPC who have progressed despite ARPI and taxane-based chemotherapy. Treatment with ^{177}Lu vipivotide tetraxetan offers improvements to patients' life expectancy and HRQoL that extend to key subgroups of especially frail patients. Furthermore, ^{177}Lu vipivotide tetraxetan's novel mechanism of action and biomarker-targeted approach facilitate a tolerable side effect profile. For these reasons, ^{177}Lu vipivotide tetraxetan meets the significant unmet need experienced by the patient population relevant to this submission.

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

Principal findings of the clinical evidence base

Clinical effectiveness

Patients with mCRPC suffer from significantly poorer OS than patients with non-metastatic or hormone-sensitive disease (Section B.1.3.4). Patients receiving SOC only in VISION had a median OS of 11.3 months (95% CI: 9.8, 13.5),[25] which is slightly lower than results reported for the control arm of recent clinical trials in patients with mCRPC who have progressed despite docetaxel, likely due to patients in VISION already having progressed despite receiving both docetaxel and ARPI.[24] Although new therapies have been introduced since this analysis, once patients have exhausted available options, prognosis remains poor with SOC only.[82, 83, 127] In particular, the role of ARPIs has been widely expanded to now include use earlier in the PC management pathway, including non-metastatic patients with high-risk disease as well as patients with metastatic hormone-sensitive PC.[82, 83, 127] Given that role of ARPIs are limited to single-use in a patients entire PC disease management pathway, the expanding earlier use of ARPI further compounds the lack of available treatment options once mCRPC is diagnosed, as an ARPI is highly likely to have already been exhausted. In this context, the importance of extending OS with new, innovative therapies is key to improving outcomes in patients with mCRPC. ^{177}Lu vipivotide tetraxetan represents a new line of therapy with the potential to significantly extend OS in this setting.

The burden of mCRPC on HRQoL for patients is significant and extends across multiple domains of health, affecting patients' physical, mental, and emotional well-being (Section B.1.3.4). In particular, given the high prevalence of bone metastases in mCRPC, SSEs play a key role in causing detriment to HRQoL.[25] VISION demonstrated that ^{177}Lu vipivotide tetraxetan extended time to first SSE by 4.7 months, corresponding to an increase in time free from SSEs of 69.1%.[25] Furthermore, VISION demonstrated significant extensions to time-to-worsening across three HRQoL questionnaires (BPI-SF, FACT-P, EQ-5D-5L).[116] Importantly, these questionnaires collectively cover physical, mental, and emotional well-being, reflecting the broad benefit to HRQoL patients yield from treatment with ^{177}Lu vipivotide tetraxetan. [25] In particular, patients showed significant extensions in time-to-worsening for all three metrics of pain assessed by the BPI-SF (pain intensity, pain interference, and worst pain intensity), which is critical given the substantial burden of pain, especially bone pain, that patients with mCRPC can experience.[48] In

summary, ^{177}Lu vipivotide tetraxetan extended patients' survival whilst allowing them to experience less pain and maintain an overall better HRQoL during that time.

^{177}Lu vipivotide tetraxetan also demonstrated benefit across a range of subgroups analysed in VISION. Of particular note were the extensions to OS and rPFS observed in patients aged ≥65, with an LDH elevated >260 IU/L, with liver metastases, and of ECOG performance status 2, as these characteristics represent some of the key vulnerabilities present in patients with mCRPC. The subgroup analyses in VISION, although should be interpreted with care due to some wide confidence intervals due to low sample sizes, provide encouraging initial evidence that ^{177}Lu vipivotide tetraxetan carries benefit even for some of the especially frail patients with mCRPC.

Safety

The safety profile of ^{177}Lu vipivotide tetraxetan as assessed in VISION demonstrated increased levels of adverse events compared to SOC only but rates of discontinuation were not proportionally raised (11.9%).[25] Furthermore, the key AEs that lead to discontinuation of ^{177}Lu vipivotide tetraxetan were cytopenias secondary to myelosuppression. It should be noted that CARD, the pivotal trial that investigated the efficacy of cabazitaxel in mCRPC patients having progressed despite docetaxel and ARPI, required all patients receiving cabazitaxel to receive primary prophylaxis G-CSF. Despite this, rates of any-grade leukopenia and neutropenia were 74.4% and 65.9%, respectively; rates of grade ≥3 leukopenia and neutropenia were 32.0% and 44.7% respectively.[113]. [113] In contrast, although prophylactic G-CSF was permitted in VISION, it was not encouraged. Despite this lack of required G-CSF prophylaxis, rates of any-grade leukopenia and neutropenia were 11.0% and 8.1%, respectively; rates of grade ≥3 leukopenia and neutropenia were 2.3% and 3.2% respectively.[25]

Besides AEs related to myelosuppression, all other grade ≥3 AEs were observed in <5% of patients receiving ^{177}Lu vipivotide tetraxetan alongside SOC. Furthermore, ^{177}Lu vipivotide tetraxetan did not substantially raise the proportion of AEs leading to an outcome of death (3.2% vs. 2.0%). Overall, these results reflect that although rates of AEs were high, likely contributed to by the frailty of the patient population and their prolonged exposure to treatment as compared with SOC only, the safety profile of ^{177}Lu vipivotide tetraxetan was consistent with that previously reported, with AEs for the vast majority of patients being tolerable and manageable with appropriate interventions.[25, 116]

Strengths and limitations of the clinical evidence base

The clinical evidence within this submission has been derived from an SLR of clinical trials investigating the efficacy and safety of a variety of treatment options, including ^{177}Lu vipivotide tetraxetan, in patients with mCRPC (see Section B.2.1). Evidence for ^{177}Lu vipivotide tetraxetan is provided by the VISION trial, a Phase III, randomised, controlled trial deemed to be of high quality, which was used as the basis of the submitted MHRA marketing authorisation application.

The VISION trial population is broadly consistent with the anticipated licenced indication for ^{177}Lu vipivotide tetraxetan and the population specified in the NICE final scope (see Section B.1). The trial baseline characteristics are consistent with the target patient population in the UK, and their generalisability has been validated by clinical experts.[5] The generalisability of VISION is further confirmed by alignment with the baseline characteristics observed in the RWE analysis.

One limitation of VISION is that ARPIs were included as a possible option within SOC due the fact it was a global study, with several countries allowing ARPI rechallenge. VISION was

designed in this manner to provide physicians flexibility in how they choose to manage frail, heavily pre-treated patients, in order to help extend life and palliate symptoms. In the UK, ARPI usage is limited to once in the entire treatment-pathway for PC.[2] Given the earlier roles of ARPI in treating PC,[78, 83] it is possible that patients with mCRPC in the UK may no longer have ARPI as an available option for their SOC. However, subgroup analysis of VISION demonstrated that both alternative primary endpoints, extension of OS and rPFS, were met regardless of ARPI inclusion as part of SOC. Therefore, this limitation of VISION is not expected to limit the generalisability of results to the UK patient population.

A further strength of the evidence base is that the OS data from VISION are reasonably mature. At the most recent data cut (27th January 2021), 62.3% of patients in the ^{177}Lu vipivotide tetraxetan + SOC arm, and 66.8% of patients in the SOC arm had died (Section B.2.5.2). Analysis of OS demonstrated a significant HR (0.62, p<0.001) with established 95% CIs (0.52, 0.74). Likewise, for rPFS, 44.4% of patients in the ^{177}Lu vipivotide tetraxetan + SOC arm, and 30.1% of patients in the SOC arm showed radiographic disease progression (B.2.5.3). Analysis of rPFS also demonstrated a significant HR (0.40, p<0.001) with established 95% CIs (0.29, 0.57).

A limitation of the evidence base was the lack of a sufficiently robust head-to-head comparison for ^{177}Lu vipivotide tetraxetan compared to the relevant comparator cabazitaxel in patients considered medically suitable for taxane-based chemotherapy. However, three key sources of evidence are available to support this comparison. The RWE provides UK-specific data and confirms the generalisability of VISION data to mCRPC patients in UK clinical practice through close alignment of baseline and clinical characteristics. Furthermore, TheraP offers strong supporting evidence in the form a Phase II clinical trial, which demonstrates a significant benefit to rPFS when patients receive ^{177}Lu vipivotide tetraxetan compared with cabazitaxel. Additionally, the rPFS HR reported in TheraP closely resembles that generated through the NMA, adding support to its accuracy despite noted inter-trial heterogeneity. The NMA demonstrated the significant benefit of ^{177}Lu vipivotide tetraxetan in both OS and rPFS, compared with cabazitaxel. Therefore, when considered in conjunction, the RWE, TheraP and the NMA provide strong evidence to support the superiority of ^{177}Lu vipivotide tetraxetan compared with cabazitaxel.

A final limitation of the VISION trial was its open label design, which led to the initial high dropout rate in the SOC only arm due to disappointment at not receiving ^{177}Lu vipivotide tetraxetan (Section B.2.3.3). Blinding was not possible due to the ease with which patients and site personnel would be able to ascertain if a radioactive dose was being administered. However, trial site education measures alongside creation of the PFS-FAS allowed for equitable distribution between the interventional and control arms of the trial with subsequent analysis of rPFS not being affected by bias due to the early high drop-out rate disproportionately affecting the SOC only arm.

End-of-life criteria

^{177}Lu vipivotide tetraxetan should be considered as an end-of-life treatment for adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes, given that (a) these patients have a limited expectancy, normally less than 2 years and (b) there is sufficient evidence to indicate that the ^{177}Lu vipivotide tetraxetan offers an extension to life of at least an additional 3 months, compared with current NHS treatment (Table 31).

Table 31: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The median OS for patients with mCRPC in the VISION SOC arm was 11.3 months (95% CI: [redacted]). The median OS for patients receiving cabazitaxel in UK clinical practice is [redacted] months. The VISION population is representative of the population addressed in this decision problem, in that they were pre-treated with both and ARPI and taxane-based chemotherapy. The RWE is directly representative of UK clinical practice for patients receiving cabazitaxel. The mean undiscounted life years predicted for patients receiving cabazitaxel and SOC in the economic model were [redacted] and [redacted] months, respectively.	Section B.2.5.2, Page 50 Section B.2.8.1, Page 60 Section B.3.7, Page 150
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The median OS for patients with mCRPC in the VISION ^{177}Lu vipivotide tetraxetan + SOC arm was 15.3 months (95% CI: [redacted]). Thus, ^{177}Lu vipivotide tetraxetan extended OS by 4.0 months (15.3 months vs. 11.3 months, p<0.001). The mean undiscounted life years for ^{177}Lu vipivotide tetraxetan were [redacted] months, corresponding to an extension of life versus cabazitaxel and SOC of [redacted] months and [redacted] months, respectively.	Section B.2.5.2, Page 50 Section B.3.7, Page 150

Abbreviations: ^{177}Lu: Lutetium-177; ARPI: androgen receptor pathway inhibition; mCRPC: metastatic castration-resistant prostate cancer, NHS: National Health Service, OS: overall survival; PSMA: prostate-specific membrane antigen, SOC: standard of care.
Source: Sartor *et al.* (2021).[25]

B.3 Cost effectiveness

^{177}Lu vipivotide tetraxetan (at PAS price) represents a cost-effective use of NHS resources compared to cabazitaxel, with a base case ICER below the £50,000 per QALY willingness-to-pay threshold for end-of-life treatments. Cabazitaxel represents the most relevant active comparator for ^{177}Lu vipivotide tetraxetan in clinical practice, and thus forms the focus of the cost-effectiveness analysis.

***De novo* cost-effectiveness model**

- A *de novo* cost-utility model was developed to evaluate the cost-effectiveness of ^{177}Lu vipivotide tetraxetan + SOC versus clinically relevant comparators (cabazitaxel and SOC) for the treatment of mCRPC.
- The model which has been developed is a cohort-based partitioned survival model consisting of three mutually exclusive health states: (I) progression-free; (II) progressed; and (III) dead
- For the ^{177}Lu vipivotide tetraxetan and SOC treatment arms, standard parametric distributions and spline models were used to extrapolate time-to-event data from VISION (rPFS and OS) for patients in the model.
- For the cabazitaxel treatment arm, rPFS was informed by application of the HR from the NMA to the extrapolated time-to-event data for the ^{177}Lu vipivotide tetraxetan treatment arm, and OS was informed directly by RWE for patients who received cabazitaxel in UK clinical practice (see Section B.2.8).
- Treatment-specific utility values for the 'pre-progression' and 'progressed' health states were derived from EQ-5D data from VISION for ^{177}Lu vipivotide tetraxetan and SOC. Based on feedback from clinical experts, the 'pre-progression' utility value for cabazitaxel was assumed to be equivalent to SOC, given its greater toxicity than ^{177}Lu vipivotide tetraxetan, and the utility value for the 'progressed' health state was sourced from NICE TA391.
- Resource use and costs included in the model were based on costs taken from the British National Formulary (BNF) [2021][128], the Drugs and pharmaceutical electronic market information tool (eMIT) [2021][129] and the National Schedule of NHS costs (2019-20).[130]
- Feedback from UK clinicians was sought in an advisory board setting in order to validate assumptions and inputs included in the model.

***Base case* cost-effectiveness results**

- Cabazitaxel represents the most relevant active comparator for ^{177}Lu vipivotide tetraxetan in clinical practice, forming the focus for the cost-effectiveness analysis. Given the substantial unmet need in clinical practice for patients who are not suitable for treatment with taxanes, results are also presented versus SOC.
- Compared to cabazitaxel, ^{177}Lu vipivotide tetraxetan was associated with an increased number of life years ([redacted]) and QALYs gained ([redacted]), but also higher total costs ([redacted]). In the base case analysis the ICER for ^{177}Lu vipivotide tetraxetan versus cabazitaxel was [redacted] at ^{177}Lu vipivotide tetraxetan list price and £49,949 at ^{177}Lu vipivotide tetraxetan PAS price.
- Compared to SOC, ^{177}Lu vipivotide tetraxetan was associated with an increased number of life years ([redacted]) and QALYs gained ([redacted]), but also higher total costs ([redacted]). In the base case analysis the ICER for^{177}Lu vipivotide tetraxetan versus SOC was £[redacted] at ^{177}Lu vipivotide tetraxetan list price and £125,687 at ^{177}Lu vipivotide tetraxetan PAS price.

Sensitivity analyses

- The DSA results identified a small number of key influential parameters (pre-/post progression utility value, and exposure to ^{177}Lu vipivotide tetraxetan) with the model being largely robust to uncertainty in the majority of parameters.
- Scenario analyses were conducted to address sources of uncertainty in the model (adjustment for informative censoring of OS/rPFS, health state utility values, concomitant treatment, subsequent treatment, therapeutic interventions).

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted to identify any relevant economic evaluations for the treatment of adult patients with pre-treated, progressive mCRPC. This population is broadly aligned to the anticipated licenced indication of adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes. Searches were performed on 3rd November 2021 and full details of the SLR search strategy, study selection process, results and quality assessment of included studies are reported in Appendix G.

The SLR identified 26 articles from 20 cost-effectiveness studies. Details of these studies are presented in Table 32. The SLR did not identify any economic evaluations or prior TAs which considered the specific population of interest to this submission, however, NICE TA391,[10] NICE TA316,[83] NICE TA259,[82] and the ongoing NICE TA ID1640,[11] as a whole have been considered to inform the structure of the *de novo* economic analysis presented in this submission, as well as various inputs utilised in the analysis.

Table 32: Summary list of published cost-effectiveness studies identified in the SLR

Study, Year	Summary of model	Patient population	Incremental QALYs gained	Incremental Costs	ICER (per QALY gained)
Bui 2016[131]	Budget impact analysis comparing the market with and without enzalutamide	NR	NA	**World with Enzalutamide vs. World without Enzalutamide** $53,2171	NA
Guirgis 2015[132]	Cost-effectiveness analysis for docetaxel	Chemotherapy naïve mCRPC patients	NR	NR	NR
Andronis 2017[133]	Cost-effectiveness analysis for zoledronic acid (+ prednisolone and docetaxel) versus prednisolone and docetaxel alone	NR	**Zoledronic acid (+ prednisolone and docetaxel) vs. prednisolone + docetaxel:** 0.031	**Zoledronic acid (+ prednisolone and docetaxel) vs. prednisolone + docetaxel:** £251	**Zoledronic acid (+ prednisolone and docetaxel) vs. prednisolone + docetaxel:** £8,005
Massoudi 2017[134]	Cost-effectiveness analysis for enzalutamide versus abiraterone acetate + prednisolone	NR	NR	**Enzalutamide vs. abiraterone acetate + prednisolone:** –$2,666	NR
Barqawi 2019[135]	Markov model to evaluate the cost-effectiveness of enzalutamide versus abiraterone + prednisolone or cabazitaxel + prednisolone after docetaxel failure	mCRPC patients with visceral metatheses	**Enzalutamide vs. abiraterone + prednisone:** 0.21 **Enzalutamide vs. cabazitaxel + prednisone:** 0.23	**Enzalutamide vs. abiraterone + prednisone:** –$6,220 **Enzalutamide vs. cabazitaxel + prednisone:** $23,876	**Enzalutamide vs. abiraterone + prednisone:** Dominates **Enzalutamide vs. cabazitaxel + prednisone:** $103,636
Tan 2018[136]	Two-state Markov model and three-state Markov model to evaluate the cost-effectiveness of mitoxantrone + prednisone or prednisolone versus docetaxel + prednisone or prednisolone	mCRPC	**Docetaxel + prednisone / prednisolone vs. mitoxantrone + prednisone or**	**Docetaxel + prednisone / prednisolone vs. mitoxantrone + prednisone or**	**Docetaxel + prednisone / prednisolone vs. mitoxantrone + prednisone or**

			prednisolone: 0.154–0.242	**prednisolone:** $4,624–5,349	**prednisolone:** $22,148–32,706
Flannery 2017[137]	Budget impact analysis	mCRPC patients previously treated with docetaxel	NA	Savings of between $49,546–86,136 dependant on uptake of cabazitaxel	NA
Bretoni 2019[138]	Cost-effectiveness and budget impact analysis for abiraterone acetate + prednisolone versus enzalutamide	Chemotherapy naïve mCRPC patients	NR	NR	**Abiraterone + prednisolone versus enzalutamide:** – €34,529.30
Su 2020[139]	A decision tree and partitioned survival model evaluating the cost-effectiveness of olaparib versus enzalutamide or abiraterone + prednisolone	mCRPC	**Olaparib vs SOC (scenario A):** 0.063 **Olaparib vs SOC (scenario B):** 0.068	**Olaparib vs SOC (scenario A):** $7,382 **Olaparib vs SOC (scenario B):** – $1,980	**Olaparib vs SOC (scenario A):** 116,903 **Olaparib vs SOC (scenario B):** – Dominates
Zhang 2021[140]	A Markov decision model to evaluate the cost-effectiveness of cabazitaxel versus an ARPI	mCRPC patients previously treated with docetaxel who had progression within 12 months while receiving an alternative inhibitor	**Cabazitaxel vs. ARPI:** 0.16	**Cabazitaxel vs. ARPI:** $49,487.03	**Cabazitaxel vs. ARPI:** $3309,294
Ten Ham 2021[141]	A Markov model to evaluate abiraterone acetate + therapeutic drug monitoring (TDM) with dose increase versus abiraterone acetate	mCRPC	**Abiraterone + TDM with dose increase vs. Abiraterone:** 0.149	**Abiraterone + TDM with dose increase vs. Abiraterone:** €22,145	**Abiraterone + TDM with dose increase vs. Abiraterone:** €177,821
Silva Miguel 2019[142]	Individual simulation model to evaluate the cost-utility of abiraterone versus enzalutamide	mCRPC patients that have failed ARPI treatment	**Abiraterone vs. Enzalutamide:** 0.003	**Abiraterone vs. Enzalutamide:** €12,564	NR
Kondo 2019[143]	Decision analytical model to evaluate cabazitaxel + peg-G versus cabazitaxel	NR	NR	NR	**cabazitaxel + peg-G vs.**

					cabazitaxel ¥9,276,805
Taheri 2019[144]	Decision-tree model to evaluate the cost-utility of abiraterone versus BSC	NR	**Abiraterone versus BSC:** 0.254	**Abiraterone versus BSC:** $684	**Abiraterone versus BSC:** $2,699
Li 2021[145]	Markov model to evaluate the cost-effectiveness of olaparib versus enzalutamide or abiraterone	mCRPC	**Olaparib versus enzalutamide or abiraterone:** 1.26	**Olaparib versus enzalutamide or abiraterone:** $157,732	**Olaparib versus enzalutamide or abiraterone:** $248,248
Ko 2021[146]	Partitioned survival model to evaluate the cost-effectiveness of olaparib versus enzalutamide or abiraterone	mCRPC	**Olaparib versus enzalutamide or abiraterone:** 0.259	**Olaparib versus enzalutamide or abiraterone:** 189,961,968	**Olaparib versus enzalutamide or abiraterone:** 734,903
Peters 2018[147]	A Markov model to evaluate the cost-effectiveness of radium-223 versus abiraterone acetate, cabazitaxel, and enzalutamide	mCRPC	**Radium-223 vs. abiraterone:** 0.02 **Radium-223 vs. enzalutamide: –0.06** **Radium-223 vs. cabazitaxel:** 0.01	**Radium-223 vs. abiraterone:** –€6,092 **Radium-223 vs. enzalutamide:** –€4,465 **Radium-223 vs. cabazitaxel:** –€7,390	N **Radium-223 vs. abiraterone:** Dominates **Radium-223 vs. enzalutamide:** NR **Radium-223 vs. cabazitaxel:** Dominates

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; mCRPC: metastatic castration-resistant prostate cancer; NA: not applicable; NR: not reported; QALYs: quality-adjusted life years; SOC: standard of care; TDM: therapeutic drug monitoring.

Table 33: Summary of previous TAs identified in the SLR

Study	Summary of model	Patient population	Incremental QALYs	Incremental Costs (£)	ICER (£ per QALY gained)
TA259, 2012[82]	Survival-based decision model based PFS and OS with a 10 year time horizon	mCRPC previously treated with a docetaxel-containing regimen	**Abiraterone vs. prednisolone:** Redacted **Abiraterone vs. Mitoxantrone +**	**Abiraterone vs. prednisolone:** Redacted **Abiraterone vs. mitoxantrone +**	**Abiraterone vs. prednisolone:** £52,851 **Abiraterone vs. mitoxantrone +**

			prednisolone: Redacted	**prednisolone:** Redacted	**prednisolone:** extendedly dominates
TA387, 2019[80]	Discrete event simulation model with a lifetime time horizon.	mCRPC not previously treated with chemotherapy	**Abiraterone vs. BSC:** 0.56	**Abiraterone vs. BSC:** £16,055	**Abiraterone vs. BSC:** £28,563
TA377, 2016[148]	Markov model based on PFS and OS with a 10 year time horizon	mCRPC for people in whom chemotherapy is not yet clinically indicated	**Enzalutamide vs. BSC:** Redacted	**Enzalutamide vs. BSC:** Redacted	**Enzalutamide vs. BSC:** £27,036
TA316, 2014[83]	Markov model based on PFS and OS with a 10 year time horizon	Adults with mCRPC who have had treatment with docetaxel-containing chemotherapy	**Enzalutamide vs. Abiraterone:** Redacted **Enzalutamide vs. BSC:** Redacted	**Enzalutamide vs. Abiraterone:** Redacted **Enzalutamide vs. BSC:** Redacted	**Enzalutamide vs. Abiraterone:** £14,795 **Enzalutamide vs. BSC:** £43,239
TA412, 2016[84]	Semi-Markov model based on PFS, OS , and occurrence of Skeletal related events (SREs) with a 10 year time horizon	Adults with hormone-relapsed prostate cancer with bone metastases who have not received docetaxel or for whom docetaxel is contraindicated or not suitable	**Radium-223 vs. BSC:** Redacted	**Radium-223 vs. BSC:** Redacted	**Radium-223 vs. BSC:** £25,963
TA376. 2016[9]	Semi-Markov model based on PFS, OS , and occurrence of Skeletal related events (SREs) with a 10 year time horizon	Adults with hormone-relapsed prostate cancer with bone metastases	**Radium-223 vs. BSC:** Redacted	**Radium-223 vs. BSC:** Redacted	**Radium-223 vs. BSC:** £49,600
TA391, 2016[10]	Partitioned survival model based on PFS and OS with a 10 year time horizon	People with metastatic prostate cancer that has come back after it was treated with docetaxel	**Cabazitaxel vs. mitoxantrone:** 0.237	**Cabazitaxel vs. mitoxantrone:** £10,682	**Cabazitaxel vs. mitoxantrone:** £45,159
TA101, 2006[127]	Cost effectiveness analysis	Adults with mCRPC	**Docetaxel vs. mitoxantrone:** Redacted	**Docetaxel vs. mitoxantrone:** Redacted	**Docetaxel vs. mitoxantrone:** £32,700

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; mCRPC: metastatic castration-resistant prostate cancer; NICE: National Institute of Care and Clinical Excellence; OS: overall survival; PFS: progression free survival; QALYs: quality-adjusted life years; SRE: skeletal related event; TA: technology appraisal.

B.3.2 *Economic analysis*

Of the 18 cost-effectiveness studies and eight previous NICE TAs identified within the SLR, none evaluated the cost-effectiveness of ^{177}Lu vipivotide tetraxetan compared with cabazitaxel or SOC. For this reason, a *de novo* cost-effectiveness analysis has been conducted to inform the economic model presented in this submission. The cost-effectiveness model employed for this economic analysis was built in Microsoft Excel® and the objective of this economic analysis was to assess the cost effectiveness of ^{177}Lu vipivotide tetraxetan compared with cabazitaxel or SOC in patients with PSMA-positive mCRPC.

In line with the NICE reference case, this analysis was conducted from the perspective of the NHS, including direct medical costs and Personal Social Services (PSS) over a lifetime time horizon.

B.3.2.1 Patient population

The patient population considered within this economic evaluation is adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes. As set out in the decision problem in Section B.1.1 above (Table 1), the population for this economic evaluation is in line with the full anticipated marketing authorisation for ^{177}Lu vipivotide tetraxetan in mCRPC. Furthermore, the population for this economic evaluation largely aligns with the VISION trial population, aside from those patients not medically suitable for taxanes, who did not meet the inclusion criteria for VISION. This sub-population is expected to represent only a small proportion of the overall patients eligible for ^{177}Lu vipivotide tetraxetan, and for equity of access it is important to include these patients within the cost-effectiveness analysis.

B.3.2.2 Model structure

As noted in Section B.3.1, no prior health economic evaluations for ^{177}Lu vipivotide tetraxetan in adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes were identified by for published economic evaluations in this indication. Therefore, a *de novo* health economic model was constructed in Microsoft Excel to evaluate the cost-effectiveness of ^{177}Lu vipivotide tetraxetan versus clinically relevant comparators.

The model which has been developed is a cohort-based partitioned survival model consisting of three mutually exclusive health states:

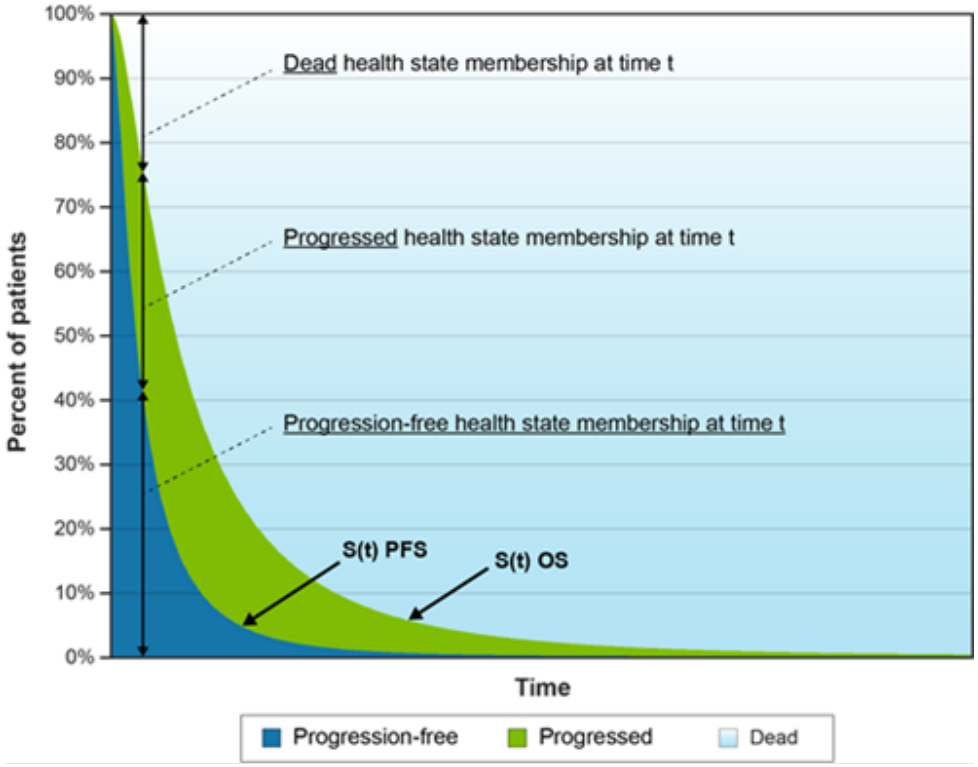
- Progression-free (PF) – Defined as the period before the patient has experienced disease progression
- Progressed disease (PD) – Defined as the period where the patient remains alive following disease progression where patients may receive treatment with subsequent anticancer therapy and supportive care
- Dead – An absorbing state into which patients transition upon their death

A graphical depiction of the partitioned survival model approach is presented in Figure 14. Patients enter into the model upon commencing treatment, and then progress through the three health states for the time horizon of the model based on the survival functions associated with each treatment. The distribution of patients in each health state is governed by VISION-derived

rPFS and OS curves. The model employed a one-week cycle length as this provided the greatest precision in the tracking of the number of patients in each health state in the early years of the model. This cycle length is relatively short compared to the model's 10-year time horizon, and as such there were no half-cycle corrections applied in the model. Within the model there are no patients remaining alive in either treatment arm at 10 years, therefore, the 10-year time-horizon utilised within the model is considered to represent a life-time horizon for this patent population.

The partitioned survival approach was selected for this analysis as it is considered the most suitable for an oncology model in which patients are expected to unilaterally progress, and no cure or spontaneous remission are considered clinically plausible with current therapies. Thus, the model structure does not allow for patients to improve their health state, which reflects the progressive nature of their condition. The partitioned survival approach also allows for modelling of OS and rPFS based on study-observed events, which facilitates the replication of within-trial data and means that the model is expected to accurately reflect disease progression and the observed survival profile of patients treated with ^{117}Lu vipivotide tetraxetan and comparator therapies. Furthermore, a partitioned survival approach is consistent with previous NICE technology appraisals (TAs) in mCRPC, including NICE TA391,[10] NICE TA316,[83] NICE TA259,[82] and the ongoing NICE TA ID1640.[11]

Figure 14: Partitioned survival model structure



The data in the figure are fictitious and used for illustrative purposes only. S(t) PFS is the survival function describing the probability that a patient remains in the progression-free health state beyond a specific time point (t) from model entry. S(t) OS is the survival function describing the probability that a patient survives in the progression-free or the progressed health states beyond a specific time point (t) from model entry. Membership in the progressed health state is determined by subtracting the progression-free state membership from the dead state membership.
Abbreviations: OS: overall survival; PFS: progression-free survival.

Features of the *de novo* analysis

Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. Cost components considered included: drug acquisition and administration costs for each treatment (^{177}Lu vipivotide tetraxetan, cabazitaxel, concomitant treatments, therapeutic interventions given as part of SOC, and subsequent active cancer-related therapies), health state costs (capturing medical resource utilisation), and cost of individual SSEs and AEs. Effectiveness measures included life years (LYs) and QALYs. The incremental cost-effectiveness ratio (ICER) of ^{177}Lu vipivotide tetraxetan versus cabazitaxel and SOC was evaluated in terms of the incremental cost per QALY gained.

The analysis was conducted from the perspective of the NHS, including direct medical costs and Personal Social Services (PSS) costs over a lifetime time horizon (10 years) for the patient cohort from the initiation of treatment. A weekly cycle length was considered in the base case, and both costs and effects were discounted at 3.5% annually.[149] The economic analysis is conducted using the most recent estimates of resource use and treatment costs available from published sources (2020/2021). Costs quoted for other cost-years or in other currencies are inflated to the model cost-year and/or converted to UK, as applicable. A summary of the features of the economic analysis is presented in Table 34. This analysis is broadly consistent with the modelling approach taken in previous appraisals for therapies used earlier in the treatment pathway.[10, 82, 83]

Table 34: Summary of the features of the economic analysis

Factor	Chosen values	Justification
Model structure	Partitioned survival model.	The partitioned survival approach was selected for this analysis as it is considered the most suitable for an oncology model in which patients are expected to unilaterally progress, and no cure or spontaneous remission are considered clinically plausible with current therapies.
Time horizon	Lifetime time horizon (10 years).	A lifetime horizon was chosen to fully capture the expected costs and health outcomes of patients over their remaining lifetime from the initiation of their treatment.
Cycle length	Weekly	Enables more accurate model predictions. The cycle length was considered short enough that a half-cycle correction was not warranted.
Discount rate	3.5%	In line with the NICE reference case.[149]
Perspective	NHS/PSS	In line with the NICE reference case.[149]
Source of utilities	Health state utility values were derived in line with the NICE reference case: pooled EQ-5D-5L scores collected in VISION were mapped to EQ-5D-3L utility index scores using the mapping function developed by the NICE DSU (Hernández Alava *et al.* [2017]), using the 'EEPRU dataset'	In line with the NICE reference case (as per the NICE manual for health technology evaluations [PMG36])[152].

	(Hernández Alava *et al.* [2020]), in line with the reference case stipulated in the NICE manual for health technology evaluations (PMG36).[150-152]	
Source of costs	• British National Formulary (BNF) [2021][128] • Drugs and pharmaceutical electronic market information tool (eMIT) [2021][129] • National Schedule of NHS Costs (2019-20)[130]	Established sources of costs within the NHS. In line with the NICE reference case and previous appraisals.
Resource use	Resource use in each health state was assumed to be the same as that reported in NICE TA259.[82]	Resource use was not captured within the VISION trials but TA259 was considered a relevant source for resource use data for patients with mCRPC.
Health effects measure	QALYs	In line with the NICE reference case.[149]

Abbreviations: BNF: British National Formulary; eMIT: Drugs and pharmaceutical electronic market information tool; NICE: National Institute of Health and Care Excellence; NHS: National Health Service; PSS: personal social services; QALY: quality-adjusted life-year.

B.3.2.3 Intervention technology and comparators

Intervention technology

The intervention of interest is 7,400 MBq (200 mCi) of ^{177}Lu vipivotide tetraxetan (1,000 MBq/mL [27 mCi/mL]) administered intravenously via injection or infusion once every 6 weeks (±1 week) for a total of 6 doses. This is aligned to the draft SmPC for ^{177}Lu vipivotide tetraxetan and broadly in accordance with the dosing regimen used in VISION.[25] Data from the ^{177}Lu vipivotide tetraxetan + SOC arm of the VISION trial were used to inform the inputs in the economic analysis.[25]

Comparators

This cost-effectiveness evaluation considers 25 mg/m^2 of cabazitaxel administered via infusion every 3 weeks for a total of 10 doses, which represents the most relevant comparator for ^{177}Lu vipivotide tetraxetan for patients eligible for treatment with further chemotherapy following treatment with an ARPI and docetaxel. As described in Section B.1.3.3, it is expected that the vast majority of patients who do receive further chemotherapy currently receive cabazitaxel and therefore this is considered the most appropriate comparator for ^{177}Lu vipivotide tetraxetan. In the absence of appropriate head-to-head clinical data to inform a comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel, clinical inputs for cabazitaxel have been informed by data from the UK RWE analysis (see Section B.2.8.1), and HRs derived from the NMA (see Section B.2.8.6) which have been applied to the survival extrapolations for ^{177}Lu vipivotide tetraxetan.[25] Cabazitaxel is considered to represent the most relevant active comparator for ^{177}Lu vipivotide tetraxetan in clinical practice, and thus forms the focus for the cost-effectiveness analysis.

This cost-effectiveness analysis considers SOC as a relevant comparator for ^{177}Lu vipivotide tetraxetan in patients who are not eligible for treatment with cabazitaxel following treatment with an ARPI and docetaxel, or patients who are medically unsuitable for treatment with taxanes,

given the substantial unmet need in this patient population. The comparison of ^{177}Lu vipivotide tetraxetan to SOC is in line with the comparison made in VISION, and therefore data from the SOC arm of VISION trial were used to inform the inputs in the economic analysis.[25] Although VISION was designed to specifically select patients who had previously received taxanes, mechanistically, there is no reason that the efficacy and safety of ^{177}Lu vipivotide tetraxetan would be significantly different in patients who have not previously received taxanes compared to patients who have previously received taxanes. Thus, the clinical efficacy and safety data from VISION is considered to be generalisable to those patients who are medically unsuitable for taxanes.

B.3.3 *Clinical parameters and variables*

B.3.3.1 Baseline characteristics

The baseline characteristics for the modelled cohort are provided in Table 35. These inputs were based on the baseline characteristics of patients in VISION. The baseline characteristics for the patients in VISION are consistent with the target patient population in the UK as evidenced through their similarity to those of the patients receiving cabazitaxel in the RWE analysis. Furthermore, the generalisability of the baseline characteristics has been validated by clinical experts.[153]

Table 35: Patient baseline characteristics in the model

Model parameter	Value	Source
Age, years	[redacted]	VISION[116]
Weight, kg	[redacted]	
Height, cm	[redacted]	
BSA, m^2	[redacted]	

Weight, heights and BSA are used for calculating dosing in derivation of treatment costs and are not model inputs.
BSA calculated using the Mostellar formula.[154]
Abbreviations: BSA: body surface area.

B.3.3.2 Radiographic Progression Free Survival (rPFS)

As described in Section B.3.2.2, the model is a cohort-based partitioned survival model consisting of three mutually exclusive health states: (i) PF, (ii) PD, and (iii) dead. The proportion of patients within each health state at each weekly model cycle was then determined for both treatment arm using cumulative survival probabilities which were derived from the VISION intention-to-treat OS and rPFS curves. As the follow-up of VISION was shorter than the model time horizon, extrapolation from the observed rPFS and OS data was required.

In accordance with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 and TSD21 guidance, a range of standard parametric distributions (e.g. exponential, Weibull, stratified Weibull, Gompertz, stratified Gompertz, log-normal, stratified log-normal, log-logistic, stratified log-logistic, gamma, stratified gamma, generalised gamma, and stratified generalised gamma) and flexible models (i.e. spline models) were explored for extrapolation.[155, 156]

The spline models explored were developed based on the algorithm by Royston and Parmar *et al.* (2002).[157] Stratified and unstratified one-, two-, and three-knot Weibull spline models were explored and the goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criterion [BIC]) were then estimated for each parametric function. Stratified

models refer to models in which all parameters can vary by treatment. These models relax the assumptions of proportional hazards (PH) or constant acceleration factors, and the use of stratified models allows model fit statistics to be used to compare the model fit across all models (unlike models fitted separately to each treatment arm, wherein model fit cannot be compared across all models).

In determining the choice of survival model for the base case, consideration was given to the following, as per the recommendations provided in NICE DSU TSD14 and TSD21.[155]

- **AIC/ BIC tests:** the AIC and the BIC provide useful statistical tests of the relative fit of different parametric survival models. These tests weight the improved fit of models with the potentially inefficient use of additional parameters. Lower AIC and BIC values indicate better fit of the selected model.
- **Visual inspection:** the visual inspection can evaluate how well a parametric survival model fits with the observed Kaplan–Meier curves. The parametric survival model that most closely follows the Kaplan–Meier curve could be considered the best fit.
- **Clinical plausibility for both short-term and long-term estimates of survival.**

Adjustments were also made in the model traces to ensure that logical inconsistencies, such as the proportion of patients alive being less than the proportion of patients alive and progression-free, could not occur (i.e. rPFS and time-to-first SSE were bound by OS as a minimum).

In addition, the VISION trial was an open-label study, and patients could withdraw from the study at any time during follow-up. There is a risk that any imbalance between study arms in the number of patients that withdrew from the study could be associated with one or more prognostic effects. This could lead to informative censoring where the patients that withdrew from the study may not be representative of the intent-to-treat (ITT) population. As such, scenario analyses were explored to where inverse probability-of-censoring weighting (IPCW) was conducted to adjust for informative censoring; full details are presented in Appendix J.

^{177}Lu vipivotide tetraxetan and SOC

The rPFS data from VISION (see Section B.2.5.3) was used to fit the parametric models. A range of parametric models were considered; however, the fit of these models were problematic because of the plateau (flat tails) to the curves in both arms. This plateau means it is difficult to fit curves that both fit the data well, and that produce plausible long-term extrapolations. Investigatory analyses were conducted to assess the proportional hazards assumption. These indicated that the proportional hazards assumption was not met (Chi-square = 15.1, 1 degree of freedom, $P < 0.0001$).

The original fit of the stratified Gompertz model produced flat curves in the extrapolation of the control arm. To make these extrapolations plausible the hazard rates in the SOC arm were constrained to be greater than or equal to those in the ^{177}Lu vipivotide tetraxetan arm after the maximum follow-up time for rPFS. The same rule was applied to the stratified flexible spline-based Weibull for 1 and 2-knot models. The knot positions of these 2 spline-based models were also manually altered to find models that gave plausible predictions, as the original models also produced flat curves for the extrapolations. A stratified flexible spline-based Weibull model with 3-knot was also attempted, but this model failed to converge.

The fit of parametric models to the VISION trial data for rPFS data is shown in Figure 15 and long-term predictions in Figure 16. The fit of Royston-Palmar parametric models to the VISION trial data for rPFS data is shown in Figure 17 with long-term predictions shown in Figure 18.

Figure 15: Radiographic progression free survival: Standard parametric models

Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

Figure 16: Radiographic progression free survival: Standard parametric models: Long-term extrapolations

Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

Figure 17: Radiographic progression free survival: Royston-Palmar spline-based models

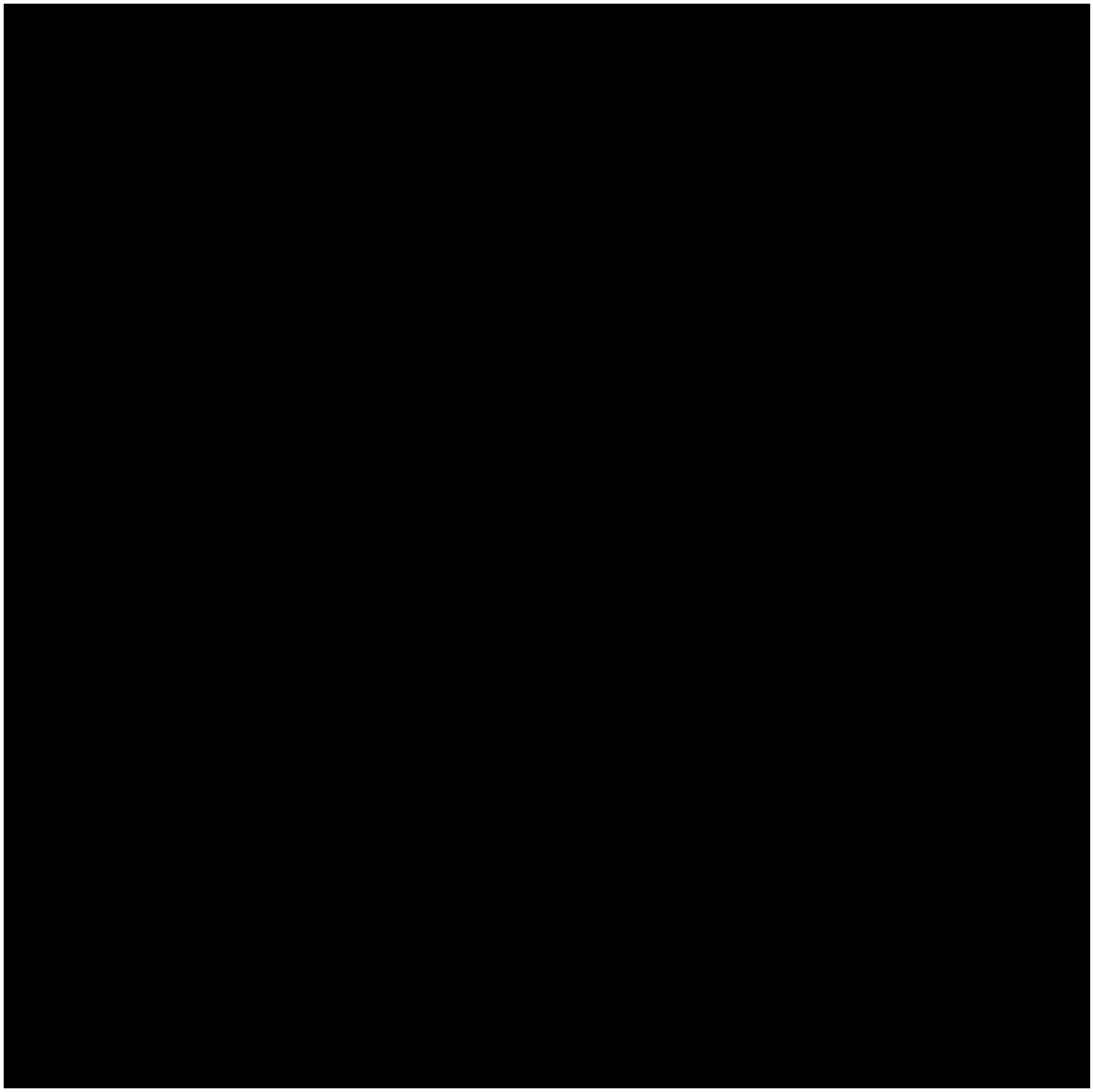
Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

Figure 18: Radiographic progression free survival: Royston-Palmar spline-based models: Long-term extrapolations

Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen

Visual assessment of the standard parametric models compared to the VISION data indicated that all models provided a poor fit to initial survival. The stratified Gompertz and generalised gamma models appeared to give the best visual fit. However, the generalised gamma model had difficulty in capturing the uncertainty of the extrapolations. The stratified flexible spline-based models provided a good visual fit with data and appeared to capture the uncertainty well for the extrapolation. The model fit statistics for the models fitted to the OS data are presented in Figure 19.

Figure 19: Radiographic progression free survival model fit: Akaike's information criterion (A) and Bayesian information criterion (B)



Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion.

The stratified flexible spline-based Weibull with 2-knots was selected for the base-case analysis as this produced the best statistical fit according to AIC and BIC, good visual fit to the VISION data, and appeared to capture the uncertainty in the SOC arm well. Clinical experts confirmed the clinical predictions for ^{177}Lu vipivotide tetraxetan and SOC based on this model were

plausible. In order to explore the impact of adjusting the survival extrapolations on the cost-effectiveness analysis, a scenario analysis was conducted using the stratified flexible Weibull (1 knot) model, representing the next best fitting curve according to AIC and BIC and also aligning with clinical predictions for ^{177}Lu vipivotide tetraxetan and SOC.

The predicted mean rPFS for the models considered are presented in Table 36, estimated through simulations of survival curves based on the model parameters and variance covariance matrices.

Table 36: Predicted mean rPFS versus SOC for selected survival extrapolations

Scenario	Model	Mean rPFS		Difference in mean rPFS, months (95% CrI)
		^{177}Lu vipivotide tetraxetan	SOC	
Base case	Stratified flexible Weibull (2 knots)	[redacted]	[redacted]	[redacted]
Scenario	Stratified flexible Weibull (1 knot)	[redacted]	[redacted]	[redacted]

Abbreviations: CrI: credible interval; rPFS: radiographic progression free survival.

Cabazitaxel

In the absence of appropriate clinical or real-world data to inform rPFS for the patient population of relevance to this economic analysis, a HR of [redacted] for cabazitaxel vs. ^{177}Lu vipivotide tetraxetan , representing the inverse of the HR presented in the NMA described in Section B.2.8 [redacted] was applied to the extrapolated rPFS data from the ^{177}Lu vipivotide tetraxetan + SOC arm of the VISION. Despite uncertainty in the NMA (as described in Section B.2.8.4 and Section B.2.8.7) this HR is very similar to the HR derived from the TheraP trial for the comparison of ^{177}Lu vipivotide tetraxetan compared with cabazitaxel (1.59 [95% CI: 1.16–2.17]), which provides external validation for the use of the NMA results within the model.[110] Clinical experts also considered the rPFS HR for cabazitaxel vs ^{177}Lu vipivotide tetraxetan to be reasonable. The resulting curves applied in the base case and scenario analyses for cabazitaxel are presented in Figure 20, and the predicted mean rPFS for the models considered are presented in Table 37.

Figure 20: Cabazitaxel rPFS curves applied in the base case and scenario analyses generated from reference ^{177}Lu vipivotide tetraxetan survival curves

Abbreviations: rPFS: radiographic progression free survival.

Table 37: Predicted difference in mean rPFS versus cabazitaxel for selected survival extrapolations

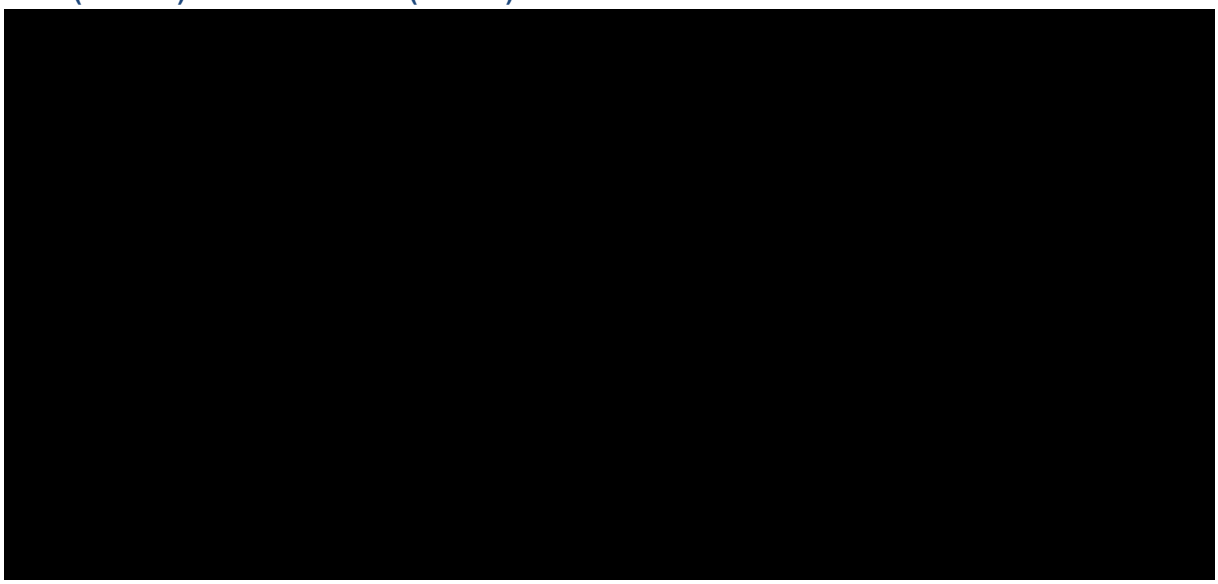
Scenario	Model selected for ^{177}Lu vipivotide tetraxetan (reference curve)	Mean rPFS		Difference in mean rPFS, months
		^{177}Lu vipivotide tetraxetan	Cabazitaxel[a]	
Base case	Stratified flexible Weibull (2 knots)	[redacted]	[redacted]	[redacted]
Scenario	Stratified flexible Weibull (1 knot)	[redacted]	[redacted]	[redacted]

[a]The mean rPFS for cabazitaxel has been determined from the area under curve of the model trace (assuming a 10-year time horizon) and as such 95% CrI are not available.
Abbreviations: CrI: credible interval; rPFS: radiographic progression free survival.

Summary of base case rPFS assumptions

The base case rPFS extrapolations for ^{177}Lu vipivotide tetraxetan, cabazitaxel and SOC are shown in Figure 21. It should be acknowledged that the rPFS curve for cabazitaxel falls below that of SOC. As described above, many of the extrapolations for the VISION control arm produced flat curves that were not clinically plausible. This included the stratified flexible spline-based Weibull 2-knot model used in the base case, which was by far the best fitting model according to AIC and BIC. As a result, the hazard rates in the SOC arm were constrained to be greater than or equal to those in the ^{177}Lu vipivotide tetraxetan arm after the maximum follow-up time for rPFS. These difficulties in extrapolating the SOC arm may explain this logical inconsistency between the cabazitaxel and SOC rPFS curves.

Figure 21: Selected distributions for extrapolating rPFS for ^{177}Lu vipivotide tetraxetan, SOC (VISION) and cabazitaxel (via HR)



Abbreviations: HR: hazard ratio; KM: Kaplan-Meier; PSMA: prostate-specific membrane antigen; rPFS: radiographic progression free survival; SOC: standard of care.

B.3.3.3 Overall Survival (OS)

The survival models for the base case were selected in line with the approach outlined for rPFS (Section B.3.3.2)

^{177}Lu vipivotide tetraxetan and SOC

The OS data from VISION (see Section B.2.5.2) was used to fit the parametric models. The OS data showed less complicated survival curves compared with the rPFS data. There was a possible departure from the proportional hazards assumption between 0 and 9 months, although this appeared to be relatively minor and may potentially be captured with accelerated failure time models. The test for proportional hazards was inconclusive (Chi-squared = 2.76; degrees of freedom = 1; p = 0.097).

The OS data in VISION is not completely mature, which can make survival extrapolation problematic. As such, a targeted literature search was performed to identify registry studies presenting Kaplan–Meier graphs for OS in populations of mCRPC patients. The purpose of this search was to identify data that could guide survival extrapolation model choice for patients receiving SOC only. Six suitable studies were identified, and the findings of this literature search are summarised in Table 38.

Table 38: Identified publications presenting Kaplan–Meier OS registry data for patients with mCRPC

Publication	Population	Sample size	Follow-up	Maturity (% survival at end of follow-up)	Survival at 2 years (VISION control = 15%)	Visual Fit with VISION trial data and usefulness for the extrapolation
Caffo *et al.* (2020)[158]	Patients with mCRPC who have experience disease progression following docetaxel	188	3 years	10%	17%	**Very good** – but provides little information for the extrapolation
Francini *et al.* (2019)[159]	mCRPC patients who are treatment naïve for mCRPC treatments (treated from 2010–2013)	272	5 years	25%	60%	**Poor** – survival much greater than VISION; provides little information for the extrapolation
Mateo *et al.* (2018)[160]	Patients with CRPC	362	12 years	10%	65%	**Poor** – survival much greater than VISION; provides little information for the extrapolation
Mehtala *et al.* (2020)[161]	Patients with mCRPC that have bone metatheses[a]	693	7 years	1%	25%	**Good** – provides useful information for the extrapolation
Ng *et al.* (2021)[162]	Patients with mCRPC	425	5 years	15%	50%	**Poor** – survival much greater than VISION; provides little information for the extrapolation
Notohardjo *et al.* (2020)[163]	Patients with mCRPC receiving third-line treatment	557	4 years	3%	15%	**Very good** – provides useful information for the extrapolation

[a]In this study patients were defined as having mCRPC if they had a metastatic prostate cancer diagnosis and had used a drugs to treat CRPC (mitoxantrone, estramustine, ketoconazole, docetaxel, cabazitaxel, abiraterone, or enzalutamide
Abbreviations: CRPC: castration resistant prostate cancer; mCRPC: metastatic castration resistant prostate cancer; OS: overall survival.

Out of the six publications identified, two appeared to provide a reasonable fit with the control arm data from VISION and provided useful long-term data to inform extrapolation: Mehtala *et al.* (2020) and Notohardjo et al. (2020). However, these studies provided incomplete data on baseline characteristics and the data presented by Mehtala *et al.* (2020) appeared to be for a less progressed patient population. The main difference found was in median time since diagnosis which was 7.4 years in VISION compared with 4.2 years in the study by Mehtala *et al.* (2020). The OS curve for SOC in the study conducted by Mehtala *et al.* (2020) was less steep than the OS curve from VISION (suggesting patients survived longer on average) [see Figure 22].

The published Kaplan–Meier data from Mehtala *et al.* (2020) were therefore digitised, and pseudo-IPD generated using the method described by Guyot *et al.* (2017) and time acceleration failure time models were fitted to the control arm data from VISION and the re-constructed data with study as a covariate.[164] A time acceleration factor of 0.78 from the best fitting model (gamma) was utilised to multiply the survival times in the re-constructed data to align with the VISION trial data and the resulting survival curves are presented in Figure 23.

Figure 22: Comparison of OS from the VISION SOC arm with OS data presented in Mehtala *et al.* (original data)

Abbreviations: OS: overall survival; mCRPC: metastatic castration resistant prostate cancer; SOC: standard of care.

Figure 23: Comparison of OS from the VISION SOC arm with OS data presented in Mehtala et al. (time accelerated adjusted data)

Abbreviations: OS: overall survival; mCRPC: metastatic castration resistant prostate cancer; SOC: standard of care.

The time accelerated adjusted data provide evidence that we can expect survival in the control arm in VISION to reach zero at around 5 years.

The population studies reported by Notohardjo *et al.* (2020) appeared to be a closer match to the VISION trial population, with similar values for proportion of patients with an ECOG score ≥2 (7.6% in VISION compared with 9.9% in Notohardjo *et al.* [2020]) and proportion of patients with bone metastases (91.5% in VISION compared with 94.3% Notohardjo *et al.* [2020]). No adjustment was therefore made for these data, and a comparison with VISION data is presented in Figure 24.

Figure 24: Comparison of OS from the VISION SOC arm with OS data presented in Notohardjo et al. (original data)

Abbreviation: LPD: life-prolonging drug

The data presented by Notohardjo *et al.* (2020) also suggested that we can expect survival in the VISION control arm to reach zero at about 5 years.

The fit of standard parametric models to the VISION trial data for OS is shown in Figure 25 and the long-term extrapolations are shown in Figure 26. The fit of spline-based models to the VISION trial data for OS is shown in Figure 27 and the long-term extrapolations are shown in Figure 28. Many of the standard parametric models appeared to fit the VISON data well. In particular, all the stratified models fitted well and also the gamma and generalised non-stratified models. The log-normal and log-logistic models produced extrapolations that exceeded the external data and so these models were disregarded.

Figure 25: Overall survival: Standard parametric models

Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

Figure 26: Overall survival: Standard parametric models: Long-term extrapolations

Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

Figure 27: Overall survival: Royston-Palmar spline-based models

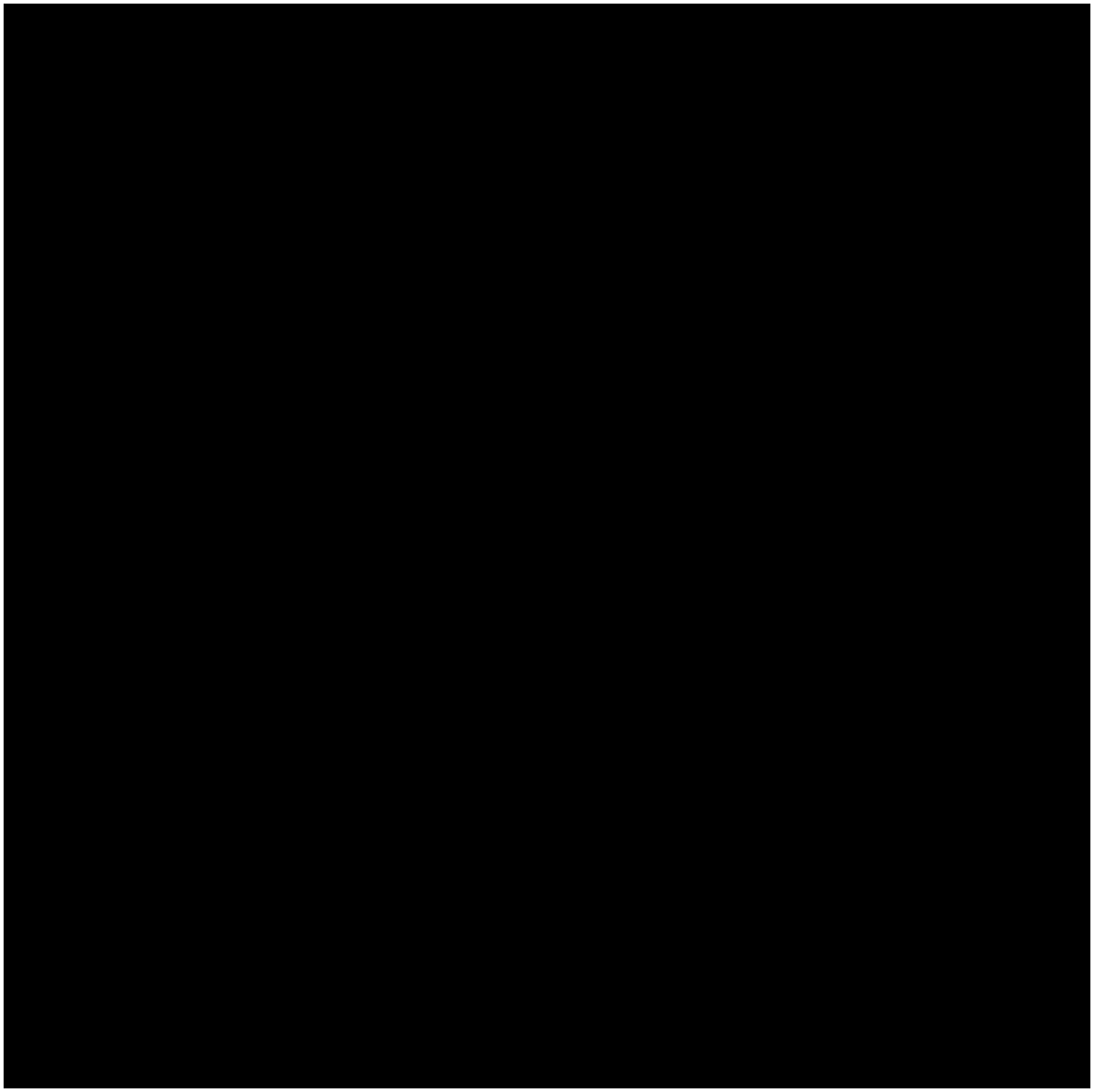
Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

Figure 28: Overall survival: Royston-Palmar spline-based models: Long-term extrapolations

Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

The model fit statistics for the models fitted to the OS data are presented in Figure 29.

Figure 29: Overall survival model fit: Akaike's information criterion (A) and Bayesian information criterion (B)



Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion.

Statistical fit did not enable differentiation between many of the models, and the order of models according to statistical fit from the AIC and BIC values was not consistent. This meant that it was problematic to select the most appropriate model based on statistical fit. Therefore, to further aid this decision ensemble models were performed. Ensemble models provide an unbiased estimate of survival and capture the uncertainty in the choice of model. After excluding the previously disregarded log-normal and log-logistic models, simulated survival curves were run for all models in proportion to their AIC weights, BIC weights, and the mean from both weights. The predicted survival curves from the ensemble models are presented in Figure 30.

Figure 30: Ensemble predictions for overall survival

Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

The ensemble models all appeared to provide similar predictions which showed a small degree of variation in the uncertainty of predictions. All of the models that provided a good fit to the VISION data and produced plausible extrapolations resulted in similar survival estimates.

The Stratified flexible Weibull (2 knots) parametric model was ultimately selected for the base-case analysis as this provided good statistical fit and reasonably similar predictions to the ensemble model. This model also aligns with clinical expert predictions, 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.[118], [a] Furthermore, this selection is aligned to the model selected for the extrapolation of rPFS data. In order to explore the impact of adjusting the survival extrapolations on the cost-effectiveness analysis, a scenario analysis was conducted using Gamma model, representing the best fitting curve in terms of BIC (and one of the best fitting as per AIC), as well as offering good visual fit, aligning with external data and providing reasonable predictions for ^{177}Lu vipivotide tetraxetan and SOC.

The predicted mean OS for the models considered are presented in Table 39, estimated through simulations of survival curves based on the model parameters and variance covariance matrices.

Table 39: Predicted difference in mean OS versus SOC for selected survival extrapolations

Scenario	Model	Mean OS		Difference in mean OS, months (95% CrI)
		^{177}Lu vipivotide tetraxetan	SOC	
Base case	Stratified flexible Weibull (2 knots)	[redacted]	[redacted]	[redacted]
Scenario	Gamma	[redacted]	[redacted]	[redacted]

Abbreviations: CrI: credible interval; OS: overall survival.

Overall Survival – Cabazitaxel

[a] Please note that the RWE OS data were not available at the time of the clinical expert interviews, which precluded discussion of this RWE within these interviews.

In the absence of appropriate RCT data to inform OS for the patient population of relevance to this economic analysis, OS data from the UK real-world database analysis (See Section B.2.8.1) was used to inform OS for patients in the cabazitaxel treatment arm in the base case analysis. OS data from the real-world database analysis were deemed the most suitable for the base case analysis given that this analysis was conducted on UK patients and the baseline characteristics from this real-world database analysis are closely aligned to VISION. As such this analysis provides the most relevant evidence relating to UK patients currently treated with cabazitaxel, who would be considered eligible for treatment with ^{177}Lu vipivotide tetraxetan. Clinicians and HE experts consulted within an advisory board setting have supported the use of this RWE to inform the base case inputs for OS in the cabazitaxel arm.[165] As the survival probability reaches zero in this RWE for cabazitaxel, there was no requirement to apply survival extrapolations to this data, and the Kaplan–Meier data were used directly in the model.

It was noted that the OS for cabazitaxel in the RWE analysis was shorter than the median OS for the SOC arm of VISION ([redacted] months vs. 11.3 months). However, patients in clinical trials receive enhanced monitoring through more frequent visits to physicians and imaging. Therefore, patients in clinical trials may have longer OS compared to what would be anticipated in real-world practice. This effect is likely greater for patients in the control arms of trials, who are expected to receive less regular oncological follow-up and imaging in real-world practice than patients receiving active oncological therapy. Therefore, it is expected that patients in real-world practice receiving SOC would experience shorter OS than that observed in VISION, and it is possible that OS may be overestimated for SOC in the model.

A scenario analysis has been conducted in which a HR of [redacted] for cabazitaxel vs. ^{177}Lu vipivotide tetraxetan, representing the inverse of the HR presented in the NMA described in Section B.2.8 [redacted] was applied to the extrapolated OS data from the ^{177}Lu vipivotide tetraxetan + SOC arm of VISION. Despite uncertainty in the NMA (as described in Section B.2.8.4 and Section B.2.8.7) the mean undiscounted life-years predicted in the model (1.28 [15.26 months]) is similar to the mean OS reported for patients receiving cabazitaxel in an analysis of a UK RWE database (13.85 months) [see Section B.2.8.1]. The OS data utilised in the base case and scenario analysis are summarised in Figure 31. Clinical experts also considered the estimated difference in mean OS of cabazitaxel vs ^{177}Lu vipivotide tetraxetan to be plausible, but likely an underestimation of ^{177}Lu vipivotide tetraxetan's clinical benefit.

Table 40: Predicted difference in mean OS versus cabazitaxel for selected survival extrapolations

Scenario	Source/Assumption for cabazitaxel OS	Mean OS		Difference in mean OS, months
		^{177}Lu vipivotide tetraxetan	Cabazitaxel[a]	
Base case	UK RWE Kaplan–Meier data	[redacted]	[redacted]	[redacted]
Scenario	HR applied from reference ^{177}Lu vipivotide tetraxetan curve: Stratified flexible Weibull (2 knots)	[redacted]	[redacted]	[redacted]

[a]The mean OS for cabazitaxel has been determined from the area under curve of the model trace (assuming a 10-year time horizon) and as such 95% CrI are not available.
Abbreviations: CrI: credible intervals; HR: hazard ratio; OS: overall survival; RWE; real-world evidence.

Figure 31: Cabazitaxel OS curves applied in the base case and scenario analyses

Abbreviations: KM: Kaplan–Meier; RWE: real-world evidence.

Summary of base case OS assumptions

The base case OS extrapolations for ^{177}Lu vipivotide tetraxetan, cabazitaxel and SOC are shown in Figure 32.

Figure 32: Selected distributions for extrapolating OS for ^{177}Lu vipivotide tetraxetan, SOC (VISION) and cabazitaxel (UK RWE)

Abbreviations: KM: Kaplan-Meier; OS: overall survival; PSMA: prostate-specific membrane antigen; RWE: real-world evidence; SOC: standard of care.

B.3.3.4 Symptomatic Skeletal Event Rate

As previously described in Section B.1.3.2, SSEs carry a considerable burden for patients with mCRPC, and as such these events were included in the model to fully capture the benefits (in terms of HRQoL and healthcare resource use [HCRU]) of treatment with ^{177}Lu vipivotide tetraxetan compared with comparator treatments.

^{177}Lu vipivotide tetraxetan and SOC

The Kaplan-Meier estimates for time-to-first SSE are presented in Figure 33; patients were censored at a change in treatment since SSE data were not collected after patients switched treatment, which typically occurred earlier in the control arm. There was a significant difference in time-to-first SSE between the ^{177}Lu vipivotide tetraxetan + SOC and SOC treatment arms of VISION, however, the data was found to be problematic because of the flat tail; several clinical experts agreed that flattening of the SSE curve would not be clinically plausible, given the number of SSEs increases as the disease progresses. This is particularly noticeable in the SOC treatment arm and is likely to increase uncertainty in the extrapolation.

Figure 33: Time-to-first SSE data from VISION

Note: This figure presents time-to-first SSE data for all patients in VISION with a known treatment end date.
Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

Figure 34 presents the standard parametric models fitted to the VISION time-to-first SSE interval-imputed data. All the models fitted appeared to give a reasonable fit to the Kaplan-Meier estimates. Figure 35 presents long-term extrapolations based on the standard parametric models fitted to the VISION time-to-first SSE data.

Figure 34: Time-to-first SSE: Parametric Models Fitted to the VISION Trial Data

Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

Figure 35: Time-to-first SSE: Long-Term Extrapolations Fitted to the VISION Trial Data

Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

Figure 36 presents the flexible spline–based Weibull models fitted to the VISION time-to-first SSE data. All the spline-based models gave a good visual fit with the Kaplan-Meier estimates.

Figure 36: Time-to-first SSE: Flexible Spline-Based Models Fitted to the VISION Trial Data

Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

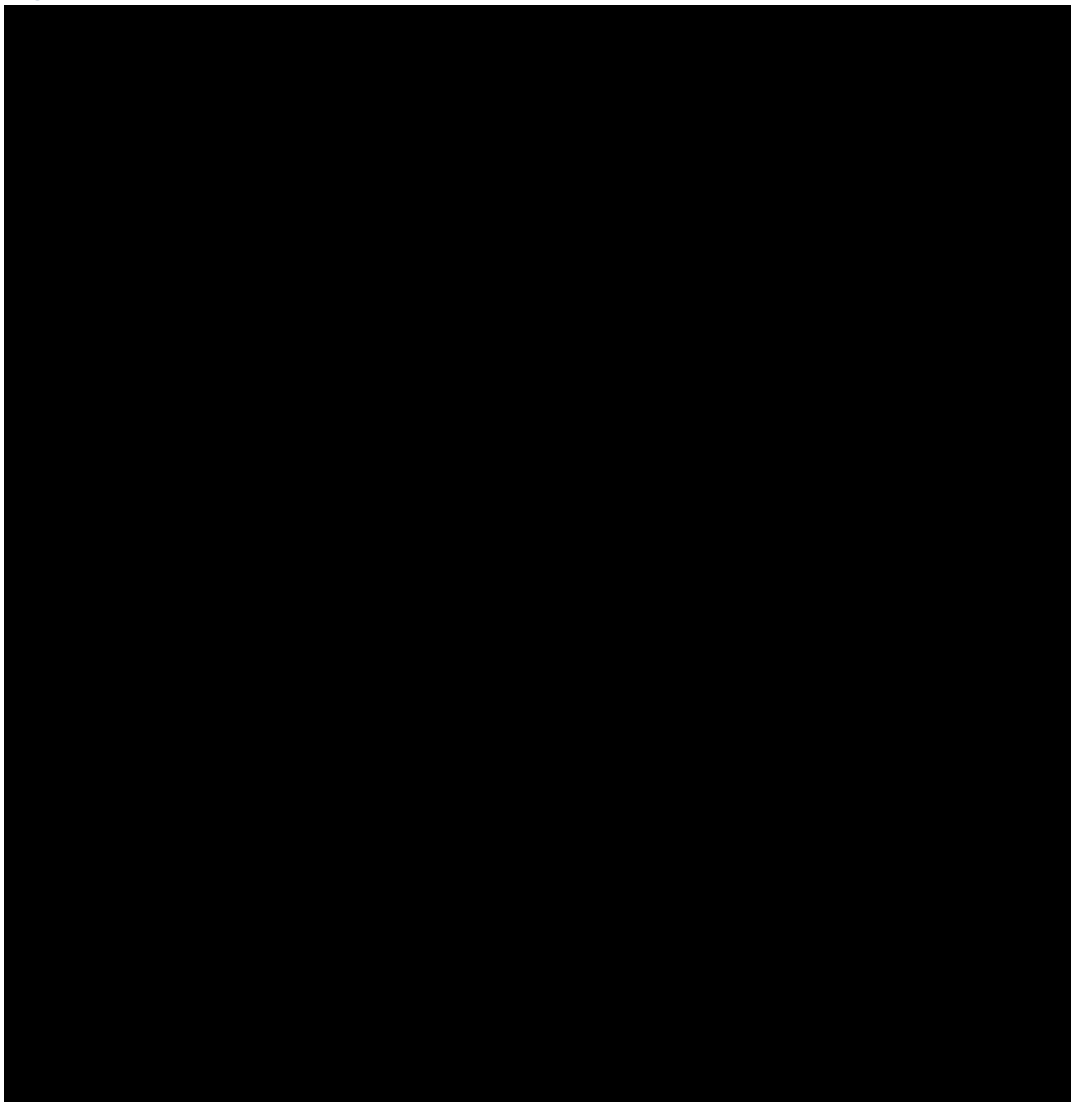
Figure 37 presents long-term extrapolations based on the flexible spline–based models fitted to the VISION time-to-first SSE data.

Figure 37: Time-to-first SSE: Long-term Extrapolations Based on the Flexible Spline-Based Models Fitted to the VISION Trial Data

Abbreviations: BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

Figure 38 presents the model fit statistics (AIC, BIC, and associated weights) from models fitted to the VISION time-to-first SSE data. The stratified Gompertz and stratified flexible Weibull model with 1 knot gave the best fit according to AIC. The log-normal and log-logistic models gave the best fit according to BIC. All these models appear to fit the flat tails of the survival curves well. The flat curves may have been the result of heavy censoring. Therefore, these results have a degree of unavoidable uncertainty associated with them.

Figure 38: Time-to-first SSE: Model Fit Statistics – A (AIC) and B (BIC)



Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion.

To aid choice of a suitable model for the base case analysis, ensemble models were conducted for each of the models that gave plausible time-to-first SSE predictions. These ensemble models are presented in Figure 39.

Predicted mean time-to-first SSE and difference in mean OS between ^{177}Lu vipivotide tetraxetan and SOC for the models explored in the base case and scenarios are presented in Table 41.

Figure 39: Time-to-first SSE: Ensemble Models

Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion; BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

The log-normal model was selected for the base-case analysis based on AIC and BIC statistics, and given the difference in mean time-to-first SSE between ^{177}Lu vipivotide tetraxetan and SOC was closest to ensemble mean ([redacted] months; 95% CI: [redacted]). The proportion of patients experiencing a first SSE is calculated in each model cycle based on the change in time to first SSE curves. The number of SSEs in each model cycle is constrained by OS to prevent logical inconsistencies.

Table 41: Predicted difference in mean time-to-first SSE versus SOC for selected survival extrapolations

Base case model	Proportion experiencing an SSE (%)		Mean time-to-first SSE		Difference in mean time-to-first SSE, months (95% CrI)
	^{177}Lu vipivotide tetraxetan	SOC	^{177}Lu vipivotide tetraxetan	SOC	
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion; CrI: credible interval; SSE: symptomatic skeletal event.

Cabazitaxel

The data for time-to-first SSE for cabazitaxel from the CARD trial presented by de Wit *et al.* (2019) were reconstructed and superimposed on the Kaplan–Meier estimates from VISION (Figure 40).[113] As the results from VISION and CARD are very similar, the rate of SSEs was assumed to be the same as ^{177}Lu vipivotide tetraxetan; however, given the number of SSEs was constrained by cabazitaxel OS, only [redacted]% of patients receiving cabazitaxel were modelled to experience an SSE, compared with [redacted]% for ^{177}Lu vipivotide tetraxetan. It should be noted that this estimate is very similar to the proportion of patients who experienced an SSE in the CARD trial (see Table 42 below).

The assumption that the rate of SSEs is the same as ^{177}Lu vipivotide tetraxetan could be considered conservative; given SSEs are associated with disease progression, it could be expected that the rate of SSEs would be lower for ^{177}Lu vipivotide tetraxetan due to improved rPFS. The view was supported by several clinical experts, who suggested that ^{177}Lu vipivotide tetraxetan would be superior to cabazitaxel in terms of time-to-first SSE, since patients in VISION were considered to have worse disease than those in CARD. As such, a scenario analysis was explored where data for time-to-first SSE for SOC were used to inform the rate of SSEs for cabazitaxel.

Figure 40: Comparison of time-to-first SSE in VISION and CARD

Abbreviations: ARPI: androgen receptor pathway inhibitor; BSC/BSoC: Standard of care; PSMA: prostate specific membrane antigen.

Alternative approach to modelling SSEs – all treatments

An alternative method of modelling SSEs was explored in a scenario analysis, where the total incidence of first SSEs is applied, in line with the approach taken in the ongoing NICE TA for Olaparib (NICE ID1640).[11] In this approach SSEs are assumed to occur upon disease progression, and costs and utility decrements associated with SSEs are calculated at that timepoint. The total incidence of SSEs for ^{177}Lu vipivotide tetraxetan and SOC treatment arms used in the model have been taken from VISION. For the cabazitaxel treatment arm the total incidence of SSEs has been taken from CARD (36.5%). The total incidence of SSEs are presented in Table 42.

Table 42: SSE incidence and rates applied in a scenario analyses

Event	^{177}Lu vipivotide tetraxetan	SOC	Cabazitaxel[a]
Total incidence	[redacted]	[redacted]	36.5%

[a]The total incidence of SSEs for the cabazitaxel treatment arm has been calculated using digitised data from the CARD study.[113]
Abbreviations: ^{177}Lu: Lutetium-177; SOC: standard of care; SSE: symptomatic skeletal event.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report);[116] de Wit *et al* (2019).[113]

B.3.3.5 Symptomatic Skeletal Event Distribution

The distribution of different SSEs was calculated from the VISION trial by treatment arm for the ^{177}Lu vipivotide tetraxetan and SOC treatment arms. It has been confirmed by consultations with clinical experts that both the distribution of SSEs seen in VISION the differences observed between treatment arms are clinically plausible.[118] For the cabazitaxel treatment arm, the distribution of SSEs was aligned with NICE ID1640.[11] Within the model, individual costs and utility decrements are applied for each SSE. The distribution of SSEs are presented in Table 43. Utility decrements and costs associated with SSEs are presented in Section B.3.4.3 and Section B.3.5.3, respectively.

Table 43: Distribution of SSEs

Event	^{177}Lu vipivotide tetraxetan	SOC	Cabazitaxel[a]
Radiation to bone	[redacted]	[redacted]	69.31%
Pathological fracture	[redacted]	[redacted]	12.70%
Surgery to bone	[redacted]	[redacted]	2.65%
Spinal cord compression	[redacted]	[redacted]	15.34%

[a]The distribution of SSE data for the cabazitaxel treatment arm has been taken from NICE ID1640 and this data has been reweighted so that total distributions sum to 100%.[11]
Abbreviations: ^{177}Lu: Lutetium-177; SOC: standard of care; SSE: symptomatic skeletal event.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report);[116] NICE ID1640.[11]

B.3.3.6 Adverse events

The probabilities of an individual AE for ^{177}Lu vipivotide tetraxetan and SOC were based on the VISION trial and those for cabazitaxel were based on CARD.[113] To ensure that the model was focused on AEs which were most likely to have an important impact on costs or HRQoL, Grade ≥ 3 AEs with at an incidence of at least 2% incidence for each intervention were included (see Table 44). Costs and utility decrements (if any) associated with each AE were included in the model and were applied in the first model cycle. Utility decrements and costs associated with AEs are presented in Section B.3.4.3 and Section B.3.5.3, respectively.

Table 44: Incidence of Grade ≥3 AEs occurring in at least 2% of patients

AE	^{177}Lu vipivotide tetraxetan	SOC	Cabazitaxel
Anaemia	[redacted]	[redacted]	7.9%
Asthenia	[redacted]	[redacted]	4.0%
Back pain	[redacted]	[redacted]	0.0%
Fatigue	[redacted]	[redacted]	0.0%
Hypokalaemia	[redacted]	[redacted]	3.2%
Neutropenia	[redacted]	[redacted]	43.7%
Thrombocytopenia	[redacted]	[redacted]	3.2%
Lymphopenia/ lymphocytopenia	[redacted]	[redacted]	0.0%
Leukopenia	[redacted]	[redacted]	31.7%
Urinary tract infection	[redacted]	[redacted]	0.0%
Haematuria	[redacted]	[redacted]	0.0%
Acute kidney injury	[redacted]	[redacted]	0.0%
Hypertension	[redacted]	[redacted]	0.0%

Abbreviations: ^{177}Lu: Lutetium-177; AE: adverse event; PSMA: prostate-specific membrane antigen, SOC: standard of care.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116] de Wit *et al* (2019).[113]

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials and mapping

The VISION trial assessed HRQoL via the EQ-5D-5L health utilities instrument.[116] For use in the model, health state utility values were derived in line with the NICE reference case: pooled EQ-

5D-5L scores collected in VISION were mapped to EQ-5D-3L utility index scores using the mapping function developed by the NICE DSU (Hernández Alava *et al.* [2017]), using the 'EEPRU dataset' (Hernández Alava *et al.* [2020]), in line with the reference case stipulated in the NICE manual for health technology evaluations (PMG36).[150-152] The utility values presented in Section B.3.4.4 are representative of the population of interest in UK clinical practice.

B.3.4.2 Health-related quality-of-life studies

An SLR was conducted to identify all relevant utilities in patients with mCRPC. The SLR was performed in June 2019, with subsequent updates performed in April 2021 and November 2021. In total, 98 records were identified that included primary utility data deriving from 96 original studies. Full details of the SLR search strategy, study selection process and the results of included studies are reported in Appendix H

The SLR yielded no utility data for patients with mCRPC treated with ^{177}Lu vipivotide tetraxetan. In line with the NICE reference case, health state utility values applied in the base case were derived from EQ-5D-5L data collected in the VISION trial.

B.3.4.3 Adverse reactions

Symptomatic Skeletal Events

The utility decrements associated with SSEs are presented in Table 45. These utility decrements were informed by Fassler *et al*. (2011),[166] which is aligned to the approach taken in the ongoing NICE appraisal for olaparib (NICE ID1640).[11]

SSE utility decrements were applied for a varying durations dependent on the SSE. The appropriate duration to apply SSE utility decrements were determined via consultation with clinical experts.[118]

As the health-state specific utility values differed by treatment arm in the base case analysis, disutility for SSEs was considered to be captured in these health-state utility values, and utility decrements associated with SSEs were not included in the base case analysis in order to avoid double-counting. However, these decrements were explored in conjunction with treatment-independent health-state utility values in a scenario analysis.

Table 45: Utility decrements associated with SSEs

SSE	Utility decrement	Duration[a]	Source
Radiation to bone	−0.07	1 month (4 cycles)	Fassler et al. (2011)[166]
Pathological fracture	−0.13	2 month (8 cycles)	
Surgery to bone	−0.13	3 month (12 cycles)	
Spinal cord compression	−0.555	6 months (24 cycles)	

[a]The appropriate duration of SSE decrements were determined via consolation with clinical experts.[118]
Abbreviations: SSE: symptomatic skeletal event.

Adverse Events

The utility decrements associated with AEs are presented in Table 46. These utility decrements have been taken from a range of published literature sources. It has been assumed that all AE

utility decrements are applied for a mean duration of one month. All utility decrements were applied at the start of the model, assuming that all AEs occur during the first year of treatment (i.e. no discounting). To avoid double counting, utility decrements for AEs were not applied in the base case analysis. However, these decrements were explored in conjunction with treatment-independent health-state utility values in a scenario analysis.

Table 46: Utility decrements and duration of disutility associated with AEs

AE	Disutility	Source	Source
Anaemia	0.12	Swinburn et al. (2010)[167]	NICE TA391 (2016)[10]
Back pain	0.07	Doyle et al. (2008)[168]	
Fatigue	0.12	Lloyd et al. (2006)[169]	
Hyperkalaemia	0.00	NICE TA316 (2014)[83]	
Neutropenia	0.09	Nafees et al (2008)[170]	
Thrombocytopenia	0.09	NICE TA391 (2016)[10]	
Leukopenia	0.09	NICE TA259 (2012)[82]	
Lymphopenia/ lymphocytopenia	0.09		Assumption
Urinary tract infection	0.02	Bermingham and Ashe (2012)[171]	Mitchell et at (2016)[172]
Haematuria	0.02	Assumption	Assumption
Acute kidney injury	0.11	NICE 2019[173]	Medcalf et al. (2016)[174]
Hypertension	0.15	NICE TA259 (2012)[82]	NICE TA316 (2014)[83]

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

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Health state utilities

EQ-5D data were collected in VISION at baseline, and then on the first day of every treatment cycle thereafter. Data were also collected on the final visit of each patient, defined as the last assessment on or after the date of disease progression. HRQoL in the VISION trial was self-reported by patients (or via interview format) using the EQ-5D-5L during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. The numbers of patients who provided EQ-5D scores at each cycle are presented in Table 47. Pooled EQ-5D-5L scores collected in VISION were mapped to EQ-5D-3L utility index scores using the mapping function developed by the NICE DSU (Hernández Alava *et al.* [2017]), using the 'EEPRU dataset' (Hernández Alava *et al.* [2020]), in line with the reference case stipulated in the NICE manual for health technology evaluations (PMG36).[150-152]

Table 47: Numbers of patients who provided EQ-5D scores at each treatment cycle in VISION

State	All treatments	SOC	^{177}Lu vipivotide tetraxetan + SOC
Baseline	[redacted]	[redacted]	[redacted]
Cycle 1	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]

Abbreviations: ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen, SOC: standard of care.

Descriptive statistics (presented in Table 48) for the utility values were calculated using patient-level EQ-5D data stratified by the following categories, corresponding to model health states:

- **EQ-5D measures for 'Progression Free':** Any EQ-5D assessments for patients in the rPFS state
- **EQ-5D measures for 'Progressed':** any EQ-5D assessments for patients in the OS state (i.e. following progression [as defined by radiographic progression in VISION; see Section B.2.3.2])

Patients in the Dead health state were assigned a utility of zero by definition.

Table 48: Descriptive statistics for EQ-5D health state utility values derived from VISION

Health state		All treatments	SOC	^{177}Lu vipivotide tetraxetan + SOC
Progression-free	Number of assessments	[redacted]	[redacted]	[redacted]
	Mean utility value (SD)	[redacted]	[redacted]	[redacted]
Progressed disease	Number of assessments	[redacted]	[redacted]	[redacted]
	Mean utility value (SD)	[redacted]	[redacted]	[redacted]

The same patient could have been in multiple health states at different visits. The statistics presented here reflect the number of patients with at least one assessment with the specified health state
Abbreviations: SD: standard deviation.

To generate health state utility values for use in the economic model, a generalised linear mixed model was fitted to the data using xtmixed in Stata, and analyses were performed according to a prespecified analysis plan, with utility index post-baseline as the dependent variable.

The following fixed effects were initially considered: planned treatment, time of visit (since randomization), age, baseline utility, baseline ECOG status, prior-ARPI use, planned treatment, and an interaction term between planned treatment and health state. Results based on marginal means from a mixed model reduced using stepwise regression included fixed effects for planned treatment and time of visit (since randomisation). Covariates included in the model included age, baseline utility scores, ECOG status and an interaction term between planned treatment, health state and the interaction between planned treatment and health state. A further simplified model was run to generate treatment-independent utilities, which did not consider planned treatment.

Health state utility values generated from the generalised linear mixed models included treatment-independent utilities as well as treatment-specific health state utility values for the ^{177}Lu vipivotide tetraxetan and SOC treatment arms (Table 49). Health state utility values from NICE TA391 were explored for cabazitaxel (Table 50).[10] The pre-progression health state utility from TA391 was deemed inappropriate, as this value was higher than the is health state utility value for ^{177}Lu vipivotide tetraxetan derived from VISION. This was considered clinically implausible by clinical experts given the greater toxicity of cabazitaxel treatment. Utility values from TA391 were derived from an open-label single-arm study of 112 patients treated with cabazitaxel (the UK early access programme); these patients are less heavily pre-treated than the patients in VISION which likely accounts for the higher health state utility value.[10] Therefore, the pre-progression health state utility for cabazitaxel is assumed to align with the value for the SOC treatment arm derived from VISION. The health state utility value from TA391 was used to inform the post-progression health state utility. This value is lower that the ^{177}Lu vipivotide tetraxetan and SOC post-progression values, reflecting the substantial toxicity associated with cabazitaxel treatment which can impact HRQoL even following disease progression; the long-lasting toxicity associated with cabazitaxel was confirmed by clinical experts. A summary of the base case utility inputs is provided in Table 51.

Table 49: EQ-5D health state utilities derived from generalised linear mixed model

Health state utility, Mean (SE)	^{177}Lu vipivotide tetraxetan	SOC
Treatment-specific utilities by health state		
Progression-free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
Treatment-independent utilities by health state		
Progression-free	[redacted]	
Progressed disease	[redacted]	

Utilities are presented in the form: mean (SE)
Abbreviations: ^{177}Lu: Lutetium-177; SE: standard error; SOC: standard of care.

Table 50: EQ-5D health state utilities derived from NICE TA391

Health state utility, Mean (SE)	Cabazitaxel	Source
Progression-free	0.737 (0.074)	NICE TA391 (2016)[10]
Progressed disease	0.627 (0.063)	

Utilities are presented in the form: mean (SE)
Abbreviations: SE: standard error.

Table 51: Base case health state utility inputs

Health state utility, Mean (SE)	^{177}Lu vipivotide tetraxetan	SOC	Cabazitaxel
Progression-free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	0.627 (0.063)

Utilities are presented in the form: mean (SE)
Abbreviations: 177Lu: Lutetium-177; SE: standard error; SOC: standard of care.

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

An SLR was conducted to identify all relevant cost and resource use in patients with mCRPC. The SLR was performed in April 2021. In total, 74 records were identified which featured relevant cost and resource use data associated with mCRPC. Full details of the SLR search strategy, study selection process and results are reported in Appendix I.

The following cost categories are included in the model:

- Drug acquisition and administration costs for interventions and comparators (Section B.3.5.1)
- Costs associated with subsequent treatments and therapeutic interventions (Section B.3.5.1)
- Monitoring costs for intervention and comparators (Section B.3.5.1)
- Costs associated with the management of SSEs and AEs (Section B.3.5.3)

The economic analysis was conducted from the perspective of the NHS and PSS and therefore only included direct medical costs that would be incurred by the NHS and PSS. Cost inputs were based on costs taken from the British National Formulary (BNF) [2021][128], the Drugs and pharmaceutical electronic market information tool (eMIT) [2021][129] and the National Schedule of NHS costs (2019-20).[130]

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs were sourced from UK list prices (Table 52). For drugs that are dosed by weight, patient body weight and body surface area estimates from the VISION trial were used. A mean body weight of [redacted] kg, and a mean body surface area (BSA) of [redacted] m^2 were used in the base case analysis. Mean BSA was calculated from body weight and mean height ([redacted] cm) reported in VISION using the Mosteller method.[154]

Treatment duration and exposures for ^{177}Lu vipivotide tetraxetan and cabazitaxel were sourced from VISION and CARD, respectively (Table 53).[25, 113] A mean treatment exposure of 6.26 months for ^{177}Lu vipivotide tetraxetan in the VISION trial was used to determine a mean value of 4.54 doses, based on a 6-week treatment cycle. The mean number of doses was used to calculate a mean ^{177}Lu vipivotide tetraxetan acquisition cost of £[redacted] at list price and £[redacted] at ^{177}Lu vipivotide tetraxetan PAS price. The mean number of doses was also used to calculate a mean administration cost of £[redacted] per patient for the base case analysis. A mean treatment exposure of 5.1 months for cabazitaxel in the CARD trial was used to determine a mean value of 7.33 doses, based on a 3-week treatment cycle. The mean number of doses was used to calculate a mean cabazitaxel treatment cost of £23,460. The mean number of doses was also used to calculate a mean administration cost of £2,871. The administration cost of £391.46 for cabazitaxel was derived

from NICE TA391 and consistent with NICE ID1640.[11] This included the cost of delivering chemotherapy (NHS Schedule of Reference Costs 2019/2020) and an additional cost of one hour of pharmacist time (PSSRU 2020/2021). No additional administration costs are applied for the three pre-medications, or the prophylactic G-CSF given alongside cabazitaxel which represents a conservative assumption. All ^{177}Lu vipivotide tetraxetan and cabazitaxel treatment acquisition and administration costs were applied within the first cycle, and as all treatment is given within the first year there was no discounting applied.

In the base case analysis it has been assumed that there are no SOC treatments associated with ^{177}Lu vipivotide tetraxetan or cabazitaxel (besides any pre-medications specified in the label). Concomitant treatments associated with SOC in the base case and applied to ^{177}Lu vipivotide tetraxetan and cabazitaxel in a scenario were taken from the VISION trial. The proportion of patients receiving each therapy was determined by treatment arm (Table 54). A weighted average was taken for the treatment arms of VISION to create an 'Overall' SOC usage utilisation, that was used to estimate SOC resource usage for patients receiving cabazitaxel. The breakdown of different drug classes and mean treatment exposure were used to calculate a mean concomitant treatment cost (acquisition + administration) of [redacted] for the ^{177}Lu vipivotide tetraxetan arm (scenario), [redacted] for the cabazitaxel treatment arm (scenario), and [redacted] for the SOC arm in the base case. The treatment acquisition and administration costs were applied within the first model cycle, however as all treatments (with the exception of bisphosphonates and antifungals) had a mean treatment duration of <12 months, this is expected to have a marginal impact on cost-effectiveness.

Table 52: Drug acquisition and administration costs

Product	Strength	Pack size	Pack price	Dose and cycle length	Cost per treatment cycle	Administration cost[a]	Source of treatment cost
Radiopharmaceuticals							
^{177}Lu vipivotide tetraxetan	7.40 GBq	1	List Price: £[redacted] PAS Price: £[redacted]	7.4 Gbq every 6 weeks	List Price: £[redacted] PAS Price: £[redacted]	£1,254.25	AAA Data on File
Radium-223 dichloride	6,000 kBq	1	£4,040.00	55 kBq per kg every 4 weeks	£3,259.67	£302.53	NICE TA412
Antiemetics							
Prochlorperazine	5 mg	84	£0.89	5–10 mg BID	£0.04	£207.79	eMIT (2021)
Antifungals							
Ketoconazole	6,000 mg	1	£4.24	1g BID	£0.21	£0.00	BNF (2021)
Antihistamines							
Chlorphenamine	4 mg	28	£0.40	Daily	£0.03	£0.00	eMIT (2021
Bisphosphonates							
Zoledronic acid	4 mg	1	£10.31	4 mg every 3weeks	£10.31	£302.53	eMIT (2021)
Corticosteroids							
Dexamethasone	4 mg	50	£12.91	8–16 mg QD	£0.77	£0.00	eMIT (2021)
Prednisolone	2.5 mg	28	£0.56	15–30 mg QD	£0.18	£0.00	eMIT (2021)
Erythropoietin stimulating agents							
Epoetin alfa	450 units/kg	1	£33.18	450 units/kg once weekly	£1,314.23	£221.35	BNF (2021)
GM-CSF							
Pegfilgrastim	6 mg	1	£411.83	6 mg every 3 weeks	£411.83	£221.35	BNF (2021)
G-CSF							
Filgrastim	48 million units	5	£395.25	0.5 million units /kg/day	£1,079.02	£0.00	BNF (2021)

H2-antagonists							
Ranitidine	150 mg	60	£12.63	150 mg BID	£0.42	£0.00	NICE TA391 (2016)
Opioid analgesics							
Morphine	100 mg	60	£38.50	100 mg BID	£1.28	£207.79	eMIT (2021)
Oxycodone	10 mg	56	£4.06	10 mg BID	£0.15	£207.79	eMIT (2021)
Tramadol	150 mg	60	£4.83	50–100 mg BID	£0.08	£207.79	eMIT (2021)
Platinum compounds							
Carboplatin	600mg	1	£232.64	360 mg/m^2 every 4 weeks	£289.97	£302.53	eMIT (2021)
Taxanes							
Cabazitaxel	60 mg	1	£3,696.00	25 mg/m^2 every 3 weeks	£3,199.13	£302.53	BNF (2021)
Docetaxel	15 mg	1	£155.80	75 mg/m^2 every 3 weeks	£155.80	£302.53	BNF (2021)

[a]The cost of £207.79 for administering oral chemotherapies was taken from the NHS national schedule of costs (2019-20) [SB11Z: deliver exclusively oral chemotherapy; outpatient setting] and applied as a one-off cost in the model. The cost for administering drugs via intravenous infusion (£302.53) [SB13Z: deliver more complex parenteral chemotherapy at first attendance; outpatient setting] or subcutaneous infusion (£221.35) [SB12Z: deliver simple parenteral chemotherapy at first attendance; outpatient setting] was taken from the NHS national schedule of costs (2019-20) and applied for each dose. The cost of £1,254.25 for administering a radionuclide therapy was taken from the NHS national schedule of costs (2019-20) [RN52Z: delivery of other radionucleotide therapy; total] and applied per dose of ^{177}Lu vipivotide tetraxetan. The cost of £391.46 for administering cabazitaxel was applied for each dose and includes the cost of an intravenous infusion and one hour of a pharmacist's time.
For cabazitaxel, corticosteroids and G-CSF were excluded to avoid double-counting (already captured with in premedications)
Abbreviations: GM-CSF: granulocyte-macrophage colony-stimulating factor; ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen; BID: twice daily; QD: once daily; SOC: standard of care.
Sources: NICE TA391;[10] NICE TA412;[84] BNF (2021);[128] eMIT (2021);[129] National Schedule of NHS costs (2019-20).[130]

Table 53: Treatment duration and costs for ^{177}Lu vipivotide tetraxetan and cabazitaxel

Treatment	Mean value	Source
Mean exposure (months)		
^{177}Lu vipivotide tetraxetan	6.26	Sartor et al. (2021)
Cabazitaxel	5.06	de Wit et al. (2019)
Cycle length (weeks)		
^{177}Lu vipivotide tetraxetan	6	Sartor et al. (2021)
Cabazitaxel	3	de Wit et al. (2019)
Maximum doses		
^{177}Lu vipivotide tetraxetan	6	Sartor et al. (2021)
Cabazitaxel	10	de Wit et al. (2019)
Total number of doses		
^{177}Lu vipivotide tetraxetan	4.54	Sartor et al. (2021)
Cabazitaxel	7.33	de Wit et al. (2019)
Total acquisition cost		
^{177}Lu vipivotide tetraxetan (PAS price)	£[redacted]	AAA Data on File
Cabazitaxel	£23,460.00	BNF (2021)
Total administration cost		
^{177}Lu vipivotide tetraxetan	£5,690.00	National Schedule of NHS costs (2019-20)
Cabazitaxel	£2,219.00	

Abbreviations: ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen.
Sources: BNF (2021);[128] Sartor et al. (2021);[25] de Wit et al. (2019);[113] National Schedule of NHS costs (2019-20).[130]

Table 54: SOC resource utilisation

Treatment	^{177}Lu vipivotide tetraxetan + SOC	SOC	Overall[a]	Cabazitaxel[b]
Proportion of patients receiving concomitant treatment				
Antiemetics	[redacted]	[redacted]	[redacted]	[redacted]
Antifungals	[redacted]	[redacted]	[redacted]	[redacted]
Bisphosphonates	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]
Erythropoietin stimulating agents	[redacted]	[redacted]	[redacted]	[redacted]
GM-CSF	[redacted]	[redacted]	[redacted]	[redacted]
Opioid analgesics	[redacted]	[redacted]	[redacted]	[redacted]
Mean treatment exposure for concomitant treatments (months)				
Antiemetics	[redacted]	[redacted]	[redacted]	[redacted]
Antifungals	[redacted]	[redacted]	[redacted]	[redacted]
Bisphosphonates	[redacted]	[redacted]	[redacted]	[redacted]

Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]
Erythropoietin stimulating agents	[redacted]	[redacted]	[redacted]	[redacted]
GM-CSF	[redacted]	[redacted]	[redacted]	[redacted]
Opioid analgesics	[redacted]	[redacted]	[redacted]	[redacted]

Concomitant treatments costs were only applied for SOC in the base case.
[a]This represents an average for patients in VISION weighted by treatment arm.
[b]Estimates for cabazitaxel are based upon either the overall resource usage or the resource usage associated with ^{177}Lu vipivotide tetraxetan.
Note: a 1% cut-off (in either arm) was used for inclusion of different concomitant treatment drug classes and a 5% cut-off was used for inclusion of individual drugs within drug classes. percentage resource use of individual drugs were re-weighted to sum to 100%
Abbreviations: ARPI: androgen receptor pathway inhibitor; GM-CSF: granulocyte-macrophage colony-stimulating factor; ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen, SOC: standard of care.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Cabazitaxel Premedication

In line with the approach taken in NICE ID1640 the model included the recommended premedication regimen for all patients in the cabazitaxel treatment arm.[11] The recommended premedication regimen is used to mitigate the risk and severity of hypersensitivity, and should be performed at least 30 minutes prior to each administration of cabazitaxel.[175]

The approach to premedication was deemed to be conservative and potentially underestimate the costs associated with cabazitaxel. The model only considers concomitant medications that were mandated for all patients receiving cabazitaxel in the CARD trial protocol or the SmPC; therefore excluding the use of some medications that could potentially be administered in clinical practice, such as luteinising hormone-releasing hormone and anti-emetics.[11]

Table 55: Resource utilisation for cabazitaxel

Cabazitaxel pre-medications	Proportion	Source
Antihistamine (chlorphenamine)	100.00%	SmPC[175] and CARD[113]
H2 antagonist (ranitidine)	100.00%	
Corticosteroid (dexamethasone)	100.00%	
G-CSF (filgrastim)	100.00%	ESMO/ASCO guidelines[29] and CARD[113]

Abbreviations: ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; G-CSF: granulocyte colony-stimulating factor; SmPC: Summary of product characteristics.

Therapeutic interventions

Therapeutic intervention costs of £739.30 for local external beam radiotherapy (HRG code: SC56Z – Other External Beam Radiotherapy Preparation) and £221.46 for blood transfusions (HRG code: SA44A – Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over) were identified from National Schedule of NHS costs (2019-20) and multiplied by the percentage breakdown and mean number of administrations from VISION.[116, 130] This resulted in a mean therapeutic intervention cost of £247.75 for ^{177}Lu vipivotide tetraxetan, £229.82 for cabazitaxel, and £194.59 for SOC (see Table 56).

Table 56: Therapeutic interventions resource utilisation

Treatment	^{177}Lu vipivotide tetraxetan + SOC	SOC	Overall[a]	Cabazitaxel[b]
Proportion of patients receiving concomitant treatment				
Blood Transfusions	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Mean number of administrations				
Blood Transfusions	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]

[a]This represents an average for patients in VISION weighted by treatment arm.
[b]Estimates for cabazitaxel are based upon either the overall resource usage or the resource usage associated with ^{177}Lu vipivotide tetraxetan from VISION.
Abbreviations: ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen, SOC: standard of care.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116]

Subsequent treatments

The cost of subsequent treatments was applied within the model as a one-off cost at the time of disease progression. The proportion of patients receiving each subsequent treatment differed by initial treatment arm, and was informed by VISION (Table 57).[116]

Table 57: Distribution of subsequent treatments

Subsequent treatment	Proportion of patients receiving subsequent treatment			Treatment cycle length	Cost per treatment cycle (£)	Mean duration of treatment (months)[b]
	^{177}Lu vipivotide tetraxetan + SOC (VISION)	SOC (VISION)	Cabazitaxel[a] (CARD[113] / NICE ID1640[11])			
Cabazitaxel	[redacted]	[redacted]	13.60%	3 weeks	£3,199.13	5.06
Docetaxel	[redacted]	[redacted]	4.70%	3 weeks	£155.80	6.90
Radium-223 dichloride	[redacted]	[redacted]	13.80%	4 weeks	£3,259.67	5.52
Carboplatin	[redacted]	[redacted]	7.22%	4 weeks	£289.97	[redacted]
Radiotherapy (local external beam)[c]	[redacted]	[redacted]	9.63%	NA	£739.30	NA

[a]The proportion of patients in the cabazitaxel arm has been informed by CARD and validated by clinical experts.
[b]With the exception of carboplatin, mean duration of treatment was aligned with NICE ID1640; carboplatin duration was assumed to be equivalent to the mean SOC exposure in VISION.
[c]Patients receiving local external beam radiotherapy received a mean of 1.21 administrations of radiotherapy
Abbreviations: ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen, SOC: standard of care.
Source: Advanced Accelerator Applications Data on File (VISION Clinical Study Report).[116] .

B.3.5.2 Health-state unit costs and resource use

Health state resource use was assumed to be the same as that modelled in the previous NICE appraisal for abiraterone (TA259), and included outpatient, diagnostic procedures, and tests (see Table 59). The associated costs were taken from the National Schedule of NHS costs (2019-20).[130]

In the base case analysis, a total weekly (per cycle) cost of £55.81 was applied in months 1–4 of the model, and a weekly cost of £23.51 was applied in month 5+ of the model for patients in the progression-free health state based on the costs associated with appointments and diagnostic procedures (see Table 58 and Table 59). Patients that had progressed also accrued a weekly cost of £23.51 regardless of the treatment duration. A one-off terminal care cost of £2,299.00 sourced from Abel *et al.* (2013) was applied on death.[176]

Table 58: Costs associated with appointments and diagnostic procedures/ tests

Resource	Unit cost	Source
Outpatient visit (consultant)	£144.61	Service code 800: Clinical Oncology [177]
Outpatient visit (nurse)	£43.46	HRG Code N02AF: District Nurse (Adult) [177]
Computed tomography scan	£120.55	HRG Code RD22Z: Computerised tomography scan of one area, with pre- and post-contrast as an outpatient [177]
Radiographic scan/magnetic resonance imaging	£211.33	HRG Code RD03Z: Magnetic resonance imaging scan of one area, with pre- and post-Contrast as an outpatient [177]
Electrocardiogram	£147.15	HRG Code EY51Z (service code 370): Electrocardiogram monitoring or stress testing as an outpatient (medical oncology) [177]
Ultrasound	£16.75	HRG Code RD41Z: Ultrasound scan with duration of less than 20 minutes, with contrast as an outpatient [177]
Bone scan	£256.29	HRG Code RN16A: Nuclear bone scan of other phases as an adult outpatient [177]
Full blood count	£2.53	HRG Code DAPS05: Haematology [177]
Liver function test	£2.53	HRG Code DAPS05: Haematology [177]
Kidney function test	£2.53	HRG Code DAPS05: Haematology [177]
Prostate-specific antigen	£1.20	HRG Code DAPS05: Haematology [177]

HCRU frequency and proportion of patients requiring resource informed from NICE TA259.[82]
Source: HRG: Health Research Group; National Schedule of NHS costs (2019-20).[130]

Table 59: Healthcare resource utilisation for appointments and diagnostic procedures/ tests

Resource	Units per month	Proportion of patients	Weekly cycle cost (months 1-4)	Weekly cycle cost (months 5+)[a]
Outpatient visit (consultant)	2.00/1.00[b]	50%	£36.15	£18.08
Outpatient visit (nurse)	2.00/1.00[b]	50%	£10.86	£5.43
Computed tomography scan	1.00/0.50[c]	5%	£1.00	£1.00
Radiographic scan/magnetic resonance imaging	0.67	5%	£1.76	£1.76
Electrocardiogram	0.67	5%	£1.23	£1.23
Ultrasound	0.67	5%	£0.14	£0.14
Bone scan	0.67	5%	£2.14	£2.14
Full blood count	0.67	100%	£0.42	£0.42
Liver function test	2.00	100%	£1.27	£1.27
Kidney function test	1.00	100%	£0.63	£0.63
Prostate-specific antigen	0.67	100%	£0.20	£0.20
Total cost	-	-	**£55.81**	**£23.51**

HCRU frequency and proportion of patients requiring resource informed from NICE TA259.[82]
Footnotes: [a]After the 3rd cycle, outpatient visits change to once a month rather than twice. Thus, the associated costs are applied in months 5+ regardless of whether a patient is in the progression-free or progressed health state. [b]Units per month: 2.00 in months 1-4 and 1.00 in months 5+.
Source: NICE TA259.[82]

B.3.5.3 Adverse reaction unit costs and resource use

Adverse events

The mean cost of each AE (per occurrence) in the economic analysis is presented in Table 60.

Table 60: Costs associated with Grade ≥ 3 adverse events

Adverse event	Cost per episode (£)	HRG codes
Anaemia	£672.11	Weighted average of SA04G-L; Iron Deficiency Anaemia with CC Score 0-14+
Back pain	£1,059.74	Weighted average of HD26D-E; Musculoskeletal Signs or Symptoms, with CC Score 0-12+
Bone pain	£1,059.74	Weighted average of HD26D-E; Musculoskeletal Signs or Symptoms, with CC Score 0-12+
Fatigue	£595.43	Weighted average of AA31C-E; Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0-11+ & DZ38Z; Oxygen Assessment and Monitoring
Neutropenia	£1,082.72	Weighted average of SA08G-J; Other Haematological or Splenic Disorders, with CC Score 0-6+

Thrombocytopenia	£770.92	Weighted average of SA12G-K; Thrombocytopenia with CC Score 0-8+
Lymphopenia	£1,082.72	Weighted average of SA08G-J; Other Haematological or Splenic Disorders, with CC Score 0-6+
Leukopenia	£1,082.72	Weighted average of SA08G-J; Other Haematological or Splenic Disorders, with CC Score 0-6+
Urinary tract infection	£1,724.59	Weighted average of LA04H-S; Kidney or Urinary Tract Infections, with & without Interventions, with CC Score 0-12+
Haematuria	£1,274.27	Weighted average of LB38C-H; Unspecified Haematuria with & without Interventions, with CC Score 0-7+
Acute kidney injury	£1,961.20	Weighted average of LA07H-P; Acute Kidney Injury with & without Interventions, with CC Score 12+
Spinal cord compression	£5,341.01	Weighted average of HC28H-M; Spinal Cord Conditions with & without Interventions, with CC Score 7+
Hypertension	£638.81	EB04Z; Hypertension

Abbreviations: CC: clinical coding; HRG: Healthcare Resource Group; NHS: National Health Service.
Source: NICE TA259.[82]; National Schedule of NHS costs (2019-20).[130]

Symptomatic skeletal events

The mean cost of each AE (per occurrence) in the economic analysis is presented in Table 61.

Table 61: Costs associated with SSEs

Event	Cost per episode (£)	HRG codes
Radiation to bone	£739.30	SC56Z; Other External Beam Radiotherapy Preparation
Pathological fracture	£4,168.52	Weighted average of HD39D-H; Pathological Fractures with CC Score 0-11+, non-elective
Surgery to bone	£4,694.93	Weighted average of HD39D-E; Pathological Fractures with CC Score 8-11+, non-elective
Spinal cord compression	£7,094.16	Weighted average of HC28H-M; Spinal Cord Conditions with and without Interventions, non-elective

Abbreviations: CC: clinical coding; HRG: Healthcare Resource Group; NHS: National Health Service.
Source: National Schedule of NHS costs (2019-20).[130]

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

B.3.6.1 Summary of base-case analysis inputs

Summary of variables applied in the cost effectiveness analysis.

Table 62: Summary of variables applied in the cost effectiveness analysis

Variable	Inputs	Reference to section in submission
Model settings		
Discount rate costs, %	3.5	Section B.3.2.2
Discount rate benefits, %	3.5	

Time horizon	Lifetime (10 years)		
Perspective	NHS and PSS		
Patient characteristics			
Weight, kg	[redacted]		Section B.3.3.1
Height, cm	[redacted]		
BSA, m^2	[redacted]		
Hazard ratios			
rPFS			
^{177}Lu vipivotide tetraxetan	1.00		Section B.2.8.6
Cabazitaxel	[redacted] (inverse of [redacted])		
OS			
^{177}Lu vipivotide tetraxetan	1.00		Section B.2.8.6
Cabazitaxel	[redacted] (inverse of [redacted])		
Survival model			
Treatment	**^{177}Lu vipivotide tetraxetan and SOC**	**Cabazitaxel**	
rPFS	Stratified flexible Weibull (2 knots)	HR of [redacted] (NMA) applied to ^{177}Lu vipivotide tetraxetan reference curve	Section B.3.3.2
OS	Stratified flexible Weibull (2 knots)	Kaplan–Meier data form UK RWE	Section B.3.3.3
Time to first SSE	Log-normal	Assumed equivalent to ^{177}Lu vipivotide tetraxetan	Section B.3.3.4
Utility inputs			
Progression free	^{177}Lu vipivotide tetraxetan: [redacted] SOC: [redacted] Cabazitaxel: [redacted]		Section B.3.4
Progressed	^{177}Lu vipivotide tetraxetan: [redacted] SOC: [redacted] Cabazitaxel: [redacted]		
AE decrement	*Various* (from various literature sources) – AE decrements are not applied in the base case analysis		
SSE decrements	Fassler et al. (2011)[166] – SSE decrements are not applied in the base case analysis		
Cost inputs			
Intervention and comparator costs per cycle	**Acquisition cost per treatment cycle**	**Administration cost[a]**	Section B.3.5.1
^{177}Lu vipivotide tetraxetan	List Price: £[redacted] PAS Price: £[redacted]	£1,254.25	
Cabazitaxel	£3,199.13	£302.53	
Components of SOC			

Radium-223 dichloride	£3,259.67	£302.53	Section B.3.5.1
Prochlorperazine	£0.04	£207.79	
Ketoconazole	£0.21	£0.00	
Chlorphenamine	£0.03	£0.00	
Zoledronic acid	£10.31	£302.53	
Dexamethasone	£0.77	£207.79	
Prednisolone	£0.18	£207.79	
Epoetin alpha	£1,667.54	£221.35	
Pegfilgrastim	£411.83	£221.35	
Filgrastim	£173.95	£221.35	
Morphine	£1.28	£207.79	
Oxycodone	£0.15	£207.79	
Carboplatin	£289.97	£302.53	
Tramadol	£0.08	£207.79	
Docetaxel	£155.80	£302.53	
Health state costs per cycle, mean			
Pre-progression (cycle 1–4)	£55.81		Section B.3.5.2
Pre-progressed (cycle 5+) and Progressed (all cycles)	£23.51		
SSE management			
Radiation to bone	£739.30		Section B.3.5.3
Pathological fracture	£4,168.52		
Surgery to bone	£4,694.93		
Spinal cord compression	£7,094.16		
Adverse events	*Various*		Section B.3.5.3

Abbreviations: ^{177}Lu: Lutetium-177; AE: adverse event; BSA: body surface area; OS: overall survival; PAS: patient access scheme; PSMA: prostate-specific membrane antigen; PSS: personal social services; SOC: standard of care.

[a]The cost of £207.79 for administering oral chemotherapies was applied as a one-off cost in the model. The cost for administering drugs via intravenous infusion (£302.53) or subcutaneous infusion (£221.35) was applied for each dose. The cost of £1,254.25 for administering a radionuclide therapy was applied per dose of ^{177}Lu vipivotide tetraxetan.

B.3.6.2 Assumptions

A list of the key assumptions made in the base case economic analysis and their justifications is provided in Table 63. Where appropriate, the exploration of the potential impact of these assumptions via scenario analyses is noted.

Table 63: Key assumptions of the cost effectiveness analysis

Parameter	Assumption	Justification	Addressed in scenario analysis
Efficacy			
OS and rPFS for VISION treatments	Base case survival analyses (OS and rPFS) use unadjusted ITT data. The VISION trial was an open-label study and there is a risk that any imbalance between study arms in the number of patients that withdrew could be associated with one or more prognostic effects.	To address potential bias created by the initial high dropout rate disproportionately affecting the SOC arm, the primary analysis of rPFS was altered to focus on patients prospectively randomised on or after 5th March 2019, when remedial measures were put in place to reduce dropouts. Unlike rPFS, OS data for dropouts could become available through mCRPC registries, so was at reduced risk of bias (see Section B.2.3.3). Survival models fitted to unadjusted OS and rPFS VISION data were presented to clinical experts for validation. Several survival models provided long-term predictions aligning with clinical estimates and external data.	Scenario analyses were explored using data adjusted for informative censoring.
OS for cabazitaxel	In the absence of appropriate RCT data to inform OS for the patient population of relevance to this economic analysis, OS data from the UK real-world database analysis was used to inform OS for patients treated with cabazitaxel.	OS data from the real-world database analysis was deemed the most suitable input for the base case analysis given that this analysis was conducted on UK patients and the baseline characteristics from this real-world database analysis are closely aligned to VISION. As such this analysis provides the most relevant evidence relating to UK patients currently treated with cabazitaxel, who would be considered eligible for treatment with ^{177}Lu vipivotide tetraxetan. Clinicians and HE experts	A scenario analysis has been conducted in which a HR of [redacted] for cabazitaxel vs. ^{177}Lu vipivotide tetraxetan , representing the inverse of the HR presented in the NMA described in Section B.2.8 ([redacted] was applied to the extrapolated OS data from the ^{177}Lu

Parameter	Assumption	Justification	Addressed in scenario analysis
		consulted within an advisory board setting have supported the use of this RWE to inform the base case inputs for OS in the cabazitaxel arm. As the survival probability reaches zero in this RWE for cabazitaxel, there was no requirement to apply survival extrapolations to this data, and the Kaplan–Meier data were used directly in the model.	vipivotide tetraxetan + SOC arm of VISION.
AEs and SSEs			
AE incidence	Grade ≥3 AEs with an incidence of at least 2% incidence for any of the interventions were included.	AE incidence data were taken from the VISION and CARD studies. A 2% cut-off for the inclusion of AEs was considered a reasonable threshold to capture important events that may differ between treatments. The incidence of grade ≥3 bone pain and spinal cord compression was set to zero to avoid double counting these events that captured as SSEs.	The incidence of individual AEs is varied in the DSA.
SSEs for cabazitaxel	The time-to-first SSE model for cabazitaxel was assumed to be equivalent to 177Lu vipivotide tetraxetan + SOC.	The data for time-to-first SSE for cabazitaxel from the CARD trial presented by de Wit et al. (2019) were reconstructed and superimposed on the Kaplan–Meier estimates from VISION. The results from VISION and CARD are very similar and a simplifying assumption was made that SSEs for cabazitaxel and ^{177}Lu vipivotide tetraxetan follow the same distribution. Clinical experts expected SSE rates to be similar for both treatments or higher for cabazitaxel. The SSEs predicted in each model cycle are constrained by OS; therefore, despite using the same distribution, the number of modelled SSEs is lower for cabazitaxel.	An alternative approach using the total probability of first SSE from the VISION and CARD studies was used in a scenario analysis.

Parameter	Assumption	Justification	Addressed in scenario analysis
		The distribution of individual SSEs were taken from the VISION and CARD studies and varied by treatment.	
Utilities			
Health state utilities for VISION treatments	Treatment-specific health-state utilities are used in the base-case analysis.	Utility values based on the EQ-5D-3L were derived from VISION using UK weights. Treatment-specific values were chosen to best reflect HRQoL experienced by patients receiving different treatments. Clinical experts confirmed that differences in HRQoL between treatments are expected. Utility decrements associated with AEs and SSEs were excluded from the base case analysis to avoid double counting.	Scenario analysis was performed using treatment-independent health state utility values. Utility decrements associated with AEs and SSEs were included.
Health state utilities for cabazitaxel	Pre-progression utility value assumed to equal SOC from VISION.	The pre-progression health state utility for cabazitaxel from TA391 was elicited from a UK early access programme study with less heavily pre-treated patients than in VISION and was deemed implausibly high by clinical experts. Therefore, the pre-progression health state utility for cabazitaxel is assumed to align with the value for the SOC treatment arm derived from VISION. The health state utility value from TA391 was used to inform the post-progression health state utility. This value is lower that the ^{177}Lu vipivotide tetraxetan and SOC post-progression values, reflecting the substantial toxicity associated with cabazitaxel treatment which can impact HRQoL even following disease progression, as confirmed by clinical experts.	Scenario analysis was performed using treatment-independent health state utility values. Utility decrements associated with AEs and SSEs were included.

Parameter	Assumption	Justification	Addressed in scenario analysis
Resource use and costs			
Drug acquisition costs	Drug acquisition costs are calculated using the minimum price per unit with no drug wastage.	^{177}Lu vipivotide tetraxetan will be given as a fixed dose of 7.4 GBq and therefore incur no wastage. For other treatments included in the model, drug acquisition costs were calculated based on the price per unit per dose using the cheapest available pack price. This may underestimate the drug acquisition costs and is a conservative assumption.	Not addressed.
Concomitant treatments	^{177}Lu vipivotide tetraxetan is modelled as monotherapy; cabazitaxel is given alongside recommended premedications; SOC concomitant treatment use is based on VISION, adjusted for the UK setting. Drug acquisition and administration costs associated with concomitant treatments were applied within the first model cycle as a simplifying assumption.	In line with the NICE final scope, ^{177}Lu vipivotide tetraxetan is modelled as a monotherapy. This is consistent with the indication and summary of product characteristics which do not require pre-medication or concomitant medication, as submitted to the MHRA for approval. Aligning with the approach taken in NICE ID1640, the model included the recommended premedications alongside cabazitaxel. The model only considers concomitant medications that were mandated for all patients receiving cabazitaxel in the CARD trial protocol or the SmPC. No additional administration costs are assumed. Concomitant treatments associated with SOC were based on the VISION trial. ARPIs were removed to reflect UK practice, based on clinical input.	Scenario analyses were performed including concomitant treatments for ^{177}Lu vipivotide tetraxetan and cabazitaxel based on VISION. ARPIs were removed to reflect UK practice. Corticosteroids and GM-CSF were removed for cabazitaxel to avoid double counting premedications.

Parameter	Assumption	Justification	Addressed in scenario analysis
		The treatment acquisition and administration costs were applied within the first model cycle, assuming no discounting for costs that are incurred beyond the first year. Only bisphosphonates ([redacted] and [redacted] months in the ^{177}Lu vipivotide tetraxetan and SOC arms, respectively) and antifungals ([redacted] months in the ^{177}Lu vipivotide tetraxetan arm) had a mean treatment duration >12 months; this assumption is expected to have a marginal impact on cost-effectiveness for analyses in which concomitant treatment costs are included.	
Subsequent therapies	The proportion of patients receiving subsequent cancer related therapies is based on clinical studies, adjusted for the UK setting. Data for carboplatin and radiotherapy were not available for cabazitaxel; an assumption was made that the proportions equal the overall proportions from VISION. The treatment duration of subsequent therapies were taken from published trials and assumed to be the same regardless of prior treatment.	The proportion of patients receiving subsequent therapies was based on the best available data from the VISION and CARD studies. Bevacizumab, enzalutamide, olaparib and pembrolizumab were removed to reflect UK practice, based on clinical input. Assumptions about the duration of subsequent therapies align with NICE ID1640, where available. The duration of carboplatin and number of radiotherapy administrations were based on VISION. No data were available to model separate treatment durations dependent on prior therapy.	A scenario analysis was performed assuming that the proportion of patients treated with cabazitaxel receiving subsequent carboplatin and radiotherapy equals the VISION SOC population.
Health state costs	Health state resource use was assumed to be the same as that modelled in the NICE appraisal for abiraterone (TA259).	The health state resource use assumptions used in the model were presented to clinical experts for validation. Generally, the assumptions were considered reasonable, but the relevance of some resources were	Health state costs were varied in univariate sensitivity analysis.

Parameter	Assumption	Justification	Addressed in scenario analysis
		questioned. However, there was no consensus and practice varies across the UK. Resource use data from NICE TA259 were used in the base case analysis and unit costs were updated to the latest values from the National Schedule of NHS costs (2019–20).	

Abbreviations: ^{177}Lu: Lutetium-177; AE; adverse event; ARPI: androgen receptor pathway inhibitor; DSA: deterministic sensitivity analysis; HE: health economic; ITT: intention-to-treat; mCRPC: metastatic castration-resistant prostate cancer; MHRA: Medicines and Healthcare products Regulatory Agency; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; OS: overall survival; rPFS: radiographic progression-free survival; RWE: real world evidence; SOC: standard of care; SmPC: summary of product characteristics; SSE: symptomatic skeletal event.

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B.3.7 *Base-case results (pairwise)*

Only pairwise comparisons were explored, since it was assumed that cabazitaxel and SOC are considered in different patient populations (those who are suitable or not suitable for taxanes, respectively). Cabazitaxel is considered to represent the most relevant active comparator for ^{177}Lu vipivotide tetraxetan in clinical practice, and thus forms the focus for the cost-effectiveness analysis. Given the substantial unmet need in clinical practice for patients who are not suitable for treatment with taxanes, results are also presented versus SOC. There are no established criteria for defining suitability for taxane treatment, with previous NICE appraisals acknowledging the challenge of defining an exhaustive list of reasons for a patient being medically unsuitable for taxane treatment.[81] Therefore, in order to maximise sample sizes informing the cost-effectiveness analyses, data for the overall population from VISION were used to inform efficacy in comparisons versus cabazitaxel and SOC.

Table 64 presents pair-wise total costs, life-years gained, QALYs, and incremental costs per QALY for ^{177}Lu vipivotide tetraxetan versus cabazitaxel and versus SOC. Compared with cabazitaxel, ^{177}Lu vipivotide tetraxetan generated [redacted] incremental QALYs and [redacted] incremental life-years gained, and had higher total lifetime costs. The ICER was [redacted] per QALY gained. Compared with SOC, ^{177}Lu vipivotide tetraxetan generated [redacted] incremental QALYs and [redacted] incremental life-years gained, and had higher total lifetime costs. The ICER was [redacted] per QALY gained.

Table 64: Base-case results at ^{177}Lu vipivotide tetraxetan list price (deterministic)

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

Abbreviations: ^{177}Lu: Lutetium-177; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

Table 65 presents total costs, life-years gained, QALYs, and incremental costs per QALY for ^{177}Lu vipivotide tetraxetan (with a PAS discount applied) versus cabazitaxel and versus SOC. Compared with cabazitaxel, ^{177}Lu vipivotide tetraxetan generated [redacted] incremental QALYs and [redacted] incremental life-years gained, and had higher total lifetime costs. The ICER was £49,949 per QALY gained. Compared with SOC, ^{177}Lu vipivotide tetraxetan generated [redacted] incremental QALYs and [redacted] incremental life-years gained, and had higher total lifetime costs. The ICER was £125,687 per QALY gained.

Table 65: Base-case results at ^{177}Lu vipivotide tetraxetan PAS price (deterministic)

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYGa	Inc. QALYs	ICER inc. (£/QALY)
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,949
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	125,687

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

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

A second-order Monte Carlo simulation was run for 5,000 iterations, in order to assess the impact of the uncertainty in costs and outcomes with respect to the model results. For inputs which did not have a standard error value, a variation of ±10% of the mean value was used in the PSA. A full summary of the PSA inputs used is provided in Appendix K.

Results of the probabilistic sensitivity analysis for ^{177}Lu vipivotide tetraxetan versus cabazitaxel and versus SOC are shown in Table 66. For the comparison against cabazitaxel, the probabilistic ICER was [redacted] per QALY gained, compared with [redacted] per QALY gained in the deterministic analysis. For the comparison against SOC, the probabilistic ICER was [redacted] per QALY gained, compared with [redacted] per QALY gained in the deterministic analysis.

Table 66: Base-case results at ^{177}Lu vipivotide tetraxetan list price (probabilistic)

Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER inc. (£/QALY)
^{177}Lu vipivotide tetraxetan vs. cabazitaxel					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
^{177}Lu vipivotide tetraxetan vs. SOC					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Figure 41 presents the cost-effectiveness plane for ^{177}Lu vipivotide tetraxetan compared with cabazitaxel, which shows that 100% of the 5,000 iterations were in the North-East quadrant. This means that ^{177}Lu vipivotide tetraxetan resulted in more QALYs and higher costs compared with cabazitaxel.

Figure 41: Scatter plot of probabilistic results on the cost-effectiveness plane for ^{177}Lu vipivotide tetraxetan at list price (^{177}Lu vipivotide tetraxetan vs. cabazitaxel)

Abbreviations: ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen; QALYs: quality-adjusted life years SOC: standard of care.

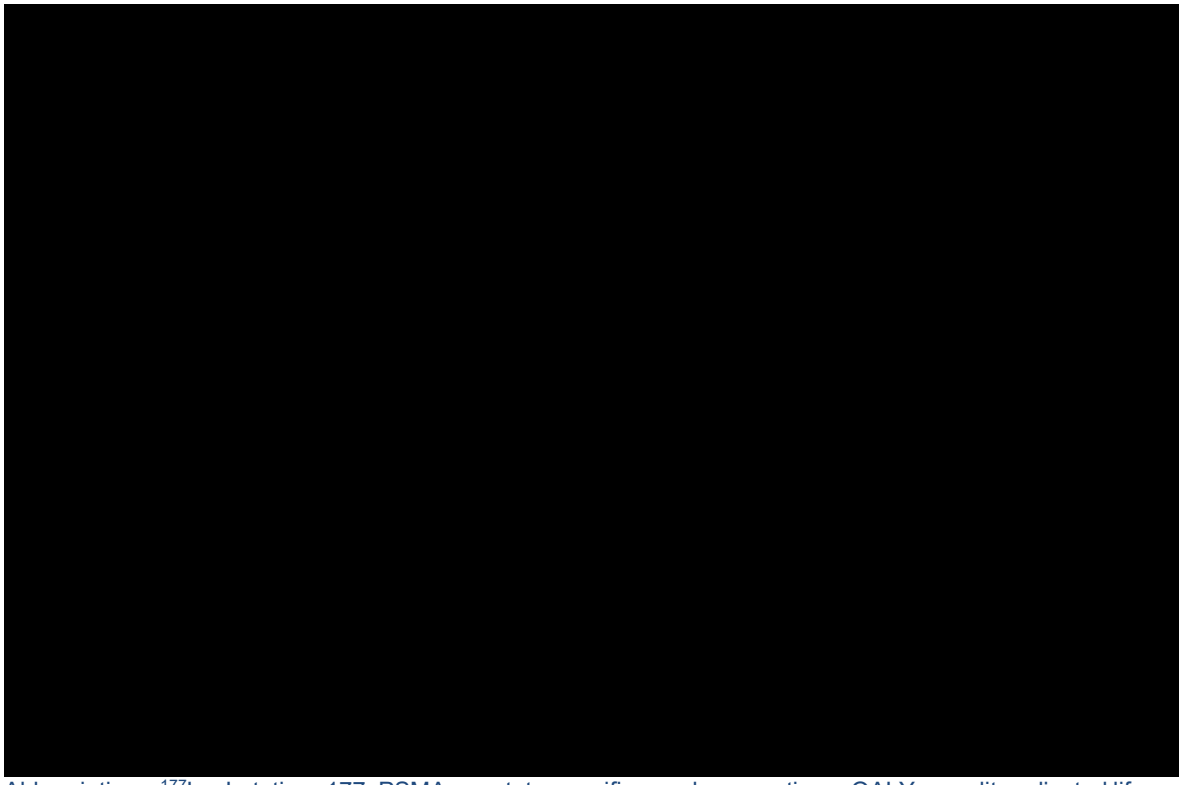
Figure 42 presents the cost-effectiveness plane for ^{177}Lu vipivotide tetraxetan compared with SOC, which shows that 100% of the 5,000 iterations were in the North-East quadrant. This means that ^{177}Lu vipivotide tetraxetan resulted in more QALYs and higher costs compared with SOC.

Figure 42: Scatter plot of probabilistic results on the cost-effectiveness plane for ^{177}Lu vipivotide tetraxetan at list price (^{177}Lu vipivotide tetraxetan vs. SOC)

Abbreviations: ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen; QALYs: quality-adjusted life years SOC: standard of care.

Figure 43 presents the cost-effectiveness acceptability curve for ^{177}Lu vipivotide tetraxetan compared with cabazitaxel. The cost-effectiveness acceptability curve shows that ^{177}Lu vipivotide tetraxetan has a [redacted] probability of being cost-effective compared with cabazitaxel at a willingness-to-pay threshold of £50,000 per QALY.

Figure 43: Cost-effectiveness acceptability curves for ^{177}Lu vipivotide tetraxetan at list price(^{177}Lu vipivotide tetraxetan vs. cabazitaxel)



Abbreviations: ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen; QALYs: quality-adjusted life years SOC: standard of care.

Figure 44 presents the cost-effectiveness acceptability curve for ^{177}Lu vipivotide tetraxetan compared with SOC. The cost-effectiveness acceptability curve shows that ^{177}Lu vipivotide tetraxetan has a [redacted] probability of being cost-effective compared with SOC at a willingness-to-pay threshold of £50,000 per QALY.

Figure 44:Cost-effectiveness acceptability curves for ^{177}Lu vipivotide tetraxetan at list price(^{177}Lu vipivotide tetraxetan vs. SOC)

Abbreviations: ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen; QALYs: quality-adjusted life years SOC: standard of care.

Results of the probabilistic sensitivity analysis for ^{177}Lu vipivotide tetraxetan (with a PAS discount applied) versus cabazitaxel and versus SOC are shown in **Error! Reference source not found.**. For the comparison against cabazitaxel, the probabilistic ICER was £49,525 per QALY gained, compared with £49,949 per QALY gained in the deterministic analysis. For the comparison against SOC, the probabilistic ICER was £126,505 per QALY gained, compared with £125,687 per QALY gained in the deterministic analysis.

Table 67: Base-case results at ^{177}Lu vipivotide tetraxetan PAS price (probabilistic)

Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER inc. (£/QALY)
^{177}Lu vipivotide tetraxetan vs. cabazitaxel					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	49,525
^{177}Lu vipivotide tetraxetan vs. SOC					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
SOC	[redacted]	[redacted]	[redacted]	[redacted]	126,505

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

Error! Reference source not found. Figure 45 presents the cost-effectiveness plane for ^{177}Lu vipivotide tetraxetan (with a PAS discount applied) compared with cabazitaxel, which shows that 100% of the 5,000 iterations were in the North-East quadrant. This means that ^{177}Lu vipivotide tetraxetan resulted in more QALYs and higher costs compared with cabazitaxel.

Figure 45: Scatter plot of probabilistic results on the cost-effectiveness plane for ^{177}Lu vipivotide tetraxetan at PAS price (^{177}Lu vipivotide tetraxetan vs. cabazitaxel)

Abbreviations: ^{177}Lu: Lutetium-177; PAS: patient access scheme; QALYs: quality-adjusted life years; PSA: probabilistic sensitivity analysis; SOC: standard of care.

Error! Reference source not found. resents the cost-effectiveness plane for ^{177}Lu vipivotide tetraxetan (with a PAS discount applied) compared with SOC, which shows that 100% of the 5,000 iterations were in the North-East quadrant. This means that ^{177}Lu vipivotide tetraxetan resulted in more QALYs and higher costs compared with SOC.

Figure 46: Scatter plot of probabilistic results on the cost-effectiveness plane for ^{177}Lu vipivotide tetraxetan at PAS price (^{177}Lu vipivotide tetraxetan vs. SOC)

Abbreviations: 177Lu: Lutetium-177; PAS: patient access scheme; QALYs: quality-adjusted life years; PSA: probabilistic sensitivity analysis; SOC: standard of care.

Error! Reference source not found. presents the cost-effectiveness acceptability curve for ^{177}Lu vipivotide tetraxetan (with a PAS discount applied) compared with cabazitaxel. The cost-effectiveness acceptability curve shows that ^{177}Lu vipivotide tetraxetan has a [redacted]% probability of being cost-effective compared with cabazitaxel at a willingness-to-pay threshold of £50,000 per QALY.

Figure 47: Cost-effectiveness acceptability curves for ^{177}Lu vipivotide tetraxetan at PAS price (^{177}Lu vipivotide tetraxetan vs. cabazitaxel)

Abbreviations: ^{177}Lu: Lutetium-177; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years SOC: standard of care.

Error! Reference source not found. presents the cost-effectiveness acceptability curve for ^{177}Lu vipivotide tetraxetan (with a PAS discount applied) compared with SOC. The cost-effectiveness acceptability curve shows that ^{177}Lu vipivotide tetraxetan has a [redacted]% probability of being cost-effective compared with SOC at a willingness-to-pay threshold of £50,000 per QALY.

Figure 48: Cost-effectiveness acceptability curves for ^{177}Lu vipivotide tetraxetan at PAS price(^{177}Lu vipivotide tetraxetan vs. SOC)

Abbreviations: 177Lu: Lutetium-177; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years SOC: standard of care.

B.3.8.2 Deterministic sensitivity analysis

Error! Reference source not found. presents univariate sensitivity analysis results for ^{177}Lu vipivotide tetraxetan (at list price) versus cabazitaxel. A summary of the DSA inputs is provided in Appendix K. The figure presents the 10 parameters that had the largest impact on the ICER when they were increased or decreased (upper or lower bounds, respectively). The pre-progression utility values for ^{177}Lu vipivotide tetraxetan and cabazitaxel impacted the ICER by over [redacted]. The mean exposure to ^{177}Lu vipivotide tetraxetan also impacted the ICER by over [redacted]. Changes to all other parameters impacted the ICER by less than [redacted]

Figure 49: Tornado plot (ICER) of deterministic sensitivity analysis for ^{177}Lu vipivotide tetraxetan at list price (^{177}Lu vipivotide tetraxetan vs. cabazitaxel)

Abbreviations: ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen; QALYs: quality-adjusted life years SOC: standard of care.

Error! Reference source not found. presents univariate sensitivity analysis results for ^{177}Lu vipivotide tetraxetan (at list price) versus SOC. The figure presents the 10 parameters that had the largest impact on the ICER when they were increased or decreased (upper or lower bounds, respectively). The pre-progression utility value for ^{177}Lu vipivotide tetraxetan impacted the ICER by over [redacted]. The pre-progression utility value for SOC also impacted the ICER by over [redacted]. The mean exposure to ^{177}Lu vipivotide tetraxetan impacted the ICER by over [redacted]. The progressed disease utility values for ^{177}Lu vipivotide tetraxetan and SOC also impacted the ICER by more than [redacted].

Figure 50: Tornado plot (ICER) of deterministic sensitivity analysis for ^{177}Lu vipivotide tetraxetan at list price (^{177}Lu vipivotide tetraxetan vs. SOC)

Abbreviations: ^{177}Lu: Lutetium-177; PSMA: prostate-specific membrane antigen; QALYs: quality-adjusted life years SOC: standard of care.

Error! Reference source not found. presents univariate sensitivity analysis results for ^{177}Lu vipivotide tetraxetan (with a PAS discount applied) versus cabazitaxel. The figure presents the 10 parameters that had the largest impact on the ICER when they were increased or decreased (upper or lower bounds, respectively). The mean exposure to ^{177}Lu vipivotide tetraxetan impacted the ICER by over [redacted] and the mean exposure to cabazitaxel impacted the ICER by over [redacted]. The ^{177}Lu vipivotide tetraxetan pre-progression utility weight also impacted the ICER by over [redacted]. Changes to all other parameters impacted the ICER by less than [redacted].

Figure 51: Tornado plot (ICER) of deterministic sensitivity analysis for ^{177}Lu vipivotide tetraxetan at PAS price (^{177}Lu vipivotide tetraxetan vs. cabazitaxel)

Abbreviations: ^{177}Lu: Lutetium-177; PAS: patient access scheme; PSMA: prostate-specific membrane antigen; QALYs: quality-adjusted life years SOC: standard of care.

Error! Reference source not found. presents univariate sensitivity analysis results for ^{177}Lu vipivotide tetraxetan (with a PAS discount applied) versus SOC. The figure presents the 10 parameters that had the largest impact on the ICER when they were increased or decreased (upper or lower bounds, respectively). The mean exposure to ^{177}Lu vipivotide tetraxetan impacted the ICER by over [redacted]. The ^{177}Lu vipivotide tetraxetan and SOC pre-progression utility weights also impacted the ICER by over [redacted] and [redacted], respectively. The ^{177}Lu vipivotide tetraxetan progressed utility weight impacted the ICER by over [redacted]

Figure 52: Tornado plot (ICER) of deterministic sensitivity analysis for ^{177}Lu vipivotide tetraxetan at PAS price (^{177}Lu vipivotide tetraxetan vs. SOC)

Abbreviations: ^{177}Lu: Lutetium-177; PAS: patient access scheme; PSMA: prostate-specific membrane antigen; QALYs: quality-adjusted life years SOC: standard of care.

B.3.8.3 Scenario analysis

Alternative extrapolation of survival

Radiographic progression-free survival

Survival modelling using long-term extrapolation of parametric functions is subject to uncertainty despite efforts to robustly and transparently provide survival curves that best represent patients in clinical practice. To test the impact of adjusting the survival extrapolations on the cost-effectiveness analysis, a scenario analysis was conducted using the stratified flexible Weibull (1 knot) model, representing the next best fitting curve according to AIC and BIC and also aligning with clinical predictions for ^{177}Lu vipivotide tetraxetan and SOC.

Table 68 and Table 69 presents the results of the scenario analyses exploring use of the Stratified flexible Weibull (1 knot) model for extrapolation of rPFS at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 68: Results from scenario analyses – Impact of utilising the stratified flexible Weibull (1 knot) model for rPFS extrapolation (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; rPFS: radiographic progression free survival; SOC: standard of care.

Table 69: Results from scenario analyses – Impact of utilising the stratified flexible Weibull (1 knot) model for rPFS extrapolation (PAS for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	50,041
SOC	[redacted]	[redacted]	125,986

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; rPFS: radiographic progression free survival; SOC: standard of care.

The VISION trial was an open-label study and patients could withdraw from the study at any time during follow-up. There is a risk that any imbalance between study arms in the number of patients that withdrew from the study could be associated with one or more prognostic effects. This could lead to informative censoring where the patients that withdrew from the study may not be representative of the intent-to-treat (ITT) population. As such, scenario analyses were explored where interval imputation of missing data was conducted to adjust for informative censoring; the stratified flexible 2-knot Weibull model was used in this analysis given it had the lowest AIC and was consistent with ITT base case. Table 70 and Table 71 present the results of the scenario analyses exploring use of interval imputation of missing data for the rPFS analysis in VISION at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 70: Results from scenario analyses – Impact of utilising interval imputation of missing data with flexible 2-knot Weibull model for the rPFS analysis in VISION (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; rPFS: radiographic progression free survival; SOC: standard of care.

Table 71: Results from scenario analyses – Impact of utilising interval imputation of missing data with flexible 2-knot Weibull model for the rPFS analysis in VISION (PAS price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	51,345
SOC	[redacted]	[redacted]	130,639

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; rPFS: radiographic progression free survival; SOC: standard of care.

Overall survival

In order to explore the impact of adjusting the survival extrapolations on the cost-effectiveness analysis, a scenario analysis was conducted using Gamma model, representing the best fitting curve in terms of BIC (and one of the best fitting as per AIC), as well as offering good visual fit, aligning with external data and providing reasonable predictions for ^{177}Lu vipivotide tetraxetan and SOC. Table 72 and Table 73 presents the results of the scenario analyses exploring use of

the Gamma model for extrapolation of OS at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 72: Results from scenario analyses – Impact of utilising the Gamma model for OS extrapolation (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year; SOC: standard of care.

Table 73: Results from scenario analyses – Impact of utilising the Gamma model for OS extrapolation (PAS price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	53,045
SOC	[redacted]	[redacted]	141,267

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; QALY: quality-adjusted life year; SOC: standard of care.

To account for potential uncertainties arising from the utilisation of UK RWE to inform the OS for patients in the cabazitaxel treatment arm, a scenario analysis has been conducted in which a HR of [redacted] for cabazitaxel vs. ^{177}Lu vipivotide tetraxetan , representing the inverse of the HR presented in the NMA described in Section B.2.8 [redacted] was applied to the extrapolated OS data from the ^{177}Lu vipivotide tetraxetan + SOC arm of VISION. Table 74 and Table 75 present the results of the scenario analyses exploring application of the NMA HR to the ^{177}Lu vipivotide tetraxetan + SOC arm of VISION to inform OS at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 74: Results from scenario analyses – Impact of utilising the application of NMA HR to the ^{177}Lu vipivotide tetraxetan + SOC arm of VISION to inform OS (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]

Abbreviations: HR: hazard ratio; ICER: incremental cost-effectiveness ratio; NMA: network meta-analysis; OS: overall survival; QALY: quality-adjusted life year; SOC: standard of care.

Table 75: Results from scenario analyses – Impact of utilising the application of NMA HR to the ^{177}Lu vipivotide tetraxetan + SOC arm of VISION to inform OS (PAS price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	69,796

Abbreviations: HR: hazard ratio; ICER: incremental cost-effectiveness ratio; NMA: network meta-analysis; PAS: patient access scheme; OS: overall survival; QALY: quality-adjusted life year; SOC: standard of care.

As previously mentioned, the VISION trial was an open-label study and patients could withdraw from the study at any time during follow-up. There is a risk that any imbalance between study arms in the number of patients that withdrew from the study could be associated with one or

more prognostic effects. This could lead to informative censoring where the patients that withdrew from the study may not be representative of the intent-to-treat (ITT) population. As such, scenario analyses were explored to where IPCW was conducted to adjust for informative censoring; the stratified flexible 2-knot Weibull model was used in this analysis given it had the lowest AIC and was consistent with ITT base case. Table 76 and Table 77 present the results of the scenario analyses exploring use of IPCW for the OS analysis in VISION at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 76: Results from scenario analyses – Impact of utilising IPCW adjustment with stratified flexible Weibull (2 knots) model to inform OS (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; IPCW: Inverse probability-of-censoring weighting OS: overall survival; QALY: quality-adjusted life year; SOC: standard of care.

Table 77: Results from scenario analyses – Impact of utilising IPCW adjustment with stratified flexible Weibull (2 knots) model to inform OS (PAS price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	61,425
SOC	[redacted]	[redacted]	214,978

Abbreviations: ICER: incremental cost-effectiveness ratio; IPCW: Inverse probability-of-censoring weighting PAS: patient access scheme; OS: overall survival; QALY: quality-adjusted life year; SOC: standard of care.

Alternative SSE modelling

An alternative approach to SSE modelling was explored in which the total incidence of first SSEs was applied. This approach is consistent with the ongoing NICE TA for Olaparib (NICE ID1640).[11] In this approach SSEs are assumed to occur upon disease progression, and costs and utility decrements associated with SSEs are calculated at that timepoint. Table 78 and Table 79 present the results of the scenario analyses exploring application of total incidence of first SSE from VISION and CARD to model SSEs at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 78: Results from scenario analyses – Impact of using total incidence to model SSEs (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SOC: standard of care; SSE: symptomatic skeletal event.

Table 79: Results from scenario analyses – Impact of using total incidence to model SSEs (PAS price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	49,120
SOC	[redacted]	[redacted]	126,877

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; SOC: standard of care; SSE: symptomatic skeletal event.

The base case assumption that the rate of SSEs in the cabazitaxel treatment arm is the same as ^{177}Lu vipivotide tetraxetan could be considered conservative; given SSEs are associated with disease progression. A scenario analysis was therefore conducted where the rate of SSEs for cabazitaxel was assumed to be the same as SOC (data for time-to-first SSE for SOC were used to inform the rate of SSEs for cabazitaxel). Table 80 and Table 81 present the results of the scenario analyses exploring the assumption that the rate of SSEs for patients in the cabazitaxel treatment arm is aligned with patients in the SOC treatment arm at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 80: Results from scenario analyses – Impact of applying SOC SSE rate to cabazitaxel treatment arm (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SOC: standard of care; SSE: symptomatic skeletal event.

Table 81: Results from scenario analyses – Impact of applying SOC SSE rate to cabazitaxel treatment arm (PAS price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	48,976

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS; patient access scheme; QALY: quality-adjusted life year; SOC: standard of care; SSE: symptomatic skeletal event.

Alternative approach to concomitant SOC treatment costs

In the base case analysis no concomitant SOC treatments costs have been considered for ^{177}Lu vipivotide tetraxetan and cabazitaxel, aside from those which are required by the treatment label. A scenario has been explored in which concomitant SOC treatment costs are applied to these patients. Table 82 and Table 83 present the results of the scenario analysis in which concomitant treatments associated with SOC are applied to ^{177}Lu vipivotide tetraxetan and cabazitaxel at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 82: Results from scenario analyses – Impact of applying concomitant SOC treatment costs to the ^{177}Lu vipivotide tetraxetan and cabazitaxel treatment arm (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SOC: standard of care.

Table 83: Results from scenario analyses – Impact of applying concomitant SOC treatment costs to the ^{177}Lu vipivotide tetraxetan and cabazitaxel treatment arm (PAS price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	49,839
SOC	[redacted]	[redacted]	141,574

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; SOC: standard of care.

Alternative approach to therapeutic interventions

In the base case analysis it has been assumed that the use of therapeutic interventions for patients receiving cabazitaxel is aligned to the average for patients in VISION weighted by treatment arm (overall). A scenario analysis has been explored in which patients in the cabazitaxel treatment arm are assumed to have the same therapeutic intervention usage as the SOC treatment arm. Table 84 and Table 85 presents the results of the scenario analysis in which patients in the cabazitaxel treatment arm are assumed to have the same therapeutic intervention usage as the SOC treatment arm at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 84: Results from scenario analyses – Impact of applying SOC therapeutic intervention use to the cabazitaxel treatment arm (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SOC: standard of care.

Table 85: Results from scenario analyses – Impact of applying SOC therapeutic intervention use to the cabazitaxel treatment arm (PAS price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	50,023

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; SOC: standard of care.

Alternative approach to subsequent treatments

In the base case analysis, the proportion of patients receiving subsequent therapies was based on the best available data from the VISION and CARD studies. A scenario analysis was performed assuming that the proportion of patients treated with cabazitaxel receiving subsequent carboplatin and radiotherapy equals the VISION SOC population. Table 86 and Table 87 present the results of the scenario analysis in which the proportion of patients treated with cabazitaxel receiving subsequent carboplatin and radiotherapy equals the VISION SOC population at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 86: Results from scenario analyses – Impact of assuming that proportion of patients treated with cabazitaxel receiving subsequent carboplatin and radiotherapy equals the VISION SOC population (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SOC: standard of care.

Table 87: Results from scenario analyses – Impact of assuming that proportion of patients treated with cabazitaxel receiving subsequent carboplatin and radiotherapy equals the VISION SOC population (PAS price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	49,842

Abbreviations: ICER: incremental cost-effectiveness ratio; PAD: patient access scheme; QALY: quality-adjusted life year; SOC: standard of care.

Alternative approach to health state utility values

The pre-progression health state utility value for cabazitaxel was assumed to be aligned with the value for the SOC treatment arm derived from VISION. This was deemed the most appropriate value as the pre-progression health state utility for cabazitaxel from NICE TA391 was elicited from a UK early access programme study with less heavily pre-treated patients than in VISION and was deemed implausibly high by clinical experts. A scenario has been explored in which patients in the cabazitaxel treatment arm are assumed to have a health state utility value which is aligned to the overall value from VISION. Table 88 and Table 89 present the results of the scenario analysis in which patients in the cabazitaxel treatment arm are assumed to have a health state utility value which is aligned to the overall value from VISION at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 88: Results from scenario analyses – Impact of applying the overall pre-progressed health state utility value from VISION to the cabazitaxel treatment arm (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SOC: standard of care.

Table 89: Results from scenario analyses – Impact of applying the overall pre-progressed health state utility value from VISION to the cabazitaxel treatment arm (PAS price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	54,333

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; SOC: standard of care.

In the base case analysis, treatment-specific health-state utility values were applied. Treatment-specific values were chosen to best reflect HRQoL experienced by patients receiving different

treatments. Clinical experts confirmed that differences in HRQoL between treatments are expected. A scenario analysis was performed using treatment-independent health state utility values derived from VISION. In this scenario analysis, utility decrements associated with AEs and SSEs were included. Table 90 and Table 91 present the results of the scenario analysis in which treatment-independent health state utility values from VISION are used in the model at ^{177}Lu vipivotide tetraxetan list and PAS price, respectively.

Table 90: Results from scenario analyses – Impact of applying treatment-independent health state utility values (list price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SOC: standard of care.

Table 91: Results from scenario analyses – Impact of applying treatment-independent health state utility values (PAS price for ^{177}Lu vipivotide tetraxetan)

Comparator	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cabazitaxel	[redacted]	[redacted]	60,856
SOC	[redacted]	[redacted]	142,398

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; SOC: standard of care.

B.3.8.4 Summary of sensitivity analyses results

The impact of uncertainty and alternative inputs/assumptions in the model were explored as part of sensitivity analyses. The results of the cost-effectiveness analysis were seen to be sensitive to changes in parameters related to the mean exposure to treatment (and resulting treatment costs), choice of survival extrapolation and utility values. The values used in the base case analysis for these parameters are considered to represent the most suitable inputs available.

B.3.9 *Subgroup analysis*

No economic subgroup analyses were conducted as part of this appraisal.

B.3.10 *Validation*

The model methodology was designed to align with NICE's preferred methods. The model was built to align with the NICE reference case, and used an NHS and PSS perspective and discount rates for cost and benefits of 3.5%. The model used a lifetime time horizon in order to capture all costs and QALY gains associated with the interventions.

Economic model verification

Quality-control procedures were undertaken to ensure the programming and physical implementation of the conceptual model was completed correctly. These procedures included verification of all input data with original sources and programming validation. Programming validation included checks of the model results, calculations, data references, model interface,

and Visual Basic for Applications code. In addition, the model was validated by an independent health economist.

Validation of economic model outputs against clinical expert opinion

Clinician opinion was used to conceptualise the economic model wherever possible, in order to ensure face validity of model structure, inputs and assumptions.

B.3.11 *Interpretation and conclusions of economic evidence*

Summary of cost-effectiveness evidence

The cost-effectiveness of ^{177}Lu vipivotide tetraxetan for the treatment of adult patients with PSMA-positive mCRPC) who have been treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes was evaluated in this submission against relevant comparators: cabazitaxel (for those suitable to receive chemotherapy) and SOC. Cabazitaxel is considered to represent the most relevant active comparator for ^{177}Lu vipivotide tetraxetan in clinical practice, and thus forms the focus for the cost-effectiveness analysis. Given the substantial unmet need in clinical practice for patients who are not suitable for treatment with taxanes, results are also presented versus SOC. In the deterministic base-case analysis, ^{177}Lu vipivotide tetraxetan demonstrated substantial incremental QALY gains versus both cabazitaxel and SOC, demonstrating that ^{177}Lu vipivotide tetraxetan offers an important development in treatment for these patients, where there is a significant unmet need.

Compared to cabazitaxel, ^{177}Lu vipivotide tetraxetan was associated with an increased number of life years ([redacted]) and QALYs gained ([redacted]), but also higher total costs ([redacted]). In the base case analysis the ICER for ^{177}Lu vipivotide tetraxetan versus cabazitaxel was [redacted] at ^{177}Lu vipivotide tetraxetan list price and £49,949 at ^{177}Lu vipivotide tetraxetan PAS price. Compared to SOC, ^{177}Lu vipivotide tetraxetan was associated with an increased number of life years ([redacted]) and QALYs gained ([redacted]), but also higher total costs ([redacted]). In the base case analysis the ICER for^{177}Lu vipivotide tetraxetan versus SOC was £[redacted] at ^{177}Lu vipivotide tetraxetan list price and £125,687 at ^{177}Lu vipivotide tetraxetan PAS price.

The PSA demonstrated that ^{177}Lu vipivotide tetraxetan (with the PAS discount applied) has a 51% probability of being cost-effective compared with cabazitaxel at a willingness-to-pay threshold of £50,000 per QALY for end-of-life treatments. The DSA results identified a small number of key influential parameters, with the model being largely robust to uncertainty in the majority of parameters. For the comparison of ^{177}Lu vipivotide tetraxetan (with the PAS discount applied) versus cabazitaxel, the most influential parameters were the mean exposures to ^{177}Lu vipivotide tetraxetan and cabazitaxel and the ^{177}Lu vipivotide tetraxetan pre-progression utility weight.

Scenario analyses were conducted to address sources of uncertainty in the model (rPFS and OS extrapolations, SSEs, concomitant SOC costs, therapeutic interventions, subsequent treatments, utility values). Considering the comparison of ^{177}Lu vipivotide tetraxetan (at PAS price) versus cabazitaxel, across the majority of scenarios there was little variation in the ICER, with the results of the cost-effectiveness analysis most sensitive to the choice of survival extrapolation (particularly OS) and assumptions surrounding utility values. The values used in the base case analysis for these parameters are considered to represent the most suitable inputs available.

Overall, the base case ICER for the comparison versus cabazitaxel falls below a £50,000 per QALY willingness-to-pay threshold and thus ^{177}Lu vipivotide tetraxetan can be considered a cost-effective use of NHS resources in patients who would otherwise be fit to receive chemotherapy. Given the low costs associated with SOC, demonstrating cost-effectiveness versus SOC was extremely challenging; despite being associated with an ICER greater than £50,000 per QALY, results were presented for ^{177}Lu vipivotide tetraxetan versus SOC, given the significant unmet need faced by this patient population, who have extremely poor prognosis and no viable treatment options.

Strengths

The clinical effectiveness evidence presented in this submission has been derived from an SLR of clinical trials investigating the efficacy and safety of a variety of treatment options, including ^{177}Lu vipivotide tetraxetan, for the treatment of mCRPC. Evidence for ^{177}Lu vipivotide tetraxetan is provided by the VISION trial, a Phase III, randomised, controlled trial deemed to be of high quality, which was used as the basis of the submitted MHRA marketing authorisation application.

Results from the VISION trial demonstrated that ^{177}Lu vipivotide tetraxetan was associated with improved rPFS, OS and time free from SSEs compared with SOC. VISION also demonstrated significant extensions to time-to-worsening across three HRQoL questionnaires (BPI-SF, FACT-P, EQ-5D-5L); in addition to extending survival, treatment with ^{177}Lu vipivotide tetraxetan results in patients experiencing less pain and maintaining an overall better HRQoL.[116] RWE for patients receiving cabazitaxel in UK clinical practice, results from TheraP and the NMA provide strong evidence to support the superiority of ^{177}Lu vipivotide tetraxetan compared with cabazitaxel. These results translate into a meaningful increase in QALYs gained for ^{177}Lu vipivotide tetraxetan in both comparisons considered. The model was built to align with the NICE reference case, adopting an NHS and PSS perspective, a lifetime time horizon to capture fully all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5%.

Limitations

A limitation of the evidence base was the lack of a sufficiently robust head-to-head comparison for ^{177}Lu vipivotide tetraxetan compared to the relevant comparator cabazitaxel in patients considered medically suitable for taxane-based chemotherapy. However, three key sources of evidence were available which supported the superiority of ^{177}Lu vipivotide tetraxetan compared with cabazitaxel, in terms of rPFS and OS: TheraP, the NMA and OS data for patients receiving cabazitaxel in UK clinical practice from the real-world database analysis, which were used in base case analysis.

Another key limitation of the VISION trial was its open label design, which led to the initial high dropout rate in the SOC only arm due to disappointment at not receiving ^{177}Lu vipivotide tetraxetan. However, trial site education measures alongside creation of the PFS-FAS allowed for equitable distribution between the interventional and control arms of the trial, with subsequent analysis of rPFS not being affected by bias. Scenario analyses were also explored to test the impact of the cost-effectiveness results when adjusting for informative censoring.

Conclusion

^{177}Lu vipivotide tetraxetan represents an important development in the treatment of patients with mCRPC, providing a more selective and targeted approach with a superior risk-to-benefit ratio, compared to currently available treatments. ^{177}Lu vipivotide tetraxetan has the potential to improve

survival outcomes alongside a more tolerable side-effect profile for patients with mCRPC, a disease which currently carries a very poor prognosis. It is expected that clinicians will use ^{177}Lu vipivotide tetraxetan as an alternative to cabazitaxel in patients eligible for treatment with further chemotherapy following treatment with an ARPI and docetaxel. Based on the evidence presented in this submission, the use of ^{177}Lu vipivotide tetraxetan can be considered a cost-effective use of NHS resources.

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Appendices

Appendix C: Summary of Product Characteristics (SmPC)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

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

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

Appendix J: Exploratory survival analyses

Appendix K: Clinical outcomes and disaggregated results from the model

Appendix L: Checklist of confidential information

Appendix M: Additional data from the VISION trial

Appendix N: Comparator evidence from UK RWE database analysis

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

April 2022

File name	Version	Contains confidential information	Date
ID3480_177Lu vipivotide tetraxetan in mCRPC_Response to ERG CQs_ACIC	Final	Yes	5th May 2022

Section A: Clarification on effectiveness data

Evidence searches

A1. Company's submission (CS), Appendix G.1.1. (Search strategy for published cost-effectiveness studies) and Appendix H.1.1. (Search strategy for identifying health-related quality of life studies). Please provide the following for the search in EconLit: i) host platform ii) coverage dates iii) search strategy if they are not the same as MEDLINE, Embase and Cochrane combined searches.

The EconLit database was searched as part of the economic systematic literature review (SLR), which comprised of two search strategies (See Table 13 and Table 18 of the company submission [CS] appendices) used to identify relevant cost-effectiveness / cost and healthcare resource use, and health related quality of life (HRQoL) evidence, respectively.

In the most recent update to the SLR, the EconLit database <1886 to October 21, 2021> was searched via the OVID platform on 3rd November 2021 using identical search strategies as those presented in the CS appendices for the MEDLINE, Embase and Cochrane combined searches.

Systematic literature review (SLR)

A2. Priority. CS, Table 1. The CS states that "*The SLR did not identify any evidence to support the use of radium-223 in mCRPC in heavily pre-treated (post-ARPI, post-taxane) patients, which limits the ability to conduct an indirect comparison.*" However, contrary to this, radium-233 is included in the network meta-analysis (Figure 11 of the CS). Please explain this discrepancy.

The population of interest for the interventional SLR was adult males (≥18 years old) with pre-treated, progressive metastatic castration resistant prostate cancer (mCRPC) which was selected in order to identify all relevant efficacy and safety data of existing and pipeline treatments for mCRPC. The SLR identified the ALSYMPCA trial, which investigated efficacy the efficacy of radium-223 + standard of care (SOC) vs. placebo + SOC in patients with progressive, symptomatic castration-resistant prostate cancer, with at least two bone metastases on bone scintigraphy, and no known visceral metastases.[1] The ALSYMPCA patient population therefore differed from the VISION study which investigated patients with mCRPC who had progressed after receipt of previous treatment both with one or more androgen receptor pathway inhibitors (ARPIs) and with either one or two taxane chemotherapy regimens.[2] As a result of the inclusion criteria, all patients in VISION had progressed following treatment with at least one ARPI and one taxane based treatment regimen.[2] On the other hand, only 57% of patients in the ALSYMPCA trial had received prior docetaxel.[1] Prior use of ARPIs was not captured in the trial as the trial commenced in 2008, prior to the widespread usage of ARPIs in the treatment of metastatic prostate cancer.[1]

As such, despite meeting the eligibility criteria for the interventional SLR, and being included in the NMA, it should be noted that the patient population in ALSYMPCA likely represents a less progressed and less heavily pre-treated population than patients in VISION. Therefore, the data

from ALSYMPCA are not generalisable to the post-ARPI population considered in the CS, limiting the ability to conduct an indirect comparison. Furthermore, ALSYMPCA did not report on rPFS and as such, indirect comparison was not carried out between ^{177}Lu vipivotide tetraxetan and radium-223 for rPFS (CS Figure 13).

A3. CS, Section B.2.1, page 35. The CS states that "*a SLR was conducted… to specifically identify evidence related to efficacy and safety of 177Lu vipivotide tetraxetan in the patient population relevant to this submission*". The TheraP trial provides direct evidence comparing 177Lu vipivotide tetraxetan to cabazitaxel in patients with metastatic castration-resistant prostate cancer (mCRPC), but was excluded in the SLR because it is a phase II trial. Please provide justification for the inclusion criterion of phase III trials only in the SLR.

The decision to limit the interventional SLR to Phase III studies was made in order to ensure that only the highest quality evidence for the comparators of relevance to the submission was ultimately considered in this submission.

As described in Section B.2.8.1 of the CS, a number of factors mean that TheraP is not suitable to inform efficacy in the economic model despite representing the only direct evidence for the comparison of ^{177}Lu vipivotide tetraxetan and cabazitaxel. Aspects of the trial that limit its role as a source of direct comparison include:

- The version of ^{177}Lu vipivotide tetraxetan used in the trial was 'hospital compounded' (i.e., not company-manufactured) and thus the molecule is potentially subject to variability from company-specific production
- Randomisation was stratified by disease burden (>20 sites vs. ≤20 sites), previous ARPI treatment, and study site. All of these differ from the stratification factors applied to randomisation in VISION
- Patients in the experimental arm of TheraP received a starting dose of 8.5 GBq of ^{177}Lu vipivotide tetraxetan, which reduced by 0.5 GBq per cycle. This differs from the recommended dose of ^{177}Lu vipivotide tetraxetan, which was used in VISION, of 7.4 GBq per cycle
- Patients in the TheraP study received ^{18}F-FDG PET/CT imaging at baseline (in addition to ^{68}Ga PET/CT) in order to exclude patients with FDG-positive disease sites with minimal PSMA expression
- TheraP was primarily designed to evaluate PSA response (defined as a reduction of PSA ≥50% from baseline) and was not powered sufficiently to evaluate secondary endpoints, OS and rPFS relevant to economic modelling.

Therefore, TheraP does not provide sufficiently robust evidence to support a direct head-to-head comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel for the indication of relevance to this submission. Although not suitable for direct comparison, evidence from TheraP may be considered alongside the main body of evidence in the CS as a source of supporting evidence for patients medically suitable for taxane-based chemotherapy, especially with regards to the safety profile of ^{177}Lu vipivotide tetraxetan.

A4. Please explain the disparity concerning the conduct of data extraction for the clinical effectiveness review: data extracted independently by two reviewers, and any discrepancies resolved by a third (CS, Appendix D.1.1, Figure 1) vs. extraction by one reviewer and checking by a second (CS, Appendix D.1.1, page 17).

The company acknowledges the error in Figure 1 of the CS appendices. Data from included studies in the interventional SLR were extracted by one researcher and then independently checked by a second researcher, which is compliant with the Centre for Reviews and Dissemination's (CRD) guidance for undertaking reviews in healthcare.[3]

A5. CS, Appendix D.1.1, page 17. Please clarify the methods and processes followed in the quality assessment of the trials included in the clinical effectiveness review (for example, the number of reviewers, checking of interpretations/judgements).

Similarly to the extraction process, quality assessment in the interventional SLR was performed using the NICE Guide Checklist for RCTs by one researcher and then independently verified by a second researcher.[4]

A6. CS, Section B.2.8.1, page 63. Please clarify why no quality assessment was conducted on the TheraP trial, given its prominence as important supporting evidence. The statement that "TheraP does not provide sufficiently robust evidence" implies a quality rather than eligibility assessment.

As stated in the company response to clarification question A3, TheraP was not included in the SLR on account of it being a Phase II study. Furthermore, there were additional aspects of the trial that limit its role as a source of direct comparison (see Section 2.8.1 of the CS).

However, because TheraP has been utilised in the CS as a source of supporting evidence for patients medically suitable for taxane-based chemotherapy, a quality assessment of TheraP using the NICE Guide Checklist for RCTs is provided in Table 1.

Table 1: Risk of bias for TheraP

Study name	TheraP (NCT03392428)[5]
1. Was randomisation carried out appropriately?	Yes
2. Was the concealment of treatment allocation adequate?	N/A
3. Were the groups similar at the outset of the study in terms of baseline characteristics including all major confounding and prognostic factors?	Yes
4. Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A
5. Were there any unexpected imbalances in drop-outs between groups?	No
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

Trial evidence

A7. Priority. CS, Section B.2.4, page 50. Please detail and justify the judgement that "*Overall, VISION is considered to be of high quality with low risk of bias*", given that the trial was open-label, and the CS states that it was unclear if randomisation was conducted appropriately, and there were unexpected imbalances between groups (Appendix D.1.6, Table 12).

As stated in Section B.2.12 of the CS, the VISION trial is a Phase III, randomised, controlled trial published in the NEJM and deemed to be of high quality, which was used as the basis of the submitted MHRA marketing authorisation application.[2]

Strengths of the VISION trial include the reasonably mature overall survival (OS) data, as well as the trial population, which is broadly consistent with the anticipated licenced indication for ^{177}Lu vipivotide tetraxetan and the population specified in the NICE final scope. The trial baseline characteristics are consistent with the target patient population in the UK, and their generalisability has been validated by clinical experts.[6] The generalisability of VISION is further confirmed by alignment with the baseline characteristics observed in the RWE analysis (see Section B.2.8.1 of the CS).

VISION was designed as an open-label study because ^{177}Lu vipivotide tetraxetan is a radioactive treatment requiring a specific room and process for administration, which means that it is difficult to secure blinding.[7] Blinding was not feasible in VISION because of the radioactive nature of the treatment, and radioactive biological trial samples. Furthermore, it should be noted that the statistical design of VISION was such that, to be declared positive, the study was required to reach statistical significance on either radiographic progression-free survival (rPFS) or OS at the respective allocated alpha level.[8] The alpha level applicable to OS in the final analysis depends upon the earlier rPFS and OS results.[8] Additionally, the planned analysis of rPFS and the analysis of OS were overseen by the Independent Data Monitoring Committee (IDMC), and for that matter, all analyses were overseen fully by an IDMC.[8] Finally, it is important to consider that OS cannot be biased by an open-label design as the event is not defined by an investigator assessment.

The risk of bias assessment conducted as part of the SLR and presented in the CS states that it is 'Not clear' if randomisation was carried out appropriately. This classification refers to the fact that the randomisation method was not specifically described in the main body of the published article, Sartor et al. 2021. However, randomisation is appropriately detailed in the published supplementary appendix for this article and considering this additional detail, this label should be revised to 'Yes', as randomisation was carried out appropriately.

The risk of bias assessment conducted as part of the SLR and presented in the CS states that there were unexpected dropouts between groups in VISION. This label refers to the initial high dropout rate in VISION in the SOC arm, as detailed in the CS Section B.2.3.3. However, when considering the remedial measures introduced on 5th March 2019, this dropout imbalance was appropriately addressed and as such VISION was considered to have balanced treatment arms and this risk of bias label would be revised to 'No'.

A8. Priority. Please explain how withdrawals from the control arm in the preliminary stages of VISION might affect the "*interpretability of radiographic endpoints*" (Sartor 2021) and "*result in bias in the analysis of rPFS*" (CS, Section B.2.3.3, page 42).

As described in Section 2.3.3 of the CS, VISION was originally designed to randomise 750 patients. However, shortly after commencement of the trial, a high, early dropout rate amongst those randomised to SOC became evident (47 of 84; 56%) with the majority of these dropouts withdrawing consent to follow-up.[2] The root cause of this was identified as disappointment among those not randomly assigned to receive ^{177}Lu vipivotide tetraxetan. This dropout meant that rPFS data could not be collected for these patients, unlike for OS data that could become available through mCRPC registries, which consequently could result in bias in the analysis of rPFS. This dropout was unlikely to be random, and thus could impact the balance of prognostic factors and treatment effect modifiers across treatment arms which independently affect rPFS. To address this, remedial measures were put in place on 5th March 2019 following discussions with the FDA, including:

- Investigation site education campaign
- Regular contact with sites to discuss management of patients in the control arm
- Production of a patient information tool to guide pre-screening discussions of expectations
- Limiting reimbursement for patients to discourage long-distance travel

To address potential bias created by the initial high dropout rate disproportionately affecting the SOC arm, the primary analysis of rPFS was altered to focus on patients prospectively randomised on or after 5th March 2019. This patient cohort comprises the progression-free survival full analysis set (PFS-FAS).

Furthermore, at time of the rPFS primary analysis, a planned interim analysis of OS was performed on an ITT basis and included all randomised patients (i.e., including those randomised before 5th March 2019). This planned interim analysis became the final OS analysis, as sufficient events had accrued by this time point for the data to be mature. To achieve these analyses, the total number of patients randomised into the trial was increased from N=750 to N=814. The hazard ratios (HRs) for rPFS from the PFS-FAS and from all randomised patients were very similar, 0.40 (99.2% CI 0.29, 0.57) and 0.43 (99.2% CI 0.32, 0.58), respectively.

A9. Please clarify the reason for the exclusion of the TheraP trial: CS Section B.2.2, page 35 and Section B.2.8.1 page 63 state that it was due to study design but CS, Appendix D.1.2, Table 4 states that it was due to population.

The company acknowledges the inconsistency in the CS. As mentioned in the response to question A3, TheraP was excluded on the basis of study design, owning to the fact that TheraP is a Phase II study.

A10. Priority. Please provide the proportion of patients in the following subgroup for each treatment group in the VISION trial: (1) patients with previous one regime of docetaxel and (2) patients with previous one regime of docetaxel followed by one regime of cabazitaxel. Please provide the Kaplan-Meier plot for each treatment group in these two subgroups for overall

survival (OS), radiographic progression-free survival (rPFS) and time to a first symptomatic skeletal event (SSE).

Please find the requested proportions and Kaplan-Meier plots for each treatment group presented below (Figure 1 – Figure 8).

Previously received docetaxel:

- 534 out of 551 (96.9%) patients in the ^{177}Lu vipivotide tetraxetan arm
- 273 out of 280 (97.5%) patients in the control arm

Previously received cabazitaxel:

- 209 out of 551 (37.9%) patients in the ^{177}Lu vipivotide tetraxetan arm
- 107 out of 280 (38.2%) patients in the control arm

Previously received docetaxel and cabazitaxel:

- [redacted] out of [redacted] ([redacted]%) patients in the ^{177}Lu vipivotide tetraxetan arm
- [redacted] out of [redacted] ([redacted]%) patients in the control arm

Figure 1: Overall survival: Patients who previously received docetaxel (FAS)

Cox Model: Hazard ratio = 0.653 (95% CI = 0.544, 0.783); P < 0.0001
Abbreviations: BSC: best supportive care; BSoC: best standard of care; CI: confidence interval; FAS: full analysis set.

Figure 2: Overall survival: Patients who previously received docetaxel and cabazitaxel (FAS)

Cox Model: Hazard ratio = 0.718 (95% CI = 0.540, 0.956); P = 0.0233
Abbreviations: BSC: best supportive care; BSoC: best standard of care; CI: confidence interval; FAS: full analysis set.

Figure 3: Radiographic progression-free survival: Patients who previously received docetaxel (FAS)

Cox Model: Hazard ratio = 0.466 (95% CI = 0.374, 0.581); P < 0.0001
Abbreviations: BSC: best supportive care; BSoC: best standard of care; CI: confidence interval; FAS: full analysis set.

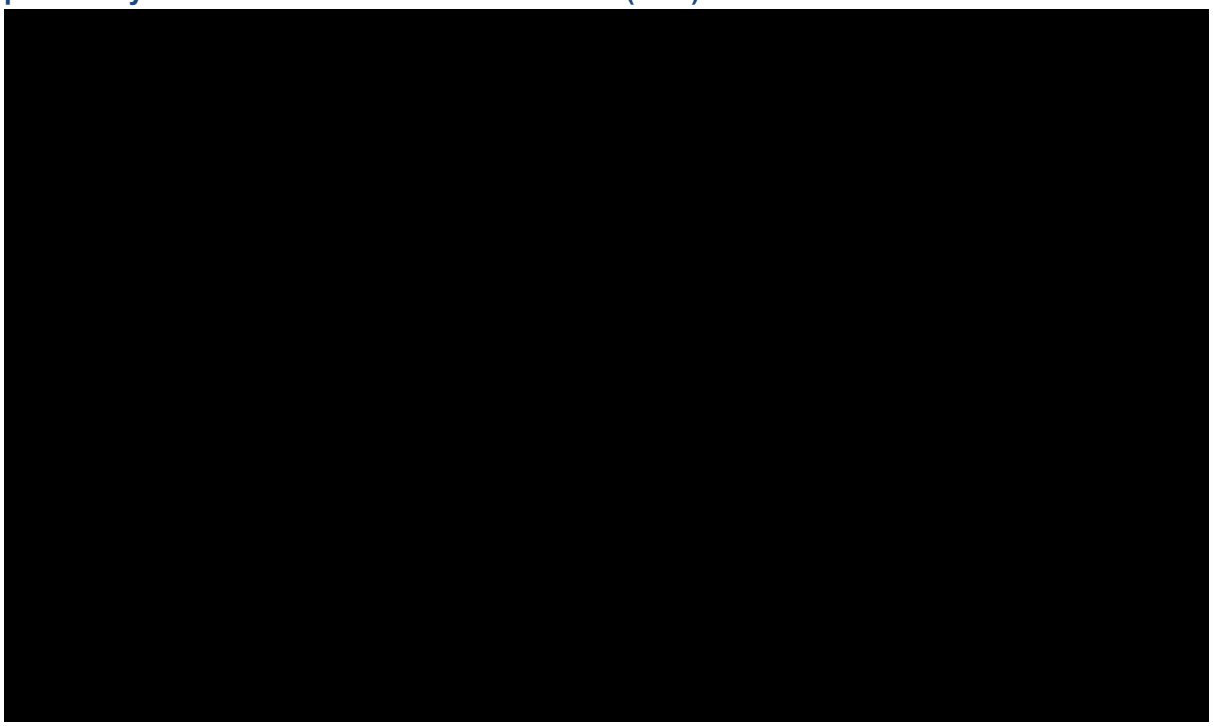
Figure 4: Radiographic progression-free survival: Patients who previously received docetaxel and cabazitaxel (FAS)

Cox Model: Hazard ratio = 0.429 (95% CI = 0.301, 0.612); P < 0.0001
Abbreviations: BSC: best supportive care; BSoC: best standard of care; CI: confidence interval; FAS: full analysis set.

Figure 5: Radiographic progression-free survival: Interval Imputation: Patients who previously received docetaxel (FAS)

Cox Model: Hazard ratio = 0.600 (95% CI = 0.509, 0707); P < 0.0001
Abbreviations: BSC: best supportive care; BSoC: best standard of care; CI: confidence interval; FAS: full analysis set.

Figure 6: Radiographic progression-free survival: Interval Imputation: Patients who previously received docetaxel and cabazitaxel (FAS)



Cox Model: Hazard ratio = 0.663 (95% CI = 0.509, 0.864); P = 0.0023
Abbreviations: BSC: best supportive care; BSoC: best standard of care; CI: confidence interval; FAS: full analysis set.

Figure 7: Time to first symptomatic skeletal event: Patients who previously received docetaxel (FAS)

Cox Model: Hazard ratio = 0.420 (95% CI = 0.283, 0623); P < 0.0001
Abbreviations: BSC: best supportive care; BSoC: best standard of care; CI: confidence interval; FAS: full analysis set.

Figure 8: Time to first symptomatic skeletal event: Patients who previously received docetaxel and cabazitaxel (FAS)

Cox Model: Hazard ratio = 0.205 (95% CI = 0.110, 0.380); P < 0.0001
Abbreviations: BSC: best supportive care; BSoC: best standard of care; CI: confidence interval; FAS: full analysis set.

Network meta-analysis (NMA)

A11. CS, Appendix D.1.3, Table 8. Please clarify the number of lines of prior androgen receptor pathway inhibitor (ARPI) and taxane therapies, as appropriate received by patients in each of the trials included in the NMA.

The number of lines of prior ARPI and taxane therapies are presented below (Table 2).

Table 2: Patient baseline characteristics across studies included in the NMA

Study name	Intervention	n	Age, median	ECOG 0–1	Gleason score ≥8	Race – White (%)	Prior surgery/ procedures	Baseline PSA levels; median (range) ng/mL	Lines of prior ARPI and taxane therapies
TROPIC[9]	Cabazitaxel plus prednisone	378	68	93%	NR	84%	52%	143.9 (51.1–416)	Received previous hormone therapy, but disease had progressed during or after treatment with docetaxel
	Mitoxantrone plus prednisone	377	67	91%	NR	83%	54%	127.5 (44–419)	
COU-AA-301[10]	Abiraterone plus prednisone/prednisolone	797	69	90%	57%	NR	54%	129 (0.4–9,253)	Previous treatment with docetaxel and a maximum of two previous chemotherapies
	Placebo plus prednisone/prednisolone	397	69	89%	59%	NR	49%	138 (0.6–10,110)	
AFFIRM[11]	Enzalutamide	800	69	91%	55%	NR	66%	108 (0.4–11,794)	Previously received docetaxel treatment and a maximum of two chemotherapy sessions
	Placebo	399	69	92%	56%	NR	61%	128 (0.6–19,000)	
	Abiraterone plus prednisone	143	68.2*	92%	72%	NR	27%	NR	Failed previous docetaxel

Sun et al. 2016[12]	Placebo plus prednisone	71	67.7*	93%	77%	NR	28%	NR	chemotherapy
ALYSYMPCA[13]	Radium-223 dichloride plus BSC	352	68	65%	NR	96%	16%	199 (4–6,026)**	Patients were receiving best standard of care and could have previously been treated with docetaxel or not (because they were not healthy enough, they declined, or the drug was unavailable). The case report form did not subdivide patients by reasons for not using docetaxel, nor did it capture the number of previous docetaxel doses or the cumulative docetaxel dose received.
	Placebo plus BSC	174	69	58%	NR	96%	16%	244 (4–14,500)**	
PROfound[14, 15]	Olaparib	256	69	94.90%	73%	NR	NR	68.2 (IQR: 24.1-294.4)	Disease had progressed during treatment with enzalutamide or abiraterone, administered for mCRPC or non-mCRPC or for mHSPC. Previous taxane chemotherapy was allowed.
	Enzalutamide or abiraterone	131	69	96.90%	75%	NR	NR	106.5 (IQR: 37.2-326.6)	
CARD[16]	Cabazitaxel	129	70	95.30%	56.60%	NR	NR	62 (1.1–15,000)	Previously treated with three or more cycles of docetaxel
	Enzalutamide or abiraterone plus prednisone	126	71	94.40%	64.30%	NR	NR	60.5 (1.5–2,868)	

VISION[2]	177Lu vipivotide tetraxetan + SOC	551	70	92.60%	58.80%	88.20%	NR	76.0 (0–6,988)	Prior exposure to taxane and a novel androgen axis inhibitor (NAAI)

*=mean value; **=mcg/L which is equivalent to ng/ml

Abbreviations: BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; NR: not reported; SOC: standard of care

A12. Please explain the disparity between the "*nine studies ultimately included in the NMA*" (CS, page 64) and the statement that, "*Including VISION, the NMA consisted of a total of eight RCTs*" (CS, page 70). Please clarify if the PROfound trial is being treated as one or two studies.

The company acknowledges this inconsistency in the CS. The NMA included a total of eight distinct RCTs, treating the short-term and long-term follow-ups of PROfound as a single study. The PROfound trial (short-term follow-up) and PROfound trial (long-term follow-up) in some cases have been presented separately in the text (for example, Table 18, page 65), but the PROfound trial was not considered as two studies. The disparity between pages 64 and 70 is a typographical error.

A13. CS, Figure 12 and Figure 13 show the pairwise results of comparing 177Lu vipivotide tetraxetan to comparators for OS and rPFS. Please also provide the NMA results for all the pairwise comparisons for OS and rPFS in a table format.

The pairwise comparison results from the NMA are presented below in Table 3 (OS) and Table 4 (rPFS).

Table 3: NMA results, pairwise comparisons (OS)

Comparison	HR	Lower CrI	Upper CrI
177Lu-PSMA-617 + BSC/BSOC vs. ARPI	[redacted]	[redacted]	[redacted]
177Lu-PSMA-617 + BSC/BSOC vs. Mitoxantrone/Placebo + Prednisone	[redacted]	[redacted]	[redacted]
177Lu-PSMA-617 + BSC/BSOC vs. Cabazitaxel + Prednisone	[redacted]	[redacted]	[redacted]
177Lu-PSMA-617 + BSC/BSOC vs. Olaparib	[redacted]	[redacted]	[redacted]
177Lu-PSMA-617 + BSC/BSOC vs. Radium-223 + BSC	[redacted]	[redacted]	[redacted]
ARPI vs. Mitoxantrone/Placebo + Prednisone	[redacted]	[redacted]	[redacted]
ARPI vs. 177Lu-PSMA-617 + BSC/BSOC	[redacted]	[redacted]	[redacted]
ARPI vs. Cabazitaxel + Prednisone	[redacted]	[redacted]	[redacted]
ARPI vs. Olaparib	[redacted]	[redacted]	[redacted]
ARPI vs. Radium-223 + BSC	[redacted]	[redacted]	[redacted]
Mitoxantrone/Placebo + Prednisone vs. ARPI	[redacted]	[redacted]	[redacted]
Mitoxantrone/Placebo + Prednisone vs. 177Lu-PSMA-617 + BSC/BSOC	[redacted]	[redacted]	[redacted]
Mitoxantrone/Placebo + Prednisone vs. Cabazitaxel + Prednisone	[redacted]	[redacted]	[redacted]
Mitoxantrone/Placebo + Prednisone vs. Olaparib	[redacted]	[redacted]	[redacted]
Mitoxantrone/Placebo + Prednisone vs. Radium-223 + BSC	[redacted]	[redacted]	[redacted]
Cabazitaxel + Prednisone vs. ARPI	[redacted]	[redacted]	[redacted]
Cabazitaxel + Prednisone vs. Mitoxantrone/Placebo + Prednisone	[redacted]	[redacted]	[redacted]
Cabazitaxel + Prednisone vs. 177Lu-PSMA-617 + BSC/BSOC	[redacted]	[redacted]	[redacted]
Cabazitaxel + Prednisone vs. Olaparib	[redacted]	[redacted]	[redacted]
Cabazitaxel + Prednisone vs. Radium-223 + BSC	[redacted]	[redacted]	[redacted]
Olaparib vs. ARPI	[redacted]	[redacted]	[redacted]
Olaparib vs. Mitoxantrone/Placebo + Prednisone	[redacted]	[redacted]	[redacted]

Olaparib vs. 177Lu-PSMA-617 + BSC/BSOC	[redacted]	[redacted]	[redacted]
Olaparib vs. Cabazitaxel + Prednisone	[redacted]	[redacted]	[redacted]
Olaparib vs. Radium-223 + BSC	[redacted]	[redacted]	[redacted]
Radium-223 + BSC vs. ARPI	[redacted]	[redacted]	[redacted]
Radium-223 + BSC vs. Mitoxantrone/Placebo + Prednisone	[redacted]	[redacted]	[redacted]
Radium-223 + BSC vs. 177Lu-PSMA-617 + BSC/BSOC	[redacted]	[redacted]	[redacted]
Radium-223 + BSC vs. Cabazitaxel + Prednisone	[redacted]	[redacted]	[redacted]
Radium-223 + BSC vs. Olaparib	[redacted]	[redacted]	[redacted]

Abbreviations: ^{177}Lu: Lutetium-177; ARPI: androgen receptor pathway inhibitor; BSC: best supportive care; BSOC: best standard of care.; CrI: credible interval; HR: hazard ratio.

Table 4: NMA results, pairwise comparisons (rPFS)

Comparison	HR	Lower CrI	Upper CrI
177Lu-PSMA-617 + BSC/BSOC vs. ARPI	[redacted]	[redacted]	[redacted]
177Lu-PSMA-617 + BSC/BSOC vs. Mitoxantrone/Placebo + Prednisone	[redacted]	[redacted]	[redacted]
177Lu-PSMA-617 + BSC/BSOC vs. Cabazitaxel + Prednisone	[redacted]	[redacted]	[redacted]
177Lu-PSMA-617 + BSC/BSOC vs. Olaparib	[redacted]	[redacted]	[redacted]
ARPI vs. Mitoxantrone/Placebo + Prednisone	[redacted]	[redacted]	[redacted]
ARPI vs. 177Lu-PSMA-617 + BSC/BSOC	[redacted]	[redacted]	[redacted]
ARPI vs. Cabazitaxel + Prednisone	[redacted]	[redacted]	[redacted]
ARPI vs. Olaparib	[redacted]	[redacted]	[redacted]
Mitoxantrone/Placebo + Prednisone vs. ARPI	[redacted]	[redacted]	[redacted]
Mitoxantrone/Placebo + Prednisone vs. 177Lu-PSMA-617 + BSC/BSOC	[redacted]	[redacted]	[redacted]
Mitoxantrone/Placebo + Prednisone vs. Cabazitaxel + Prednisone	[redacted]	[redacted]	[redacted]
Mitoxantrone/Placebo + Prednisone vs. Olaparib	[redacted]	[redacted]	[redacted]
Cabazitaxel + Prednisone vs. ARPI	[redacted]	[redacted]	[redacted]
Cabazitaxel + Prednisone vs. Mitoxantrone/Placebo + Prednisone	[redacted]	[redacted]	[redacted]
Cabazitaxel + Prednisone vs. 177Lu-PSMA-617 + BSC/BSOC	[redacted]	[redacted]	[redacted]
Cabazitaxel + Prednisone vs. Olaparib	[redacted]	[redacted]	[redacted]
Olaparib vs. ARPI	[redacted]	[redacted]	[redacted]
Olaparib vs. Mitoxantrone/Placebo + Prednisone	[redacted]	[redacted]	[redacted]
Olaparib vs. 177Lu-PSMA-617 + BSC/BSOC	[redacted]	[redacted]	[redacted]
Olaparib vs. Cabazitaxel + Prednisone	[redacted]	[redacted]	[redacted]

Abbreviations: ^{177}Lu: Lutetium-177; ARPI: androgen receptor pathway inhibitor; BSC: best supportive care; BSOC: best standard of care.; CrI: credible interval; HR: hazard ratio.

A14. Priority. CS, page 66. The CS states that to include the VISION trial in the NMA, a subpopulation of patients in the standard of care (SOC) arm who received an ARPI as a component of SOC at the time of initial randomisation (SOC-ARPI) was used in the NMA. Please comment on the generalisability of the NMA results to SOC without an ARPI.

The VISION study was a global trial, with SOC varying between countries according to physician discretion and local guidelines. The consistency of treatment effect across subgroups such as those receiving or not receiving ARPI as a component of SOC provides confidence in the generalisability of VISION to UK clinical practice, and this generalisability has been confirmed by

UK clinicians in an advisory board setting. In addition, as described in Section B.2.6 of the CS, well-balanced subgroup analyses were also performed to ensure generalisability of results, including the NMA.

As stated in Section 2.8.3, it was necessary to conduct a post-hoc analysis on those patients in the SOC treatment arm that received ARPI as a component of SOC at the time of initial randomisation (the cohort referred to as SOC-ARPI in the CS) in order to connect VISION to the trial network via the common ARPI comparator, and thus facilitate the inclusion of VISION in the NMA. This was considered appropriate to facilitate the connection of the network given that a pre-specified sub-group analysis in the primary outcomes for VISION demonstrated that patients with and without ARPI as a component of SOC had very similar outcomes (CS Figure 8 [p59], CS Figure 9 [p60]; reproduced below (Figure 9 and Figure 10).[2]

It should be noted that the data from the SOC-ARPI arm was only used to facilitate an indirect comparison and thus generate relative efficacy estimates for ^{177}Lu vipivotide tetraxetan versus cabazitaxel, and was not used to inform efficacy of SOC in the cost-effectiveness analysis. Data from the overall SOC cohort from VISION were used to inform the efficacy of SOC in the model.

Figure 9: Subgroup analyses of OS – Forest plot of HR with 95% CI (FAS)

n/N: number of events/number of patients in treatment arm.
Vertical line shows HR for the overall population.
Abbreviations: ^{177}Lu: Lutetium-177; ARPI: androgen receptor pathway inhibition; CI: confidence interval; ECOG: Easter Cooperative Oncology Group; HR: hazard ratio; LDH: lactate dehydrogenase; PFS-FAS: progression-free survival full analysis set; PS: performance score; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Sartor *et al.* (2021).[2]

Figure 10: Subgroup analyses of rPFS per independent central review – forest plot of HR with 95% CI (PFS-FAS)

n/N: number of events/number of patients in treatment arm.
Vertical line shows HR for the overall population.
Abbreviations: ^{177}Lu: Lutetium-177; ARPI: androgen receptor pathway inhibition; CI: confidence interval; ECOG: Easter Cooperative Oncology Group; HR: hazard ratio; LDH: lactate dehydrogenase; PFS-FAS: progression-free survival full analysis set; PS: performance score; PSMA: prostate-specific membrane antigen; SOC: standard of care.
Source: Sartor *et al.* (2021).[2]

A15. Priority. Please provide an updated NMA for OS and rPFS only including the subgroup population with ARPI as part of assigned SoC for both treatment arms in the VISION trial.

Results for the NMA only including the subgroup population with ARPI as part of assigned SOC are presented below. However, as described in CS B.1.3.3 p26, as ARPIs are only permitted to be used a single time in the prostate cancer treatment pathway (in accordance with NICE guidelines). As ARPIs are expected to be used prior to ^{177}Lu vipivotide tetraxetan, these results are not generalisable to UK clinical practice.

^{177}Lu vipivotide tetraxetan plus ARPI demonstrated significant benefit in OS compared against cabazitaxel plus prednisone (Figure 11). Similarly, 177Lu vipivotide tetraxetan showed greater rPFS benefits compared against cabazitaxel plus prednisone (Figure 12), though statistical significance was not reached.

The NMA results show a higher survival benefit as assessed by OS with ^{177}Lu vipivotide tetraxetan + SOC compared with Olaparib (Figure 11). According to rPFS, NMA results show lower survival benefit with ^{177}Lu vipivotide tetraxetan + SOC compared to Olaparib (Figure 12) However, statistical significance was not reached.

Figure 11: NMA results – OS (fixed-effects model) (ARPI as SoC)

Abbreviations: ARPI: androgen receptor pathway inhibitor; BSC: best supportive care; CrI: credible interval; NMA: network meta-analysis; OS: overall survival; SoC: standard of care.

Figure 12: NMA results – rPFS (fixed-effects model) (ARPI as SoC)

Abbreviations: ARPI: androgen receptor pathway inhibitor; BSC: best supportive care; CrI: credible interval; NMA: network meta-analysis; rPFS: radiographic progression-free survival; SoC: standard of care.

Table 5: DIC and residual deviance values for OS using fixed effects and random effects models

Value	Fixed Effects Model	Random Effects Model
DIC	[redacted]	[redacted]
Dbar	[redacted]	[redacted]
pD	[redacted]	[redacted]
gelman.diag	[redacted]	[redacted]

Abbreviations: DIC: deviance information criterion; OS: overall survival.

Table 6: DIC and residual deviance values for rPFS using fixed effects and random effects models

Value	Fixed Effects Model	Random Effects Model
DIC	[redacted]	[redacted]
Dbar	[redacted]	[redacted]
pD	[redacted]	[redacted]
gelman.diag	[redacted]	[redacted]

Abbreviations: DIC: deviance information criterion; rPFS: radiographic progression-free survival.

Figure 13: Trace plots for OS

Abbreviations: OS: overall survival.

Figure 14: Trace plots for rPFS

Abbreviations: DIC: deviance information criterion; rPFS: radiographic progression-free survival.

Figure 15: NMA results – OS (random-effects model) (ARPI as SoC)

Abbreviations: ARPI: androgen receptor pathway inhibitor; BSC: best supportive care; CrI: credible interval; NMA: network meta-analysis; OS: overall survival; SoC: standard of care.

Figure 16: NMA results – rPFS (random-effects model) (ARPI as SoC)

Abbreviations: ARPI: androgen receptor pathway inhibitor; BSC: best supportive care; CrI: credible interval; NMA: network meta-analysis; rPFS: radiographic progression-free survival; SoC: standard of care.

A16. Priority. Please provide justification for assuming constant hazard ratios for OS and rPFS in the NMA.

Commonly, the comparative efficacy of one drug versus another (or placebo) on the endpoint of time from randomisation to imaging-based progression or death (rPFS) or OS is measured in terms of the difference in median survival and the HR. The estimate of drug effect on rPFS using the HR requires that the proportional hazards assumption is valid over the duration of the study. Where this assumption is violated, the HR effect may not provide an adequate estimate of drug effect because the result is dependent on follow-up time (e.g., with longer or shorter follow-up, the HR will change). Further, the application of this HR in an economic model can lead to biased estimates by potentially over- or under-predicting future outcomes depending on whether the HR over or under-predicts health gains at the tail of the survival curve.

For any endpoint to follow the proportional hazards (PH) assumption, the ratio of cumulative hazards for OS/rPFS must be approximately constant and hence proportional over time. The crossing of hazard curves or the increasing or decreasing separation of curves over time is evidence that this assumption has been violated. We tested the PH assumption by regenerating individual patient data from published Kaplan-Meier curves as per Guyot et al. (2012).[17]

The -log(-log(S(t))) vs log(t) curves were derived from the empirical survival functions for each study contributing to the OS and rPFS network. These analyses provided an early assessment of non-proportionality (indicated by non-parallel -log(-log) curves or crossing survival curves. Additionally, statistical testing was performed using Harrell and Grambsch-Therneau's tests (Global Test for PH assumption) as per A. Campbell and C.M. Anderson (2011).[18]

The details related to the PH assumption tests for OS (n=7) and rPFS (n-=6) Kaplan Meier curves are provided in Table 7 below.

Table 7: Details of the proportional hazards assumption tests by publication/trial name

Publication/Trial name	Outcome	Global test Ch-sq., p values	Ph assumption true (Yes/No) by log-log plot	Log-log plot
PSMA-617-01 (VISION)	OS	2.21, p=0.1367	Yes	Study 1
De 2011 (TROPIC)	OS	0.87, p=0.3500	-	Study 2
Hoskin 2014 (ALSYMPCA)	OS	0.35, p=0.5532	Yes	Study 3
De Wit 2019 (CARD)	OS	0.05, p=0.8164	Yes	Study 4
De Bono 2020 (PROfound)	OS	0.00, p=0.9657	Yes	Study 5
Scher 2012 (AFFIRM)	OS	0.83, p=0.3612	-	Study 6
Fizazi 2012 (COU-AA-301)	OS	8.03, p=0.0046	No	Study 7
Sun 2016	OS	1.13, p=0.2884	Yes	Study 8
PSMA-617-01 (VISION)	rPFS	9.49, p=0.0021	No	Study 1
De 2011 (TROPIC)	rPFS	9.49, p=0.0021	No	Study 2
De Wit 2019 (CARD)	rPFS	3.20, p=0.0735	Yes	Study 4
De Bono 2020 (PROfound)	rPFS	6.28, p=0.0122	No	Study 5
Scher 2012 (AFFIRM)	rPFS	3.27, p=0.0706	Yes	Study 6
Fizazi 2012 (COU-AA-301)	rPFS	0.05, p=0.8232	Yes	Study 7

Abbreviations: OS: overall survival; rPFS: radiographic progression-free survival.

As per Grambsch-Therneau's test, the output is non-significant for all the studies except one reporting OS, indicating lack of evidence to contradict the proportionality assumption. For studies reporting rPFS, the output is non-significant for three studies, showing no evidence to contradict the proportionality assumption and significant for three studies showing violation of the proportionality assumption.

A17. Priority. Please provide an assessment of inconsistency checking for OS and rPFS using the node-splitting analysis. Please also provide an explanation for potential inconsistencies if any were found.

As per NICE TSD 4: "Inconsistency in networks of evidence based on randomised controlled trials", the choice of method should be guided by the evidence structure. Since the network included only one closed loop with one study for each pairwise comparison, we did a simple comparison of direct vs indirect results. We chose a contrast-based NMA, and, since the framework we used was not Bayesian, node-splitting was not the better technique.

As seen in Figure 17, the horizontal tips of the diamonds cross the vertical null effect line, showing that the combined result is potentially not statistically significant - if the 95% confidence interval contains the null value, we cannot be certain that the null value (trials are consistent) is not the true value.

Figure 17: Inconsistency plot for OS

Abbreviations: ARPI: androgen receptor pathway inhibitor; CI: confidence interval; HR: hazard ratio; OS: overall survival.

Figure 18: Inconsistency plot for rPFS

Abbreviations: ARPI: androgen receptor pathway inhibitor; CI: confidence interval; HR: hazard ratio; rPFS: radiographic progression-free survival.

A18. Priority. CS, page 69. The CS states that the key limitation of the NMA was inter-trial heterogeneity between 177Lu vipivotide tetraxetan and comparator populations in terms of disease severity. Please provide justification for why population-adjusted indirect comparisons

such as matching-adjusted indirect comparison and simulated treatment comparison were not conducted to adjust for this population difference.

A feasibility assessment for a population-adjusted indirect comparison between ^{177}Lu and comparator population was performed. Substantial heterogeneity was identified between CARD and VISION in terms of trial inclusion/exclusion criteria, and patient baseline demographic and clinical characteristics. For example, the key differences across the included trials were not only disease severity, but also prior treatment status, prostate-specific membrane antigen (PSMA) positivity, and median PSA levels. These differences would not have been corrected in any population-adjusted indirect treatment comparison and would have potentially had a confounding effect on the results, and contravened conventional effect modifier assumptions. In addition, NICE DSU Technical Support Document 18: "Methods for population-adjusted indirect comparisons in submissions to NICE", highlighted the need for caution with using anchored MAIC and STC methods, which, as currently practiced, represent a "major departure from the models that are usually used", indicating a preference for the conventional NMA method where possible as it offers more data points for the data synthesis then MAIC.

Furthermore, discussions with NICE as part of early scientific advice received prior to the appraisal of ^{177}Lu vipivotide tetraxetan indicated that a simple approach to indirect treatment comparison was most appropriate given the limited availability of data in the network of evidence. This approach was further endorsed by expert opinion received as part of an advisory board supporting the company submission.

A19. Please clarify what software was used to conduct the NMAs.

This analysis was performed using NMA implemented in R Shiny platform using coding by Dias et al. The NMA used Markov Chain Monte Carlo (MCMC) techniques using the statistical package WinBUGS.

A20. Priority. Please provide all relevant data used to perform the NMAs, sufficient to permit the ERG to check and/or reanalyse the NMAs, including:

a. All data files (in the format ready to be loaded in software) and the treatment coding (e.g., 1 for placebo, etc)

b. All BUGS "initial value" files

c. Tables of all trial data used in the NMAs

All relevant data used to perform the NMAs have been provided in the reference pack accompanying this response.

Real-world evidence (RWE)

A21. Please clarify how many patients in the RWE cabazitaxel cohort received cabazitaxel as the second line treatment in the metastatic castration-resistant prostate cancer setting.

Due to the nature of data collected in the RWE analysis, interpretation of 'lines' of therapy for mCRPC patients is challenging due to uncertainty in the timing of therapy receipt and the

evolving nature of the prostate cancer treatment pathway during the timeframe of the RWE analysis. However, the RWE does indicate that of the whole mCRPC cohort (n=[redacted]), [redacted] ([redacted]%) of patients received both an ARPI and a taxane. Of the cabazitaxel cohort (n=[redacted]), [redacted] ([redacted]%) had documented prior receipt of both an ARPI and docetaxel.

A22. CS, page 61. The ECOG data were available for [redacted] patients in total, with [redacted] patients of unknown ECOG status. Please clarify how a patient with missing ECOG status was dealt with when calculating the percentage for ECOG <=1.

The RWE cabazitaxel cohort was composed of [redacted] patients. Of these, ECOG scores were available for [redacted]. From patients with available ECOG scores, [redacted] ([redacted]%) were ECOG ≤1. The [redacted] patients with missing ECOG scores were not included in this calculation for the percentage of patients with ECOG ≤1.

Section B: Clarification on cost-effectiveness data

B1. Priority. The CS states in Table 1 that radium-223 is not considered a relevant comparator because it is indicated only in patients with symptomatic bone metastases but without any visceral metastases, limiting comparability with 177Lu vipivotide tetraxetan, which is intended for use regardless of metastasis site. However, it is unclear why radium-233 would not be a relevant comparator in those patients who meet the licensed indication for 177Lu vipivotide tetraxetan and who have bone metastases without visceral metastases. It is also stated in Table 1 that the literature review did not identify any evidence to support the use of radium-223 in heavily pre-treated (post-ARPI, post-taxane) mCRPC patients, which limits the ability to conduct an indirect comparison. However, contrary to this, radium-233 is included in the NMA (Figure 11 of the CS). Please provide an economic model comparing the cost-effectiveness of 177Lu vipivotide tetraxetan to radium-233 in the subgroup of patients with bone metastases but without visceral metastases.

As mentioned in Table 1 of the CS, radium-223 is not considered a relevant comparator in this appraisal as it is indicated in patients with symptomatic bone metastases but without any visceral metastases, limiting comparability with ^{177}Lu vipivotide tetraxetan, which is intended for use regardless of metastasis site. Radium-223 also has different mechanism of action compared with ^{177}Lu vipivotide tetraxetan, which offers targeted delivery of radiotherapy to the primary tumour and PSMA-positive metastases, where radium-223 mimics calcium and delivers radiotherapy preferentially at sites of bone metastases which relies on bone metabolism.[19] As reflected in NICE's recommendation for treating symptomatic PC bone metastases,[20] radium-223's primary action is to palliate bone pain rather than extend life or delay progression of disease.

As stated in the company response to clarification question A.2, the interventional SLR did not identify any evidence to support the use of radium-223 in mCRPC in heavily pre-treated (post-ARPI, post-taxane) patient and the ALSYMPCA trial included in the NMA had a patient population that differed from the VISION study and represented a less heavily pre-treated population. Therefore, the data from ALSYMPCA are not generalisable to the post-ARPI population considered in the CS, limiting the ability to conduct a comparison between ^{177}Lu vipivotide tetraxetan and radium-223. Furthermore, ALSYMPCA did not report on rPFS, further

limiting the comparability between ^{177}Lu vipivotide tetraxetan and radium-223. Radium-223 was only included in the NMA to align with its inclusion in the NICE final scope.

The company has conducted further consultation with a clinical expert which has confirmed that only a minority of patients would receive radium-223 in the post-ARPI and taxane setting. In the RWE cohort, of the [redacted] patients who received both an ARPI and a taxane, [redacted] ([redacted]%) went on to receive radium-223. In this minority of patients for whom radium-223 may represent a relevant comparator for ^{177}Lu vipivotide tetraxetan, it has not been feasible to provide a robust comparison due to the limited data for radium-223 in this setting, and as such it has not been possible to provide an economic analysis for a comparison of ^{177}Lu vipivotide tetraxetan and radium-223.

B2. CS, pages 94 and 95. The CS states that data from the 177Lu vipivotide tetraxetan plus SOC and SOC arms of the VISION trial were used to inform the inputs in the economic analysis. Please clarify if the data used to inform the inputs for the 177Lu vipivotide tetraxetan and SOC treatment groups included patients who have received ARPI as part of the concomitant SOC.

The Company confirm that the data used to inform the base case inputs for the ^{177}Lu vipivotide tetraxetan and SOC treatment groups within the economic model included patients who have received ARPI as part of the concomitant SOC.

As described in question A14, a pre-specified sub-group analysis of patients who did and did not receive concomitant ARPI (as a component of SOC) in VISION has demonstrated that similar outcomes were achieved by patients regardless of concomitant ARPI usage (Figure 9 and Figure 10). Furthermore, the generalisability of VISION to UK clinical practice has been confirmed by UK clinicians in an advisory board setting. As such, the company deemed it most appropriate to use the survival data for the total VISION population to maximise the sample size informing the economic model inputs.

B3. CS, Table 1 and page 91. In page 91, the CS states that patients not medically suitable for taxanes represent only a small proportion of the overall patients eligible for 177Lu vipivotide tetraxetan. However, CS Table 1 provides an estimate of 50% of mCRPC patients being identified ineligible for taxane-based chemotherapy. Please clarify what proportion of patients would be expected to be in the third subgroup of the target population (as defined in the subgroup row of Table 1 and in Figure 2 of the CS) for this appraisal (unsuitable for taxanes and eligible for 177Lu vipivotide tetraxetan), and why some of the unsuitable for taxanes patients would not be eligible for 177Lu vipivotide tetraxetan.

The estimates for the patient populations eligible for treatment with ^{177}Lu vipivotide tetraxetan are presented in the Budget Impact Analysis, Table 2. This table is re-produced below for clarity.

Table 8: Data and assumptions used to calculate the eligible patient population

#		Input	Value (2023)	Source/ Assumptions
1	Incident prostate cancer patients	-	50,142	AAA Data on File
2	Proportion mCRPC	(2) * 15%	7,521	Kirby et al. (2011)

3	PSMA-positive in the mCRPC population	(3) * 86.6%	6,513	Proportion of screened patients meeting criteria for PSMA-positivity in VISION
4	Proportion tested for PSMA positivity	(4) * 85%	5,536	AAA Data on File
5	Received ARPI	(5) * 84%	4,651	AAA Data on File
6	Received ARPI and taxane therapy	(5) * 50%	2,323	NICE (TA391)[21]
7	Eligible for further chemotherapy	(6) * 55%	**1,277**	NICE (TA391)[21]
8	Medically unsuitable for cabazitaxel (following prior docetaxel)	(6) * 45%	1,045	NICE (TA391)[21]
9	Eligible for ^{177}Lu-PSMA-617	(8) * 60%	**627**	Clinical expert feedback
10	Medically unsuitable for taxanes (no prior taxanes)	(5) * 50%	2,323	NICE (TA391)[21]
11	Eligible for ^{177}Lu-PSMA-617	(10) * 60%	**1,394**	Clinical expert feedback
12	**Total**	**(7) + (9) + (11)**	**3,298**	Calculation

[a] This is the projected total population for 2023 and changes with each model year.

Patients medically unsuitable for taxanes having not received prior taxanes, but who are eligible for ^{177}Lu vipivotide tetraxetan (the third subgroup of the target population, as defined in the subgroup row of Table 1 and in Figure 2 of the CS) are expected to represent ~42% of the total patient population eligible for ^{177}Lu vipivotide tetraxetan. Reasons for patients unsuitable for taxanes also being ineligible for ^{177}Lu vipivotide tetraxetan may include inadequate renal/hepatic/bone marrow function, clinical frailty, pre-existing comorbidities, or lack of social support such that the treating physician deems the risks of treatment to outweigh potential benefits.

B4. Priority. Please provide evidence to support the statement in the CS, page 95: "*(...)there is no reason that the efficacy and safety of 177Lu vipivotide tetraxetan would be significantly different in patients who have not previously received taxanes compared to patients who have previously received taxanes. Thus, the clinical efficacy and safety data from VISION is considered to be generalisable to those patients who are medically unsuitable for taxanes*." A similar statement is provided also in page 32 of the CS.

Given the absence of data for patients medically unsuitable for taxanes, the company has sought further input from a clinical expert to clarify this statement. The clinical expert advised that patients who previously received taxane-based chemotherapy (the VISION trial population) are possibly more likely to experience fatigue, myelosuppression, and dry mouth with ^{177}Lu vipivotide tetraxetan than patients who have not received prior taxane therapy. Thus, the VISION trial data potentially overestimates the adverse event burden of patients receiving ^{177}Lu vipivotide tetraxetan who have not received prior taxanes. The clinical expert did not provide any reason to believe a differential efficacy for ^{177}Lu vipivotide tetraxetan between patients who have and have not received prior taxanes. Furthermore, eligibility for taxanes is not based on ability to respond to treatment, but rather on risk of severe side effects limiting treatment tolerability or outweighing any potential benefits of treatment. There is therefore no reason to believe that the efficacy of ^{177}Lu vipivotide tetraxetan should differ in patients suitable or unsuitable for taxanes. Clinical expert feedback highlighted that, if anything, efficacy may be improved in those patients who have not had prior treatment with a taxane.

B5. CS, Table 42, page 126. Please clarify how the SSE rate for cabazitaxel was calculated using digitised data from the CARD trial. Please also clarify how the SSE rate for 177Lu vipivotide tetraxetan and SOC were calculated.

Table 42 in the CS presents the incidence of SSEs based on time-to-first SSE Kaplan-Meier data from the VISION and CARD trials. The incidences were calculated as one minus the last available value from the time-to-first SSE Kaplan-Meier curves. In VISION (see Figure 33 in the CS), the time-to-first SSE Kaplan-Meier curve for ^{177}Lu vipivotide tetraxetan reached 62.09% at 31.41 months and for SOC reached 66.86% at 27.07 months. The digitised time-to-first SSE Kaplan-Meier curve for cabazitaxel from the CARD trial (see Figure 40 in the CS) reached 63.52% at 30.05 months. The data and calculations are included on the "KM_SSE" worksheet in the submitted model.

B6. CS, Table 54 (footnote b) and page 133. Page 133 and footnote b of Table 54 state that estimates for SOC resource usage for patients receiving cabazitaxel in the scenario analyses were based on either a weighted average for the treatment arms of VISION ('Overall' SOC usage utilisation) or the resource usage associated with 177Lu vipivotide tetraxetan. However, Table 54 shows that the proportion of patients receiving each type of concomitant treatments is assumed to be equal to the overall usage, whilst the mean duration of each treatment is assumed to be equal to the 177Lu vipivotide tetraxetan treatment group. In addition, the proportion of patients receiving corticosteroids and GM-CSF are assumed to be zero. Please clarify these differences.

The submitted model includes options allowing the user to select different assumptions for cabazitaxel SOC resource usage and treatment exposure. In the scenario analyses including SOC concomitant treatments for ^{177}Lu vipivotide tetraxetan and cabazitaxel (presented in CS Table 82 and Table 83), resource usage and treatment exposure for cabazitaxel are assumed equal to the 'Overall' VISION data. The mean SOC concomitant treatment exposure data for cabazitaxel presented in CS Table 54 are incorrect.

The mean SOC concomitant treatment usage data for cabazitaxel presented in CS Table 54 are correct. The proportion of patients receiving concomitant corticosteroids and GM-CSF are assumed to be zero to avoid double-counting with cabazitaxel premedications, presented in CS Table 55.

B7. CS, Table 63. It is stated that ARPIs were removed from concomitant treatments to reflect UK practice, based on clinical input. However, use of ARPIs was allowed in the VISION study and these may have contributed to clinical outcomes reported. Please provide a scenario analysis in which ARPIs are included within the cost of concomitant treatments for both SOC and 177Lu vipivotide tetraxetan treatment groups.

In the UK, sequential use of ARPIs is not recommended; ARPIs can be used only once in the PC treatment pathway.[22] The CS covers the technology's full anticipated marketing authorisation for 177Lu vipivotide tetraxetan "for the treatment of adult patients with PSMA-positive, mCRPC who have been treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes". Thus, in line with UK clinical practice, patients are not anticipated to receive an

ARPI concurrently with ^{177}Lu vipivotide tetraxetan, as they would have received an ARPI prior to commencing ^{177}Lu vipivotide tetraxetan.

The VISION trial had prespecified subgroups for patients who did or did not have ARPI included as part of their SOC. These results are presented in the CS, Section B.2.6, and are reproduced in this document (Figure 9 and Figure 10). This subgroup analysis demonstrated that concurrent ARPI treatment made no significant difference in the efficacy of ^{177}Lu vipivotide tetraxetan. As such, the company do not feel that the scenario analysis proposed by the ERG is appropriate, as it would not reflect anticipated UK clinical practice.

Survival extrapolation

B8. Priority. Please clarify the following methodology used in the survival extrapolation:

a. Please clarify what software was used to conduct the survival analysis.

All survival analyses were conducted in R (R Foundation for Statistical Computing; Vienna, Austria) using the following functions and packages:

- Standard parametric models were fitted using the flexsurvreg procedure in the flexsurv package[23]
- Spline-based models were fitted using the flexsurvspline procedure in the flexsurv package[23]

b. Please clarify if the stratified modelling approach only includes the treatment group as a covariate and fits a parametric survival distribution to the two treatment groups in a combined way.

All the stratified models allowed all parameters to vary by treatment. They were equivalent to fitting separate models by treatment but allowed models to be compared using AIC and BIC statistics. An example with a stratified Weibull model is given below:

flexsurvreg(Surv(Month, Event) ~ Treatment, anc = list(shape = ~ Treatment), dist="weibull", data=Survival.data)

c. When using the unstratified modelling approach, please clarify whether the same parametric distribution is fitted independently to the two treatment groups.

An unstratified model only allows the intercept parameter to vary by treatment. An example with a Weibull model is given below:

flexsurvreg(Surv(Month, Event) ~ Treatment , dist="weibull", data=Survival.data)

d. Please explain what a Weibull spline model is. Please clarify for a Weibull spline model, whether log cumulative hazard, or log cumulative odds or $-\Phi^{-1}(S(t))$

was modelled as a spline function. Please also provide the rationale for choosing a Weibull spline model.

The spline-based models refer to the models described by Royston and Parmar (2002).[24] When the log-cumulative hazard is modelled as a spline and the model contains no knots then this gives a Weibull model. When the log-cumulative odds are modelled as a spline and the model contains no knots then this gives a log-logistic model. When the inverse normal distribution function is modelled as a spline and the model contains no knots then this gives a log-normal model.

We used spline-based Weibull models i.e., the log-cumulative hazard was modelled as a spline. Spline-based models may fit the follow-up time well but are likely to have more problems with the extrapolation compared to non-spline-based models. A Weibull models is more likely to go to zero in a more plausible way compared to a model with decreasing hazards at the end of follow-up such as a log-logistic model or log-normal model. Adding splines allows a model to fit the data in a more flexible way such as model data with multiple distributions or model changes to the hazards over time such as caused by changes in treatment.

e. Please provide the knot positions used when a spline model (both stratified and unstratified) was fitted to outcomes rPFS, OS and SSE.

The default knot positions were used in the flexsurvspline package for most models. The package chooses knots at equally spaced quantiles of the log uncensored survival times. The exception to this were the models fitted to the original rPFS data, where knot locations were changed manually to achieve convergence. Jackson (2016) argues that spline-based models are typically robust to the choice of knot locations.

Spline positions: Original OS – default knot locations

- 1 knot = 9.74 months
- 2 knots = 7.07, 12.57 months
- 3 knots = 5.56, 9.74, 14.45 months

Spline positions: Original rPFS – user specified and default locations

- 1 knot = knots at 3 months (user specified)
- 2 knots = knots at 2, 2.5 months (user specified)
- 3 knots = knots at 2.27, 4.00, 8.57 months (default)

Spline positions: Interval imputed – default knot locations

- 1 knot = 5.39 months
- 2 knots = 3.07, 8.37 months
- 3 knots = 2.37, 5.39, 9.56 months

f. Please provide an example code used for a stratified Weibull spline model and unstratified Weibull spline model.

Unstratified Weibull model with 2 knots – only intercept varies by treatment (assumes proportional hazards)

- flexsurvspline(Surv(Month, Event) ~ Treatment, data = Survival.data, k=2, scale="hazard")

Stratified Weibull model with 2 knots – all parameters allowed to vary by treatment

- flexsurvspline(Surv(Month, Event) ~ Treatment, anc=list(gamma1=~ Treatment, gamma2=~ Treatment, gamma3=~ Treatment), data = Survival.data, k=2, scale="hazard")

The method follows that described by Jackson (2016).[23]

g. When comparing the Akaike's information criterion (AIC) and Bayesian information criterion (BIC) between a stratified modelling approach and unstratified modelling approach, please explain how AIC/BIC for each treatment group were combined for the unstratified approach. Please comment on the comparability between the AIC and BIC from a stratified approach and unstratified approach.

Stratified models add additional parameters to simple covariate models. They can therefore be directly compared to each other using AIC and BIC statistics.[25] In contrast, if models are fitted to treatment arms separately AIC and BIC cannot be used to compare the fit of models fitted to both treatment arms simultaneously and those fitted to treatment arms separately. We are only aware of Latimer (2013) using the approach of fitting separate model to treatment arms. Latimer (2013) did not provide an explanation for not following the textbook approach.[26]

h. Please provide details of how survival curves were predicted from the ensemble models, in particular how AIC and BIC weights were determined and how the survival curves were simulated.

The equations to calculate AIC and BIC weights followed that described by Jackson et al. (2009) and Jackson et al. (2011).[27, 28] The AIC and BIC weights give the probability that each model gives the best fit. Models that did not give plausible extrapolations were excluded by giving them a weight of zero. The remaining weights were then re-calculated to sum to one. A mean weighted value for AIC and BIC was estimated by averaging these weights. AIC is likely to pick a model that overfits the data whereas BIC is more likely to pick a model that underfits the data. The mean weighting method gives equal weight to both models. We do not know of a publication that has tried to estimate how much weight should be given to AIC versus BIC.

It is worth noting that ensemble models are recommended by the publication by Jackson et al. (2017), in which Nick Latimer is also a co-author.[29]

B9. Priority. Please provide an assessment of the hazard function for each treatment group for outcomes rPFS, OS and SSE.

a. Please provide a plot of the empirical/unsmoothed and smoothed hazard function for the data used in the analysis.

Empirical Cumulative Hazard Function

Figure 19: Empirical cumulative hazard function for OS data

Figure 20: Empirical cumulative hazard function for rPFS data

Figure 21 Empirical cumulative hazard function for time to first SSE

Smoothed Hazard Rates

Figure 22: Smoothed hazard rates for OS data

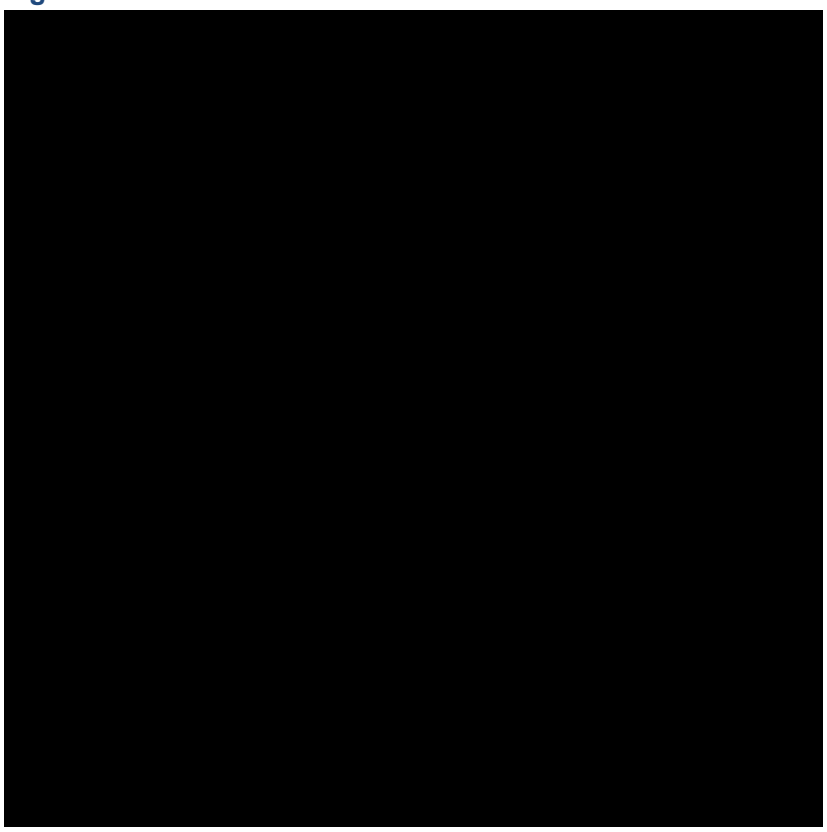


Figure 23: Smoothed hazard rates for rPFS data

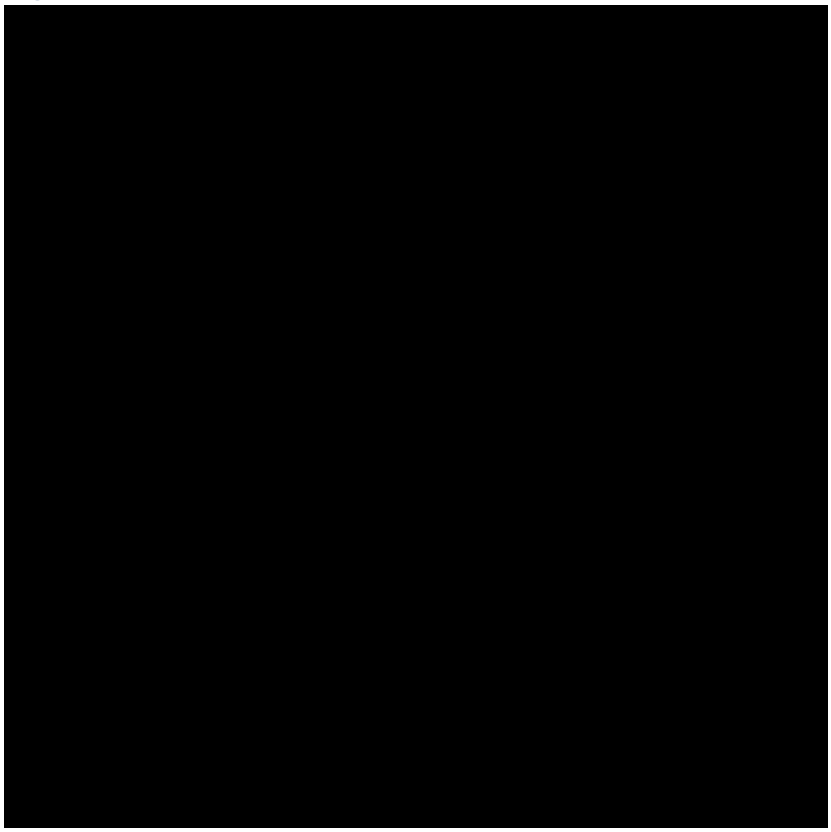


Figure 24: Smoothed hazard rates for the time to first SSE

b. Please also plot the hazard function of the base case parametric model and scenario parametric model on top of the empirical and smoothed hazard.

Figure 25: Predicted cumulative hazard rates from standard parametric models fitted to OS data from VISION

Figure 26: Predicted cumulative hazard rates from spline-based models fitted to OS data from VISION

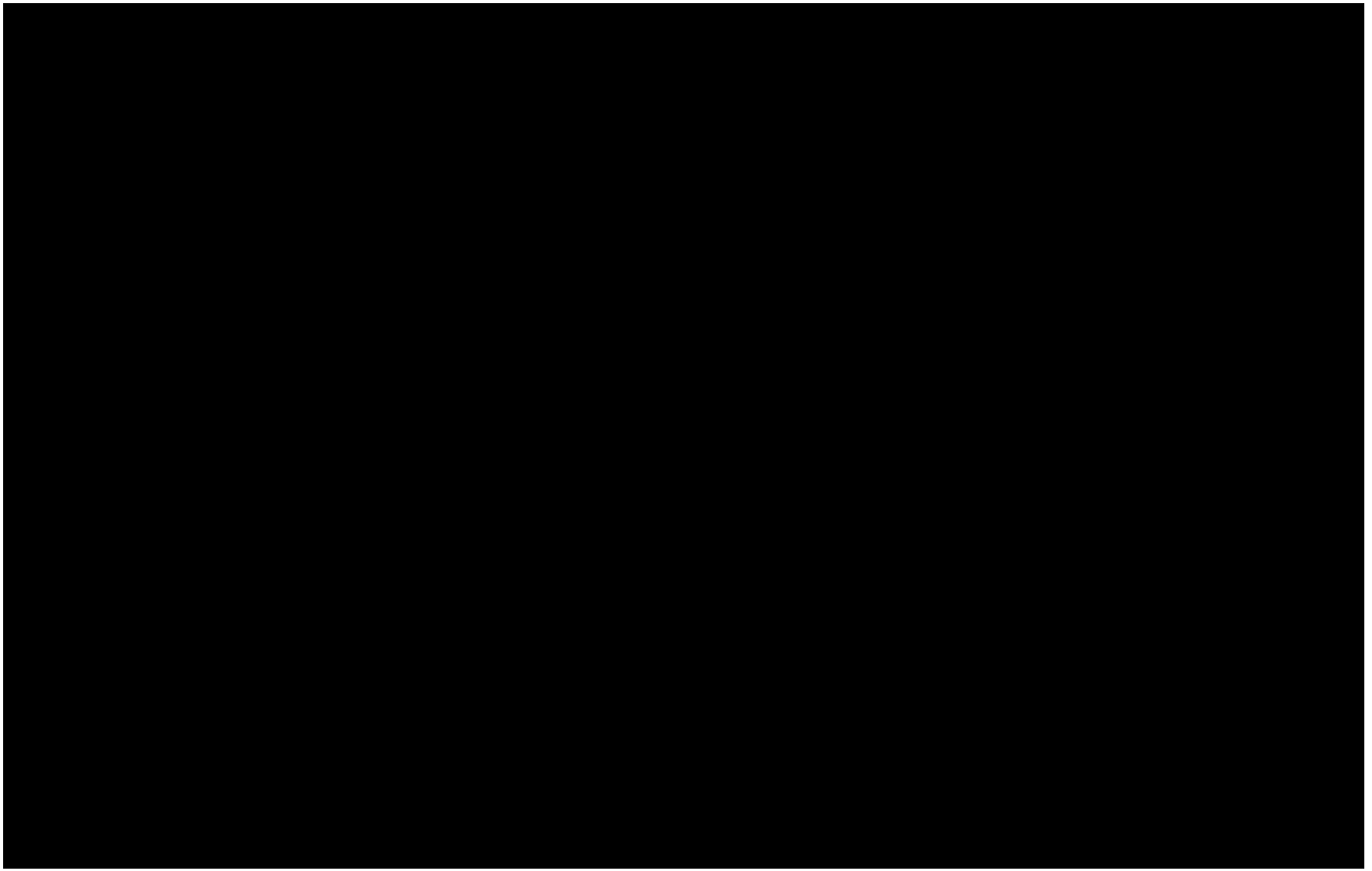


Figure 27: Predicted cumulative hazard rates from standard parametric models fitted to rPFS data from VISION

Figure 28: Predicted cumulative hazard rates from spline-based models fitted to rPFS data from VISION

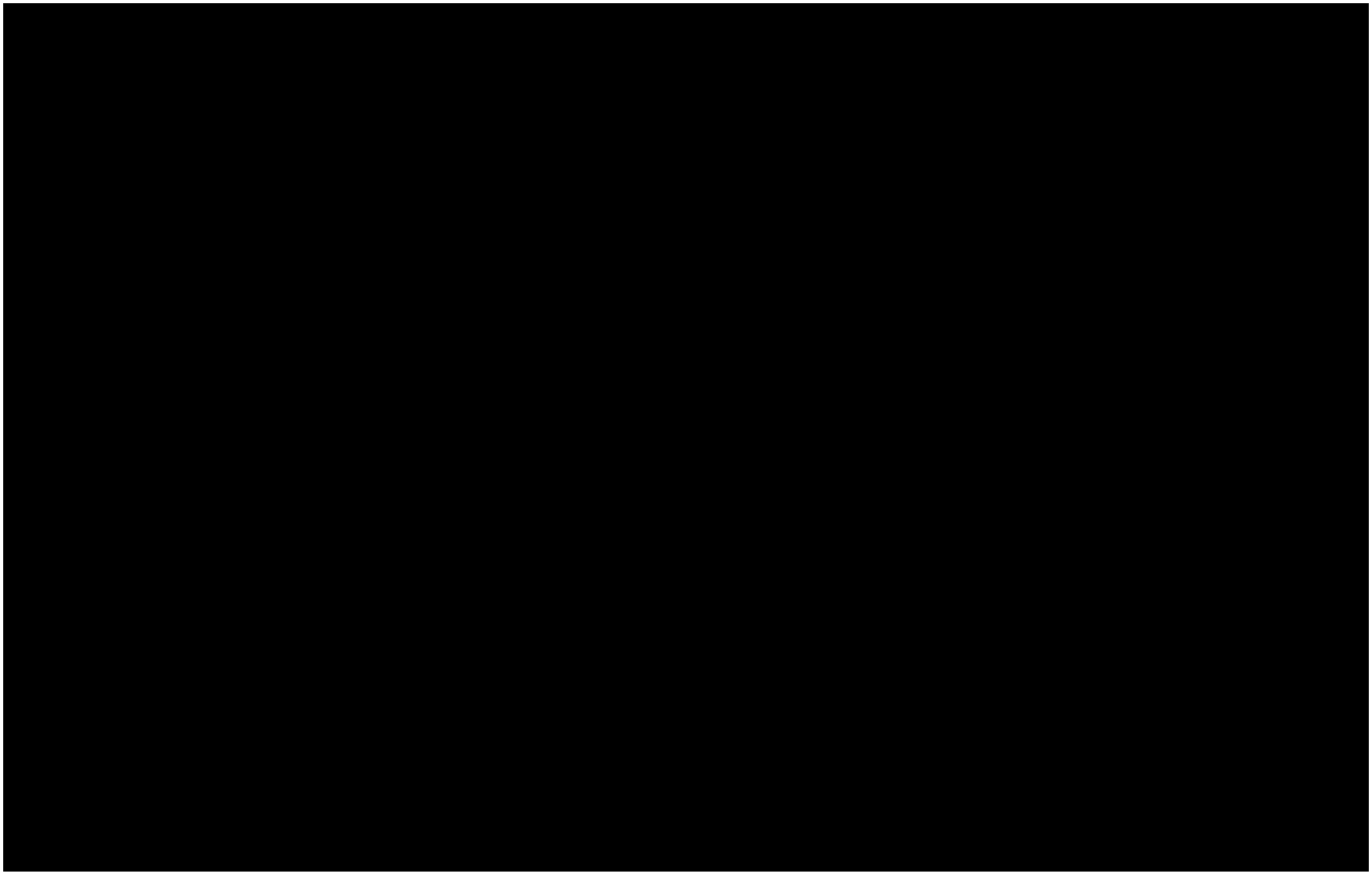


Figure 29: Predicted cumulative hazard rates from standard parametric models fitted to time to first SSE

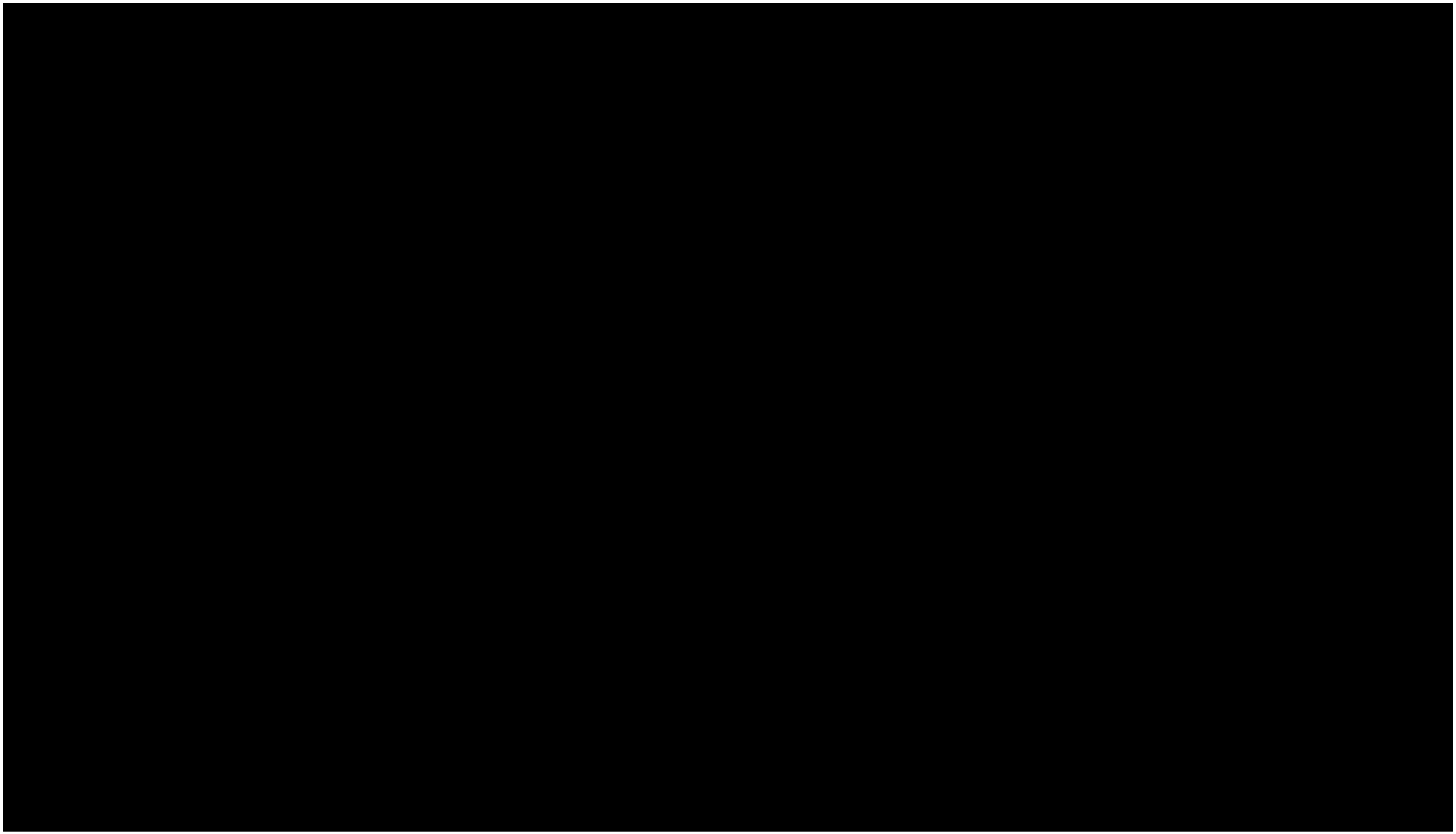


Figure 30: Predicted cumulative hazard rates from spline-based models fitted to time to first SSE

Figure 31: Predicted hazard rates from standard parametric models fitted to OS data from VISION

Figure 32: Predicted hazard rates from spline-based models fitted to OS data from VISION

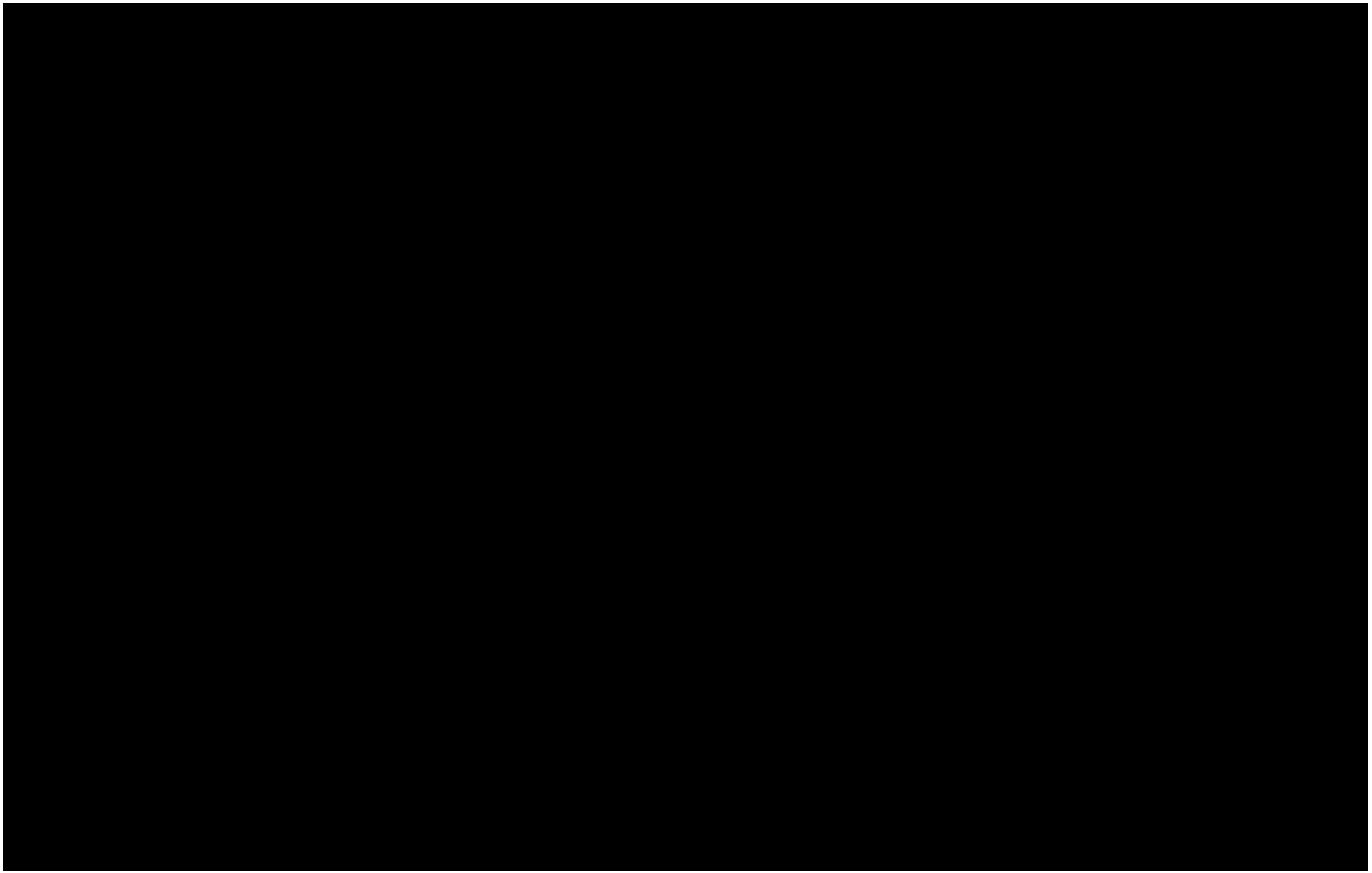


Figure 33: Predicted hazard rates from standard parametric models fitted to rPFS data from VISION

Figure 34: Predicted hazard rates from spline-based models fitted to rPFS data from VISION

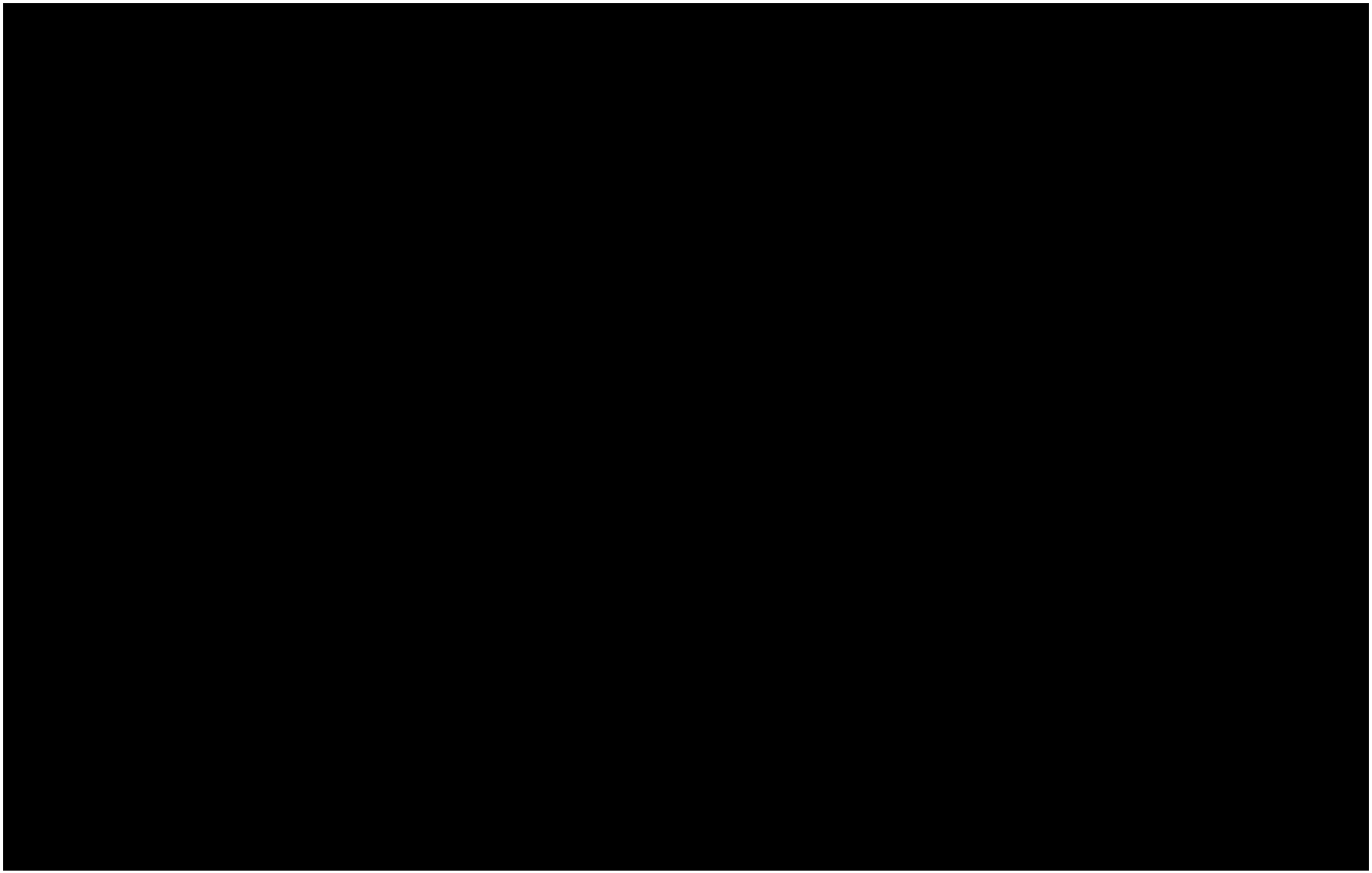


Figure 35: Predicted hazard rates from standard parametric models fitted to time to first SSE

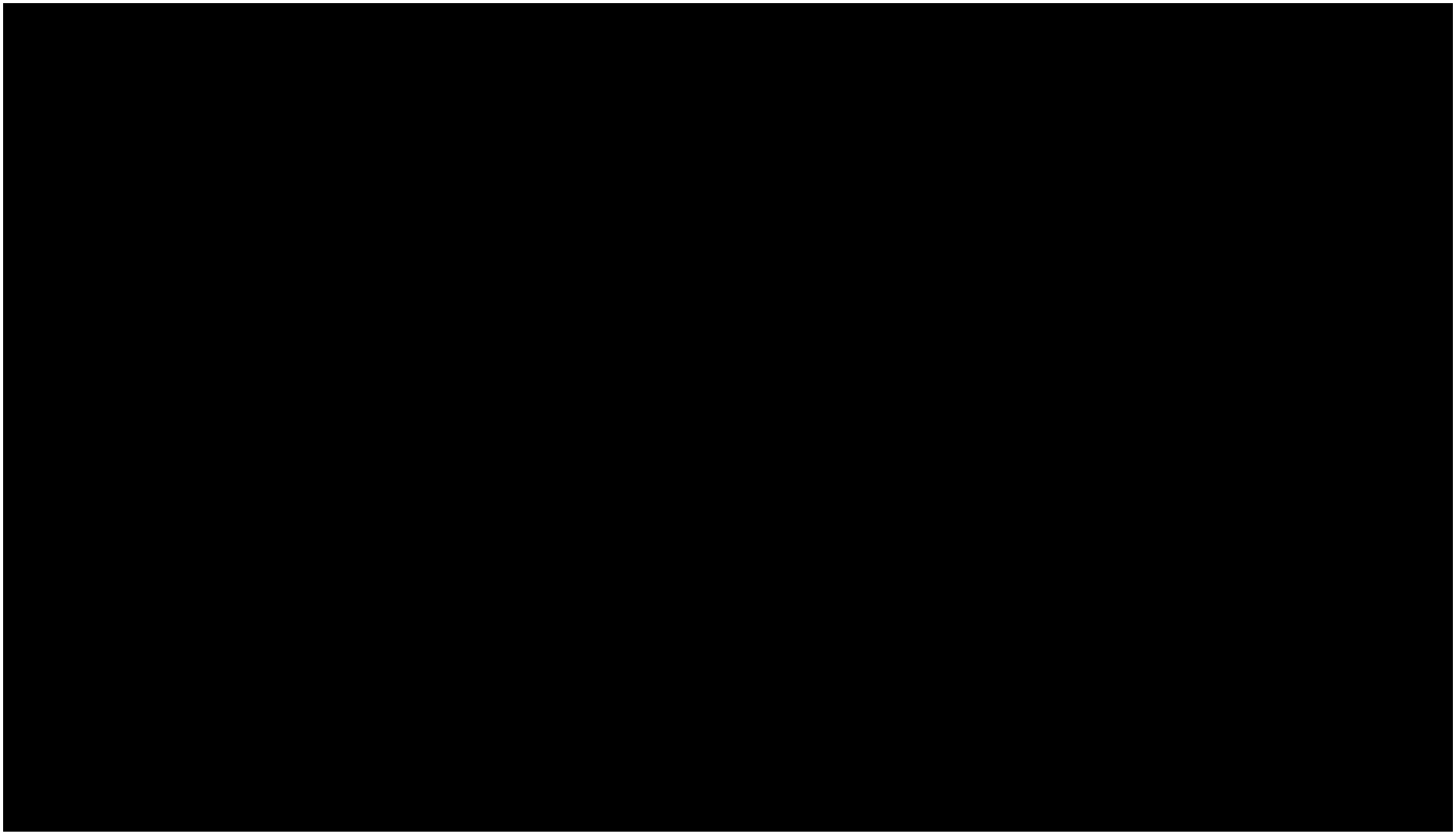
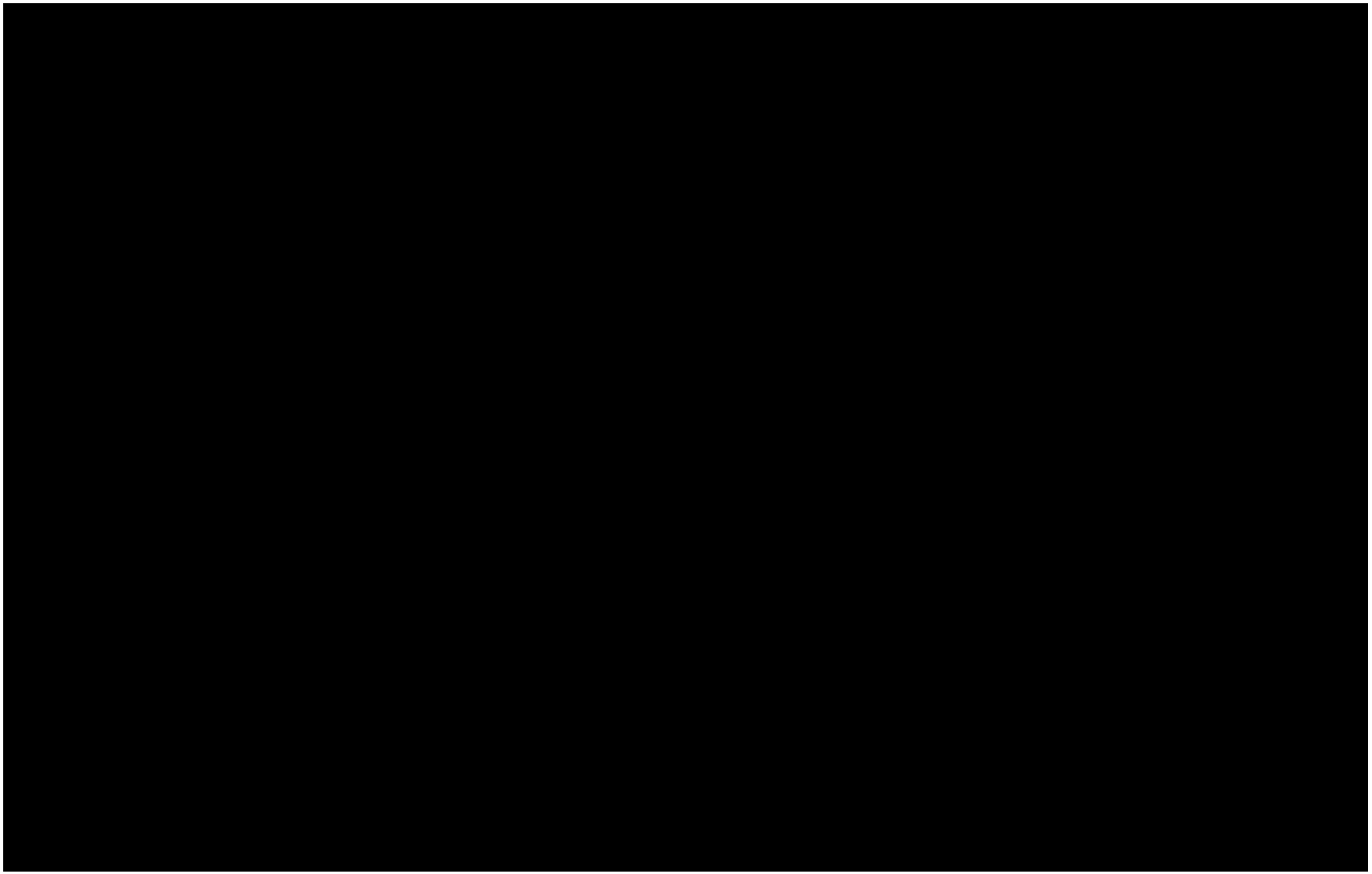


Figure 36: Predicted hazard rates from spline-based models fitted to time to first SSE



c. Please also provide a plot of the estimated hazard ratio (HR) over time for the base case and scenario parametric model.

Figure 37: Smoothed hazard ratios with 95% bootstrap intervals for the original OS data from VISION

Figure 38: Smoothed hazard ratios with 95% bootstrap intervals for the original rPFS data from VISION

Figure 39: Smoothed hazard ratios with 95% bootstrap intervals for the interval imputed rPFS data from VISION

Figure 40: Smoothed hazard ratios with 95% bootstrap intervals for time to first SSE

Figure 41: Predicted hazard ratios from standard parametric models fitted to the original OS data from VISION

Figure 42: Predicted hazard ratios from spline-based models fitted to the original overall survival data from VISION

Figure 43: Predicted hazard ratios from standard parametric models fitted to the original rPFS data from VISION

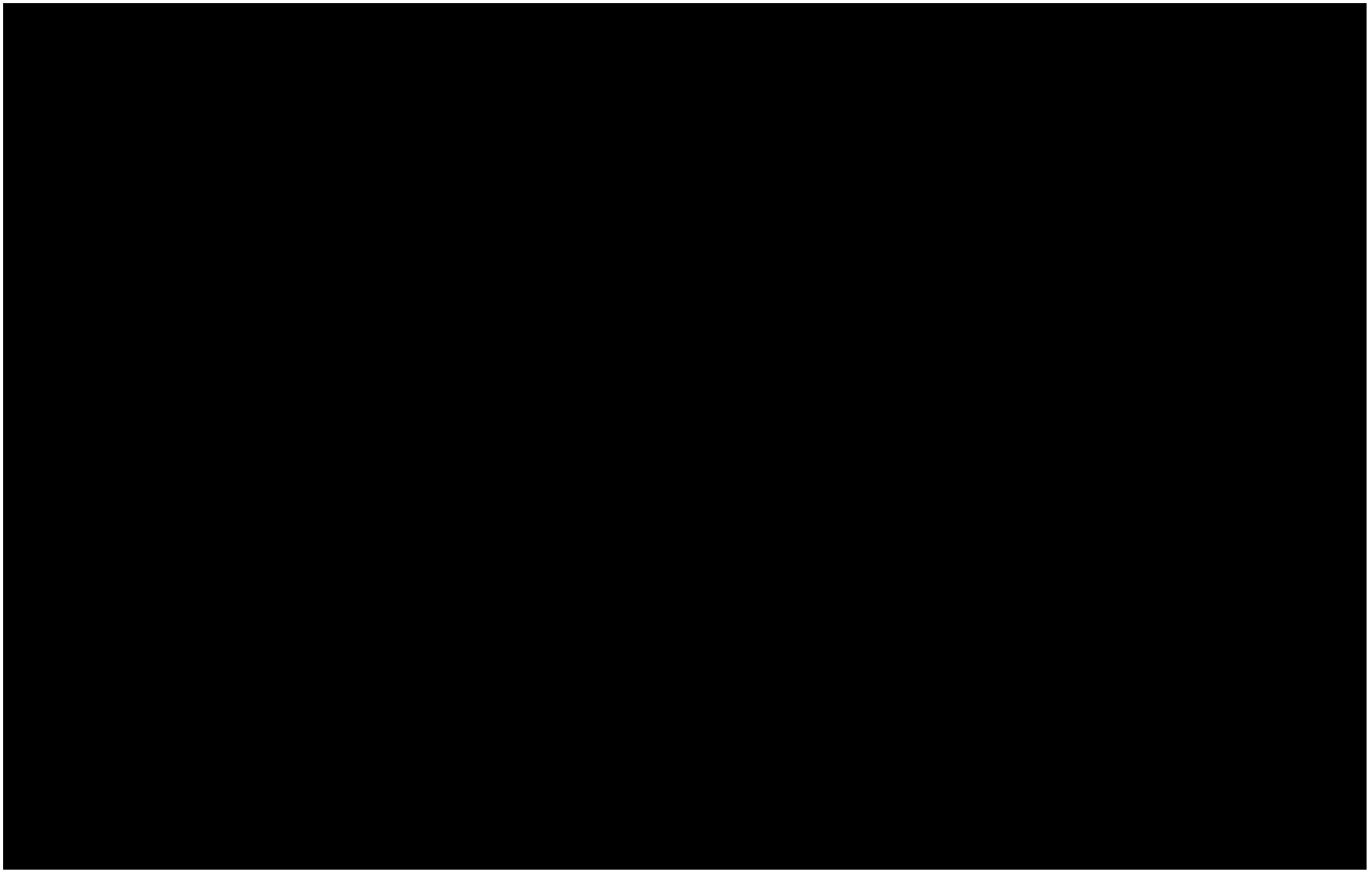
Figure 44: Predicted hazard ratios from spline-based models fitted to the original rPFS data from VISION

Figure 45: Predicted hazard ratios from standard parametric models fitted to the interval imputed rPFS data from VISION

Figure 46: Predicted hazard ratios from spline-based models fitted to the interval imputed rPFS data from VISION

Figure 47: Predicted hazard ratios from standard parametric models fitted to time to first SSE

Figure 48: Predicted hazard ratios from spline-based models fitted to time to first SSE



B10. PSMA-617-01 Study report, page 44. It states that SSE data were collected up through the end of treatment (EOT) visit. The censoring date was the date of the last study visit (on or before the EOT visit).

a. CS, page 118. Please clarify how the change of treatment was defined in the 177Lu vipivotide tetraxetan and SOC arm. Please clarify what the difference is between the change of treatment used and EOT visit defined in the Study report.

End of Treatment

In VISION, the end of treatment (EOT) visit was scheduled approximately 30 days after the last dose of ^{177}Lu vipivotide tetraxetan or the date of the SOC EOT decision (whichever occurred later), but before the initiation of subsequent anti-cancer treatment, outside of what was allowed on study. Once a patient discontinued the randomised treatment part of the study for any reason, an EOT visit was scheduled.

Discontinuation of randomised treatment

Patients could discontinue the randomised treatment part of the study for any of the following reasons:

- Evidence of tumour progression based on Investigator's assessment per PCWG3 criteria
- Unacceptable toxicity to ^{177}Lu vipivotide tetraxetan or SOC
- Patient non-compliance or voluntary withdrawal
- Required the use of a prohibited treatment (equivalent to 'Change of Treatment')
- Evidence that the patient was no longer clinically benefiting
- At the Sponsor's or Investigator's discretion

Patients in the investigational arm who discontinued ^{177}Lu vipivotide tetraxetan due to unacceptable toxicity continued to receive SOC only as long as the investigator felt they were clinically benefiting (regardless of radiographic progressive disease based on Investigator's assessment per PCWG3 criteria) or until they required a treatment regimen not allowed on this study.

If a patient chose to discontinue from the randomised treatment in the study for a reason other than radiographic progression, the patient was asked to confirm if they consented to continue to be followed for long-term safety, rPFS, and OS. If the patient did not specifically withdraw consent for long-term follow-up evaluations, the patient was included in the long-term follow-up.

b. Please provide justification for not using the SSE data directly from the VISION trial but using censored at a change of treatment in the economic model.

No data were recorded for SSEs from 30 days after the first change in treatment. The data in VISION imputed SSE censored data with OS data, making the SSE data effectively OS data for many patients and so for many patients do not provide information on SSEs.

Utility

B11. CS, Page 128 and Table 46. The mean duration of all disutility associated with adverse events is assumed to be one month (company's scenario analysis). Please provide the source or justification for that assumption.

Previous NICE TAs for prostate cancer treatments have included AE duration data either directly from the pivotal trial or from a previous appraisal. Data for the duration of individual AEs was not available from the VISION study and published data were not identified for all AEs included in the model. AE duration data are used in the model for the application of AE utility decrements. Because of the data gaps and exclusion of AE utility decrements in the base case analysis, a simplifying assumption was made that all AEs have a duration of 1 month. This assumption is expected to be an overestimate because the majority of AE durations used in NICE TA391, NICE ID1640, NICE TA580 and NICE TA316 were between 7 and 14 days (minimum of 2 days and maximum of 91 days). Despite likely overestimating the impact of AEs, including AE utility decrements has a small impact on the model results.

B12. CS, Section B.3.4.3, page 128. Please clarify the reason why the utility decrements associated with SSEs included in a scenario analysis performed by the company were informed by Fassler et al (2011) and not the utility analysis with data from the VISION trial.

Utility decrements associated with SSEs were not analysed in the VISION utility analysis. This analysis was not considered to be a priority because utility decrements are not included in the base-case analysis. Utility decrements for SSEs were sourced from NICE ID1640, which was were informed by Fassler et al (2011).[30] Further to this, clinical expert opinion was sought to validate the utility decrements and duration of SSEs.

a. Please also clarify why the duration of each SSE utility decrement varies in relation to the mean duration of 30.44 days used in previous NICE ID1640 (olaparib for previously treated, hormone-relapsed metastatic prostate cancer with homologous recombination repair gene mutations, ongoing).

UK clinical experts agreed that the SSE utility decrements used in NICE ID1640 were reasonable, but the mean durations were not.[31] The mean duration of utility decrements associated with SSEs were determined based on estimates provided by clinical experts.

b. Please clarify how the decrement for surgery to bone and spinal cord compression were determined as Fassler et al. (2011) did not report them.

Fassler et al. (2011) reported spinal cord compression utility decrements varied from 0.50–0.61 and the mean value of 0.55 was taken.[30] Surgery to bone was assumed equal to a pathological fracture. Both assumptions are consistent with NICE ID1640.

B13. CS, Table 46. Please clarify the rationale/source of the assumption of the utility decrement of 0.02 for haematuria and of 0.09 for lymphopenia/lymphocytopenia.

Adverse event utility decrements were not identified for haematuria or lymphopenia/ lymphocytopenia. Therefore, it was assumed that lymphopenia/lymphocytopenia had an equivalent utility decrement to neutropenia, and haematuria had an equivalent utility decrement to urinary tract infection. These assumptions were based on the classification of the adverse events. Although affecting different types of white blood cells different, lymphopenia/ lymphocytopenia and neutropenia refer to a reduced level of white blood cells and consequently an increased risk of infection, whereas urinary tract infections are the most common cause of haematuria.

B14. Please clarify whether the full analysis set (FAS) or the progression-free survival full analysis set (PFS-FAS) were used to calculate the EQ-5D health state utility values in CS Table 48 and Table 49.

The full analysis set (FAS) was used to generate the dataset used for the EQ-5D analysis.

B15. Priority. Please provide the descriptive statistics for the baseline utility values among the patients who dropped out and those who continued for both treatment groups.

Descriptive statistics for the utility values stratified by dropout status are presented in Table 9.

Table 9: Utility values in VISION by dropout status

Treatment	Dropout	Mean	Standard deviation	n
SOC only	No	[redacted]	[redacted]	[redacted]
SOC only	Yes	[redacted]	[redacted]	[redacted]
^{177}Lu vipivotide tetraxetan + SOC	No	[redacted]	[redacted]	[redacted]
^{177}Lu vipivotide tetraxetan + SOC	Yes	[redacted]	[redacted]	[redacted]

Abbreviations: SOC: standard of care.

B16. Priority. CS, page 131. Please clarify the methodology used in the utility analysis.

a. The CS states that "*analyses were performed according to a prespecified analysis plan*". Please provide details of this prespecified analysis plan.

The statistical analysis plan will be shared in reference pack supplied alongside these clarification question responses.

b. The CS states that "*The following fixed effects were initially considered: planned treatment, time of visit (since randomisation), age, baseline utility, baseline ECOG status, prior-ARPI use, planned treatment, and an interaction term between planned treatment and health state.*" Please provide rationale for excluding health state as a covariate but including an interaction between treatment and health state.

Models which included the interaction between treatment and health state, also included main effects for both treatment and health state.

c. Please provide details of the definition of time of visit (since randomisation) and clarify whether this is a time-varying covariate.

For models which included time, the time of visit for post baseline visit was considered as the time since randomisation in the initial model. This related to the difference between the time of the visit at which the EQ-5D data was measured and the time of randomisation for each participant. Multiple visit times for EQ-5D data were included post baseline in the model, with the value for time taking on different values according to the different visit times associated with EQ-5D for that participant.

d. The CS states that covariates included in the model were "*age, baseline utility scores, ECOG status and an interaction term between planned treatment, health state and the interaction between planned treatment and health state*", and "*Results based on marginal means from a mixed model reduced using stepwise regression included fixed effects for planned treatment and time of visit (since randomisation)*". Please clarify if the final model only included planned treatment and time of visit as fixed effects. Please provide details of how the final model was selected and the estimated coefficients for the final model. Please also clarify how the marginal means were calculated, in particular what value of time of visit was used when calculating the mean utility. If health state was not included in the final model, please clarify how the mean utility was obtained for the progression-free and progressed disease state.

The final model included the following variables: EQ-5D utility at baseline, ECOG status, treatment, health state and the interaction between health state and treatment. In order to output marginal means a dummy categorical variable was generated which included four groups for BSOC and ^{177}Lu vipivotide tetraxetan for the pre-progression health state and BSOC and ^{177}Lu vipivotide tetraxetan for the post-progression health state. The results of the marginal means were output at the means of covariates in the model as per the results below. As visit time was not contained within this model the results are not output for a specific visit time, but did consider the repeated measures across visit times. Results from the full model which included visit time are provided below and were relatively comparable to the final model results.

The STATA code for the reduced model is provided below along with the model results and the marginal means:

Code in STATA for reduced model, as per the SAP the model uses stepwise regression to determine the final model where coefficients that were not significant were removed from the model in a stepwise fashion:

egen groupprogplannedtrt=group(prog planned_trt)

xtmixed eq5d5l_u_uk eq5d5l_u_uk_bas ecog_crf i.groupprogplannedtrt || usubjid: , var reml cov(un)
margins groupprogplannedtrt , atmeans

Variable descriptions:

- eq5d5l_u_uk represents: EQ-5D utilities post baseline calculated as per the SAP
- eq5d5l_u_uk_bas: EQ-5D utilities at baseline calculated as per SAP
- ecog_crf: ECOG status
- groupprogplannedtrt: categorical variable which has the following groups 1: pre prog control, 2: pre prog LU-PSMA, 3: post prog control, 4: post prog LU-PSMA
- usubjid: subject identifier

Table 10: Coefficients for reduced model

Parameters	Coefficient	Standard error	z	P>|z|	95% Confidence Interval
eq5d5l_u_uk_base	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ecog_crf	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-prog, LU-PSMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-prog control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-prog LU-PSMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of observations: [redacted]. Reference group: pre-progression control arm.

Table 11: Random effects parameters for reduced model

Random-effects Parameters	Estimate	Standard error	95% Confidence Interval
var(_cons)	[redacted]	[redacted]	[redacted]
var(Residual)	[redacted]	[redacted]	[redacted]

Table 12: Adjusted predictions for reduced model

	Marginal mean	Standard error	z	P>|z|	95% Confidence Interval
Pre-prog BSOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-prog LU-PSMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-prog BSOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-prog LU-PSMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of observations: [redacted].

B17. Priority. Please provide the mean utility for the progression-free and progressed disease state for 177Lu vipivotide tetraxetan and SOC using the full model with the initial set of fixed effects.

The STATA code for the full model is provided below along with the model results and the marginal means:

xtmixed eq5d5l_u_uk eq5d5l_u_uk_bas ecog_crf i.groupprogplannedtrt age i.naad_crf timefromrand || usubjid: , var reml cov(un)

margins groupprogplannedtrt , atmeans

Table 13: Results for marginal means for full model

	Marginal mean	Standard error	z	P>|z|	95% Confidence Interval
Pre-prog BSOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-prog LU-PSMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-prog BSOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-prog LU-PSMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B18. Priority. Please provide the data and code used for the utility analysis, sufficient to permit the ERG to check and/or reanalyse the utility data using a mixed effect model.

The full code for the reduced and full models is presented in Appendix B. The individual patient data that would be required to run these analyses cannot be shared as it is confidential.

B19. Priority. CS, Section B.3.4.4, page 131. Please provide justification, using evidence if available, for the assumption used in the model that the pre-progression health state utility for cabazitaxel is aligned with the utility value for the SOC treatment arm from the VISION trial rather than closer to the HRQoL for patients receiving 177Lu vipivotide tetraxetan.

The company sought additional clinical expert opinion to validate this assumption. One clinical expert advised that the pre-progression utility value for cabazitaxel is likely lower than that for ^{177}Lu vipivotide tetraxetan, given the substantial toxicity associated with cabazitaxel treatment. The second clinical expert concurred, highlighting that cabazitaxel-induced-diarrhoea particularly impacts patients' quality of life. Furthermore, the first clinical expert advised that there is psychological impact associated with cabazitaxel treatment, particularly in the post-docetaxel setting, where many patients have a poor experience with docetaxel treatment and associate this with cabazitaxel, given they are both taxane-based chemotherapies. This negative association is supported by the low proportion of patients eligible for cabazitaxel who go on to receive it – patients may opt not to receive cabazitaxel despite it representing a life-extending treatment option.

B20. Priority. CS, Section B.3.4.4, page 131. Please justify the assumption that patients receiving cabazitaxel would incur a lower utility value whilst in post-progression state than patients receiving SOC or 177Lu vipivotide tetraxetan.

The company sought additional clinical expert opinion to validate this assumption. Both clinical experts advised that it is plausible that the post-progression utility score for cabazitaxel would be lower than that for SOC, given the substantial toxicity associated with cabazitaxel can impact quality of life even following disease progression.[32] Furthermore, the UK Early Access Programme (EAP) for cabazitaxel reported a post-progression utility value of 0.6266, as the patients in the UK EAP were less heavily pre-treated than patients in VISION (previously treatment with an ARPI was not a requirement of the EAP), it is possible that the post-progression state utility value for cabazitaxel in clinical practice could be even lower.[32]

Model implementation

B21. Model, worksheet 'Cost Calcs', cells M41 and M47. The calculations for subsequent treatment costs assume admin costs for cabazitaxel and for radium-223 dichloride as being

the same as for IV treatments (instead of for cabazitaxel and for radionuclide therapy). Please confirm if this is an error, in case not, justify this assumption.

The calculations for administering cabazitaxel as a subsequent treatment were incorrect in the model, 'Cost Calcs' worksheet cells M41 and Q41 and have been updated in the model. The impact of this change to model results is presented in Appendix A.

The cost for administering radium-223 as a subsequent treatment was set equal to an IV infusion based on the assumption used in NICE TA412; there is not an error in the model, 'Cost Calcs' worksheet cell M47. The TA412 Committee notes state that "there were costs associated with a radiopharmaceutical product such as radium-223 that had not been taken into account, for example, resourcing for radiopharmacy, radiation protection and training". The Company acknowledge that using an IV infusion cost may underestimate the cost associated with the preparing and administering radium-223.

B22. Model, worksheets 'Calc-Int', 'Calc-Comp', and 'Cost Calcs'. Please provide the rationale behind the approach adopted to calculate costs (with exception of costs related to SSEs, health state costs and end-of-life costs), in which an estimated overall cost applied at the first cycle to all patients, and does not take in consideration patients' survival or disease progression.

The timing of SSE, health state and end-of-life costs are linked to survival curves and can occur over the time horizon of the model. Costs associated with drug acquisition and administration were based on mean treatment exposures, which accurately capture the number of doses received. Treatment exposure data already account for treatment discontinuation due to any reason so there is no need to link to survival or disease progression. The mean treatment exposures for ^{177}Lu vipivotide tetraxetan, SOC and cabazitaxel are less than 1 year. Moreover, ^{177}Lu vipivotide tetraxetan and cabazitaxel are given for a maximum number of cycles and cannot be given for more than 1 year. Therefore, no discounting of these costs is applicable, and costs were simply accrued in the first model cycle. Treatment-related adverse events are expected to occur whilst a patient is on treatment and therefore occur in the first year. Of the subsequent therapies included in the model, only docetaxel treatment (mean duration = 6.9 months) could occur after 1 year following ^{177}Lu vipivotide tetraxetan treatment (mean duration = [redacted] months) and incur discounting of costs. Therefore, applying subsequent therapy costs in the first model cycle is a conservative assumption.

In CS, Table 63 it was acknowledged that a simplifying assumption was made regarding the application of SOC drug acquisition and administration costs in the first model cycle, assuming no discounting of these costs. Only bisphosphonates ([redacted] and [redacted] months in the 177Lu vipivotide tetraxetan and SOC arms, respectively) and antifungals ([redacted] months in the 177Lu vipivotide tetraxetan arm) had a mean treatment duration >1 year; this assumption is expected to have a marginal impact on cost-effectiveness for analyses in which concomitant treatment costs are included.

B23. Model, worksheet 'Controls', cell C38. The model rounds down the number of weeks per year (52.00), which in consequence assumes a year has 364 days. Please confirm if this is an error.

The number of weeks per year was assumed to be 52 to ensure that the last model cycle equals exactly 120 months when the base case time horizon of 10 years is selected. However, the Company acknowledge that this simplification slightly underpredicts the number of model cycles over the 10-year time horizon. The model has been updated to use 52.18 weeks per year and 365.25 days per year. Cell C38 on the 'Controls' worksheet has been updated, and 2 additional model cycles have been added to calculation worksheets, where relevant, so that the 10-year time horizon is reached. As presented in Appendix A, this correction leads to a small decrease in the base-case ICER.

B24. Model, worksheets 'Calc-Int' and 'Calc-Comp'. In some of the calculations for both intervention and comparator, the number of days in one year is rounded down to 365. Please clarify if these are errors, and in case they are, please provide an updated version of the model where these are fixed.

These were errors in the model; the number of days in a year has been updated to 365.25 in formulae on the 'Calc-Int' and 'Calc-Comp' worksheets. As presented in Appendix A, this correction has no impact to the base-case ICER because SSE utility decrements are not included.

B25. CS, pages 128/129 and model, worksheets 'Calc-Int' and 'Calc-Comp'. The CS states that "It has been assumed that all AE utility decrements are applied for a mean duration of one month". However, the assumption does not seem to be included in the calculations for the comparator. Please clarify if this is an error.

There was an error in the model on the 'Calc-Comp' worksheet; the formula in cell AD19 has been updated to include a mean duration of one month. As presented in Appendix A, this correction has no impact to the base-case ICER because AE utility decrements are not included.

B26. Priority. Model, worksheet 'Survival_Curves'. Please clarify why survival curves are calculated relative to an 'anchor' of ARPI when this is not a comparator in the cost-effectiveness analysis.

Calculations in the model, 'Survival_Curves' worksheet, anchoring to ARPI are for the purpose of HR tapering. Treatments included in the NMA are anchored to ARPI, which is the common link in the network of evidence and best represents the control arms. However, HR tapering has not been applied in any of the analyses presented in the CS. HR tapering, anchored to ARPI, can be applied in the model to ^{177}Lu vipivotide tetraxetan and cabazitaxel via the HR NMA but please note that HR tapering calculations are not applied to cabazitaxel when UK RWE Kaplan–Meier data are used.

B27. Please confirm whether the functionality to taper the HR has been applied in any of the scenarios presented in the CS (i.e., whether cells H208 and J208 of Controls sheet were set

to 1 for all presented analyses). If it has been used, then please explain the assumptions underpinning this analysis.

HR tapering has not been applied in any of the scenarios presented in the CS (cells H208 and J208 of Controls worksheet were set to 1 for all analyses; i.e., no adjustment).

B28. Model, worksheet 'Survival_Curves'. Please confirm if there is an error in the formulae in columns E and H with respect to the selection of data from the rows of the lookup table. For example, our interpretation is that data for cycle 3 are coming from the row intended for cycle 2.

There was an error in the formulae in the model, 'Survival_Curves' worksheet columns E and H, which meant the data being referenced were out by one cycle. This has been updated in the model and, as presented in Appendix A, the correction leads to a small decrease in the base-case ICER.

B29. Model. Please clarify if any constraints for gender and age-matched general population mortality and general population utilities have been included in the model.

There are no constraints included in the model for gender and age-matched general population mortality or general population utilities. General population mortality was considered in the VISION survival analysis. All OS extrapolations had hazard rates that remained higher than general population mortality rates; therefore, there was no need to include mortality constraints in the model. Due to poor survival outcomes in mCRPC, adjusting utilities would be anticipated to only minimally impact results.

B30. Priority. CS, Section B.3.7 and Model. Please explain the steps required to change from the base-case analysis for 177Lu versus cabazitaxel to the base-case analysis for 177Lu versus SOC. A single change for the comparator selected on the 'Analysis settings' sheet does not seem to produce results that match Table 65 of the CS for the SOC arm.

When the model is opened, the analysis is set to the base-case for ^{177}Lu vipivotide tetraxetan versus cabazitaxel. To change this to the base-case analysis versus SOC, the user must change the comparator in cell E11 on the 'Analysis Settings' worksheet and update the SOC concomitant treatments to be 'Included' for the comparator (drop-down menu in row 76 on the 'Costs' worksheet).

Section C: Textual clarification and additional points

C1. Please clarify the status of the data for HRQoL marked as academic in confidence in the CS, Section B.2.5.5., page 56 and 57 and Figures 34 and 37 (CS, Appendix M.3). These are published in the Sartor 2021 Supplement: hazard ratios for Brief Pain Inventory – Short Form (BPI-SF) and Functional Assessment of Cancer Therapy – Prostate (FACT-P). The same

issue applies to certain response data marked as academic in confidence in the CS, Section B.2.5.6, Table 15.

Thank you for highlighting these points. The company acknowledge that the hazard ratios for BPI-SF and FACT-P presented on p56 and p57 of the CS do not require AIC highlighting, as with their corresponding KM curves shown in Figures 34 and 37 of Appendix M.3.

The company also acknowledge that AIC marking is not required for data pertaining to BOR, ORR, or DCR in Table 15 of the CSR, although AIC highlighting is required for data pertaining to DOR in the same table.

C2. CS, Table 46. Please clarify if the two columns with headers “Source” relate to, respectively, the source of utility decrements, and source of the duration of disutility.

The company confirm that the left ‘Source’ column refers to the source of the utility decrements and that the right ‘Source’ column refers to the source of the duration of disutility.

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Appendix A: Revised base case cost-effectiveness analysis

Table 14 presents the revised base-case cost-effectiveness results, at ^{177}Lu vipivotide tetraxetan list price, with corrections made to the model in response to clarification questions. The correct model is provided in the reference pack accompanying this submission.

Table 14: Revised base-case results at ^{177}Lu vipivotide tetraxetan list price (deterministic)

Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER inc. (£/QALY)
Submitted base case					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Correction in response to clarification question B21					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Correction in response to clarification question B23					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Correction in response to clarification question B24					
No change to base case results					
Correction in response to clarification question B25					
No change to base case results					
Correction in response to clarification question B28					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised base case (including all corrections)					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ^{177}Lu: Lutetium-177; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

Table 15 presents the revised base-case cost-effectiveness results, at 177Lu vipivotide tetraxetan PAS price, with corrections made to the model in response to clarification questions.

Table 15: Revised base-case results at ^{177}Lu vipivotide tetraxetan PAS price (deterministic)

Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER inc. (£/QALY)
Submitted base case					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	49,949
SOC	[redacted]	[redacted]	[redacted]	[redacted]	125,687
Correction in response to clarification question B21					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	49,967
SOC	[redacted]	[redacted]	[redacted]	[redacted]	125,622
Correction in response to clarification question B23					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	49,720
SOC	[redacted]	[redacted]	[redacted]	[redacted]	125,634
Correction in response to clarification question B24					
No change to base case results					
Correction in response to clarification question B25					
No change to base case results					
Correction in response to clarification question B28					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	49,924
SOC	[redacted]	[redacted]	[redacted]	[redacted]	122,105
Revised base case (including all corrections)					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	49,714
SOC	[redacted]	[redacted]	[redacted]	[redacted]	122,003

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

Appendix B: Model code for marginal means

Full code for the reduced and full model are shown in Table 16 and Table 17, respectively.

Table 16: Code for reduced model

[redacted]

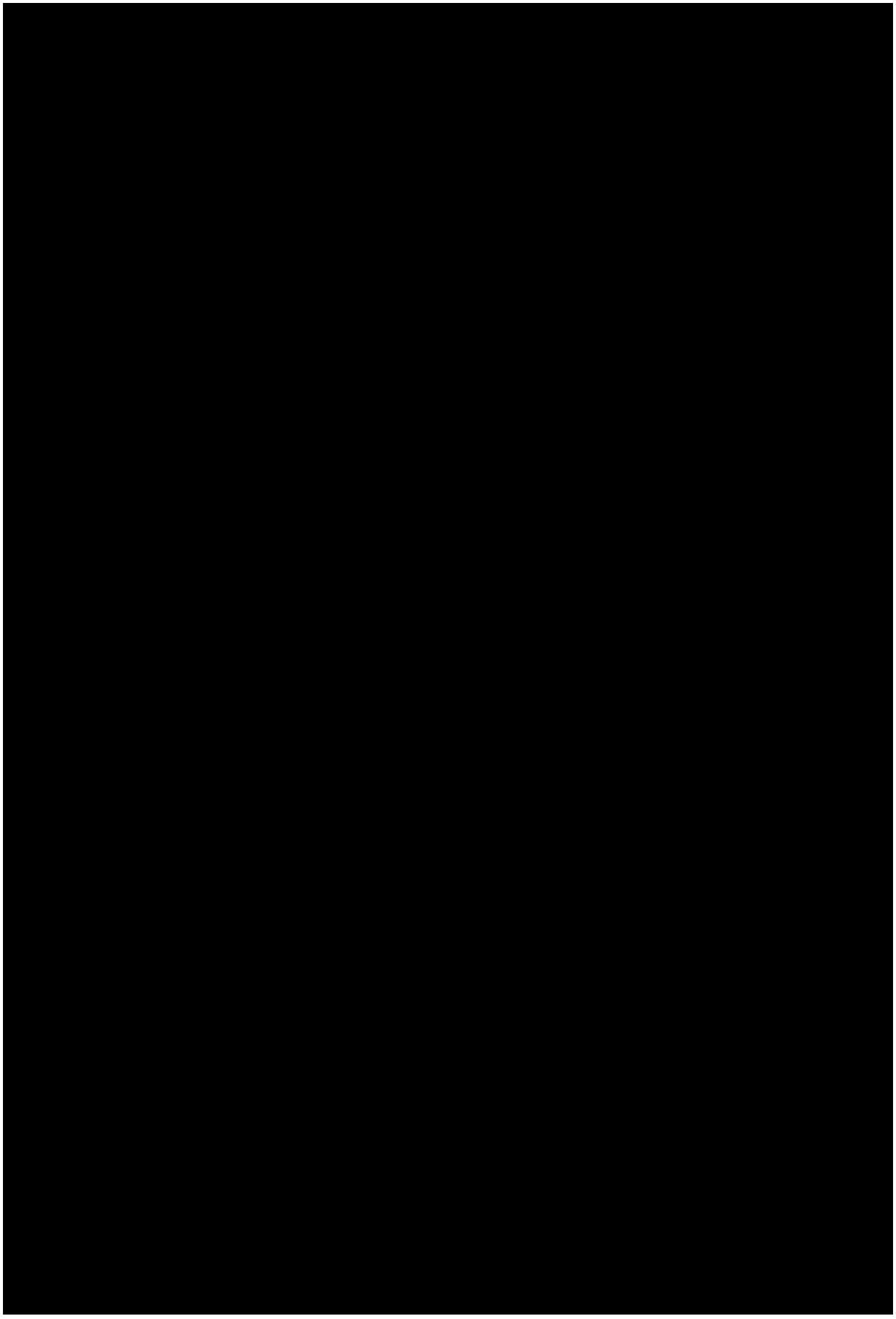

Table 17: Code for full model

NICE National Institute for Health and Care Excellence

Professional organisation submission

177Lu-PSMA-617 for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Nuclear Medicine Society**

3. Job title or position	**Consultant Physician in Nuclear Medicine & PET/CT**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Professional organisation representing the Nuclear Medicine community including medical, technological, nursing, radiopharmacy, administrative professionals in the UK**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Palliative treatment, to stop disease progression, to improve the quality of life and to prolong survival.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	To reduce the tumour size, to lower the tumour marker, to relieve disease related symptoms and to prolong survival.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. More effective treatments are urgently needed.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	There are several palliative treatment options including hormonal, chemo and targeted treatments.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. ESMO guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The pathway of care is quite well defined, but more effective treatments are needed.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It has demonstrated efficacy in this group of patients and, with very little side effects.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No.
• How does healthcare resource use differ between the technology and current care?	The treatment uses radioactive pharmaceutical, given intravenously. A relatively small number of hospitals have experience in this area.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics/hospitals.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Relevant medical training, radiation protection knowledge and facilities would be essential.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with metastatic prostate cancer.
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It will be more difficult to use because primarily it involves the usage of radioactive material which has a short half life and thus limited shelf time; the treatment also requires strict radiation protection precautions.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, it requires several additional tests such as PET/CT scans and regular blood tests.
15. Do you consider that the use of the technology will	Yes.

result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes.
• Is the technology a 'step-change' in the management of the condition?	Yes.
• Does the use of the technology address any particular unmet need of the patient population?	Yes.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	I have treated over 200 patients using this technology and there are very little treatment related or induced side effects.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improved quality of life and prolonged survival.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance **[TA660], [TA712], [TA740]**	No.
21. How do data on real-world experience compare with the trial data?	Quite comparable.
Equality	

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

Key messages

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

- Innovative new treatment
- effective
- less toxic
- better quality of life
- longer survival

Thank you for your time.

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

.....

Your privacy

NICE National Institute for Health and Care Excellence

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

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……

NICE National Institute for Health and Care Excellence

Patient organisation submission

177Lu-PSMA-617 for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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

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

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

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

Information on completing this submission

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

About you	
1.Your name	[redacted]

2. Name of organisation	Prostate Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	We regularly speak with pharmaceutical companies, particularly those with prostate cancer products, to seek funding for specific projects. We ensure that donations from pharmaceutical companies make up no more than 5% of income each year – in practice, it is significantly lower. We maintain strict contractual independence and control of our work when acting in partnership with pharmaceutical companies. In 2020-21, we received £990 from AAA/Novartis as an honorarium for staff participation in a workshop. There were no conditions attached to receiving this money.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	Desk research and organisational knowledge of the experiences of men, including that of our Specialist Nurses who speak to approx. 15,000 patients, family members and concerned members of the public each year.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The condition affects every man differently. Evidenced symptoms for advanced prostate cancer can include: 1. Fatigue. 2. Pain, most commonly caused by prostate cancer that has spread to the bones. 3. Urinary problems, this includes problems emptying the bladder, incontinence, blood in urine and kidney problems. 4. Bowel problems including constipation, diarrhoea, faecal urgency, faecal incontinence, pain, bowel obstruction and flatulence. 5. Broken bones, fractures caused by bone thinning. 6. Sexual problems, including reduced libido and difficult getting or keeping an erection. 7. Lymphoedema, primarily around the legs. 8. Anaemia, caused by damage to bone marrow. 9. Metastatic spinal cord compression, as cancer cells grow in or near the spine, which evidence suggests can occur in 1 to 12% of patients. 10. Hypercalcaemia, caused by calcium leaking from the bones into the blood. 11. Eating problems

	As advanced prostate cancer progresses, men may experience different symptoms (depending on where their cancer is) from their prostate cancer including those below: Pain may develop, particularly severely for those with bone metastases, and for some men this can be life-altering. The level of pain is distressing for both men and their families, and impacts on quality of life of the patient and carers. Men with advanced prostate cancer who have bone metastases, including in the spine, may develop spinal cord compression. These men require urgent treatment to prevent permanent nerve damage and potential paralysis. This can be a debilitating and life-changing problem. Bone metastasis can also result in spontaneous fractures, without trauma and increased risk of fracture associated with trauma. For men whose prostate cancer affects their bone marrow, they may become anaemic (so be more tired or become breathless) requiring blood transfusion, thrombocytopenic (be more prone to bruising and bleeding) and low white blood cell counts (making them more susceptible to infection). Visceral metastases most commonly involve the liver and the lungs, causing considerable and intractable morbidity; Brain metastases commonly result in significant and distressing neurological deficits. Weight loss and reduced appetite can often be a particular concern for carers. If prostate cancer advances in the region around the prostate, men may experience urinary tract problems and renal problems. It is important to note that men are unlikely to experience all the above symptoms, as some will depend on the treatments received, while others will be the result of metastases and therefore dependent on their location. The severity of symptoms will also differ among men, while the likelihood of some of the most severe symptoms, for example Lymphoedema can be rare and vary between 1-20%. For some men, living with metastatic prostate cancer can be hard to deal with emotionally, especially as there are no current curative treatments for this stage of the disease. Symptoms and treatments can be draining and make men feel unwell. And some treatments, including hormone therapy, can make men feel more emotional and cause low moods. The pressure of advanced cancer can also put a strain on relationships. Metastatic prostate cancer and its treatments might mean that partners or family need to do more for patients, such as running the home or caring responsibilities. Additionally, the symptoms of metastatic prostate cancer and the side effects of treatments can make it difficult to work. A partner providing care might not be able to work as much either. Everyday tasks may become more difficult and respite care may be required to give carers a break. As the disease progresses, more palliative care and treatments will be offered. This includes palliative radiotherapy to ease bone pain, blood in urine and swollen lymph nodes.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**Docetaxel chemotherapy** is only offered to those felt fit enough to receive it. It will be offered in the hormone-sensitive stage, but there is an opportunity for rechallenge or new administration in the castrate-resistant setting. Docetaxel offers a median survival benefit of 16 months if given first in the hormone-sensitive stage and less than 3 months if given first in the castrate-resistant stage. While there are side-effects from chemotherapy, severe side effects are reported mostly during treatment and in the first 6 months after treatment, but, after one year men can return to the same quality of life they had before treatment. Many men and their families are fearful of chemotherapy and the significant side effects it can produce. Most men develop low blood counts making them vulnerable to infection, some of which are potentially life-threatening infections. Many men say that the taste changes that the chemotherapy can cause is extremely difficult to live with, adversely affecting their quality of life. Treatment means going into hospital, often to clinic on one day followed by chemotherapy the next day approximately every three weeks for 6 cycles of treatment. Some men travel long distances to receive their treatment. They are also required to self-monitor between visits, to be vigilant, recognise and to present back to hospital should any adverse reactions to treatment occur, for example, should they become febrile. Many men find this onerous and extremely anxiety provoking. We note that, while Lu-PSMA-617 requires prior exposure to taxane chemotherapy, there is an increasing cohort of men who do not receive it. Publicly available data from Public Health England released in 2019 links age, stage of disease and treatment received across cohorts of prostate cancer patients from 2013-2017. Prostate Cancer UK analysed these data to understand docetaxel chemotherapy uptake in patient cohorts with stage IV disease by age, focusing specifically on the treatments data from 2016. The results showed significant disparity in access to chemotherapy by age. 63.6% of men with a new diagnosis of metastatic prostate cancer aged under 70 receive chemotherapy. This starkly decreases to 21.9% for men aged over 70 and drops further to 5.7% for men aged 80 and above. Further, over the period of the covid-19 pandemic, chemotherapy has been avoided due to its immunosuppressive action, with men going straight to novel hormonal agent treatment. NICE should be aware that the matter of prior chemotherapy must be revisited in future or fewer and fewer men will be able to benefit from Lu-PSMA-617 therapy. **Abiraterone and enzalutamide** are both androgen receptor signalling inhibitors. These would usually be offered after the patient has been treated with docetaxel chemotherapy and progressed to a castrate-

Commented [AR1]: I wonder if it is worth saying "justifiably fearful"? I also wonder, in the context of our wider argument about not making "prior-chemo" essential to the prescribing of these new treatments whether it is worth including some of the facts and figures about non-take up of chemo and about the impact of the pandemic on chemo as a safe treatment?

	resistant stage. Without a direct comparison, they offer similar survival benefit, 3 months for abiraterone and 5 months for enzalutamide. They are both available to patients after docetaxel, or to patients who have not received docetaxel. NHS England has a policy that no patient can receive both treatments, since there is no evidence of their efficacy in combination or in sequence. The treatments have different side-effect profiles, but broadly abiraterone will be less likely to be prescribed if the patient has any liver problems and enzalutamide less likely to be prescribed if the patient has heart trouble. When given as a first treatment for hormone-sensitive advanced prostate cancer the survival gain from abiraterone or enzalutamide is similar to that of docetaxel, but the patient cannot receive a further novel hormonal agent after progressing. They may, if suitable and able to tolerate it, receive docetaxel. **Cabazitaxel chemotherapy** is another taxane chemotherapy, available only in the castrate-resistant setting after administration of docetaxel. It is available as an alternative to abiraterone, enzalutamide or rechallenge with docetaxel. It can be prescribed either before or after abiraterone or enzalutamide at this stage, however it is more frequently prescribed afterwards. It offers a similar survival benefit to docetaxel at this stage. Evidence suggests it is more effective than enzalutamide or abiraterone following administration of docetaxel and an androgen signalling targeted inhibitor (enzalutamide or abiraterone). At this late stage of disease, many men will be too frail or have too many comorbidities to tolerate chemotherapy. It is not widely prescribed. Side-effects are similar to docetaxel. **Radium 223** is a treatment for men whose cancer has spread to the bones. It offers a median of just under 3 months of additional life. 70% of men also get some pain relief benefit from the treatment. However, the treatment is not offered at all hospitals because the treatment involves administration of a radioisotope.
8. Is there an unmet need for patients with this condition?	Yes. Currently, treatment options for patients with metastatic hormone-resistant prostate cancer who have progressed while taking a Novel Hormonal Agent (NHA) are limited. These patients have already experienced a number of lines of treatment and are often quite ill with advanced disease. Their existing options are limited to further chemotherapy with docetaxel or cabazitaxel, or radium-223. The side-effect burden of further chemotherapy can be severe, particularly if cabazitaxel is given, so patients are often not fit enough for this treatment. Radium-223 can only be given if the patient's metastases are confined to the bones, and generally considered a palliative treatment with small life-extending potential. There is an unmet need for a further treatment modality that patients can access after failure on a NHA that offers

	additional life. For the majority of prostate cancer patients that show PSMA positivity (up to ~90%), this treatment addresses that unmet need. There are no approved precision medicines for prostate cancer patients in England. Given the diagnostic scan for PSMA positivity, Lu-PSMA-617 can be considered a precision treatment. Current treatments are not personalised to patients' individual cancer and therefore their likely response is hard to predict. This treatment offers the advantage that the response to therapy can be determined through a PSMA-PET scan prior to treatment, indicating whether they will benefit from the treatment.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The advantages of the technology are that it offers a benefit in terms of additional months of life, giving men valuable time to spend with family and friends. Sartor et al (2021) showed that there was a benefit in terms of overall survival with an additional 4 months of life (median, 15.3 vs. 11.3 months; hazard ratio for death, 0.62; 95% CI, 0.52 to 0.74; P<0.001). Further, there is a benefit in terms of progression free survival, with a benefit of an additional 5 months (median, 8.7 vs. 3.4 months; hazard ratio for progression or death, 0.40; 99.2% confidence interval [CI], 0.29 to 0.57; P<0.001).
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The side effect profile of Lu-PSMA-617 includes fatigue, dry mouth and nausea as the most common adverse events. In order to determine if a patient's cancer expresses PSMA, a PSMA-PET scan is required. PET-CT scanning facilities are specialised equipment, meaning patients may need to travel quite far to undergo this scan. In the VISION trial, a particular PET tracer based on gallium-68 was required (Ga-PSMA-11). The limited availability of gallium generators further reduces the number of centres able to provide this scan. In order to overcome this difficulty, we recommend allowing any PSMA-PET scan using a fluorine or gallium tracer be used to determine treatment eligibility. As well as the need to travel for a scan, patients may also need to travel to receive the treatment, as nuclear medicine facilities are also not widespread. While on treatment, there are difficulties associated

	with receiving a radiopharmaceutical such as the patient excreting radioactive waste. However, these issues also apply to radium-223, another radiopharmaceutical.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There are patients who may not have had both a prior taxane and novel hormonal agent (NHA), as required in the trial. Patients who are older and with a poorer ECOG status are less likely to have had docetaxel. Further, during the COVID-19 pandemic, patients with newly diagnosed hormone sensitive metastatic prostate cancer were given enzalutamide or abiraterone instead of docetaxel, as they were particularly vulnerable to COVID-19. This means that they will not have had docetaxel at this stage in the pathway and may become too unwell to have docetaxel as their disease progresses. However, it is likely that these patients will still benefit from Lu-PSMA-617 therapy. We believe that evidence should be gathered on the treatment effect in this group, potentially via the Cancer Drugs Fund, if an approval for the wider population requires prior taxane treatment. As Lu-PSMA-617 is currently used late in the pathway, it is possible that evidence for this subgroup could be generated within the maximum five-year timescale of the CDF.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As detailed above (Qu 7), provision of docetaxel chemotherapy falls greatly with increasing patient age. This means that, even though patients are likely fit enough to receive Lu-PSMA-617 therapy, eligibility for it will also be less likely with increasing patient age. We are concerned this represents an issue of indirect discrimination against older patients in giving them access to a tolerable, life-extending treatment.

Other issues	
13. Are there any other issues that you would like the committee to consider?	As is often the case, it must be recognised that the treatment pathway has changed since the key trial of this treatment was designed. One of the impacts of the pandemic (and of continuing research such as the STAMPEDE trial) is that the treatment landscape for advanced prostate cancer is fundamentally different now, with patients far less likely to receive docetaxel. NICE must be cautious that they do not create an approval category that will discriminate against patients diagnosed post-March 2020 if they fail to recognise the impact of this effect against the treatment eligibility criteria.

Key messages

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

- Lu-PSMA-617 is the first of a novel family of targeted radiopharmaceutical treatments for advanced hormone refractory prostate cancer, opening up a new treatment possibility for patients at this stage of the pathway.
- Lu-PSMA-617 provides a life extension benefit of, on average, four months for patients who are identified as eligible by PSMA-PET.
- There are potential issues of access to both the companion diagnostic scan and the treatment given the specialised nature of the facilities required. These would be eased by using any PSMA scan as the diagnostic, rather than stipulating Ga-PSMA-11.
- Current eligibility requirements stipulate the patient must have had at least one course of taxane chemotherapy and one course of a novel hormonal agent. However, patients unsuitable for chemotherapy could still benefit from this treatment. Further, a cohort of patients treated during the COVID-19 pandemic will not have had access to chemotherapy due to the circumstances of this time, but would still benefit from Lu-PSMA-617.
-

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Patient organisation submission

177Lu-PSMA-617 for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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

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

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

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

Information on completing this submission

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

About you	
1.Your name	[redacted]

2. Name of organisation	**TACKLE Prostate Cancer**
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Tackle is a patient centred charitable organisation whose aims are to support men and their families whose lives are affected by prostate cancer. In addition we aim to represent the opinions of patients on any subject which is relevant to the diagnosis and treatment of prostate cancer. We also support local prostate cancer support groups around the UK. We represent nearly 100 support groups in England and Wales and through them have several thousand members - men and their families whose lives have been affected by prostate cancer.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**NO**

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**
5. How did you gather information about the experiences of patients and carers to include in your submission?	Tackle gain regular feedback from our members via face to face contact at local and national meetings, from direct contact by telephone from individuals and from the questions and queries of patients through our patient helpline. We have a medical advisory board who advise when and where necessary. I do not have personal experience of being treated with 177Lu-PSMA-617. The treatment under discussion is not in current NHS use for the treatment of advanced prostate cancer. However, I have spoken with one patient who is currently undergoing treatment privately. I have also spoken with patients who are faced with the clinical scenario of advanced prostate cancer and who have metastatic disease now not responding to treatment. I can understand their needs and concerns. Tackle believe that it is appropriate for me to speak on their behalf.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Patients with advanced prostate cancer / metastatic prostate cancer will know that they have a limited life span. Many of these men will experience, or go on to experience, considerable side effects. Commonly these will be fatigue, chronic pain (often with exacerbations of acute pain), urinary and bowel problems, low mood or frank depression. Metastases in bone can be particularly painful and can lead to pathological fractures sometimes requiring complex surgical intervention. Soft tissue, visceral or lymph node involvement can become symptomatic by virtue of the expansion of the tissue or by causing pressure on vital organs, nerves or spinal cord. The quality of life of those patients may be very poor. They will have already exhausted the currently approved therapy pathway of hormone treatment (e.g. Zoladex), chemotherapy and Abiraterone/Enzalutamide. For some whose metastases are confined only to bone, the use of Radium 223 is an option. However a considerable number of patients will also have visceral / soft tissue metastases for whom Radium 223 is inappropriate. The only course currently open to them is purely that of symptom relief and palliative care.

	There will always be some men who do not wish to have further treatment and will choose the option of palliative care and symptom relief. However, currently the opportunity to make a choice between palliative care and further treatment simply does not exist. Patients, family and carers will all have experienced considerable ups and downs during the treatment journey of prostate cancer. This new treatment now offers some degree of hope for many who currently feel that the end of their life is now becoming a reality.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	At the stage where 177Lu-PSMA-617 might be used, patients will have already exhausted the range of treatments currently available to them. For them, treatment will have simply just failed to work or will have produced intolerable side effects. They will not 'blame' the individual treatments for their failure but will obviously be distressed that available treatments have led to such a poor future outcome. For patients, the term 'current treatments' may well only refer to treatments that each individual patient has been offered by their clinicians. There may be regional variations in what is offered. A small number of patients may have experience of research / trial programs involving newer therapies, such as the treatment under discussion. Some may have been able to access this treatment privately. Some may have learned about 177Lu-PSMA-617 and question why it is not available to them under the NHS. For them a positive outcome of this appraisal could mean the difference literally between prolonging life and facing the future of an earlier and possibly painful death.
8. Is there an unmet need for patients with this condition?	Patients with advancing disease that is no longer controlled by the standard range of treatments available have very few options. There is undoubtedly an unmet need for an addition to the treatment pathway. 177Lu-PSMA-617 therapy uses a totally new approach to treatment: It combines two separate technologies. There is the ability to selectively identify prostate cancers cells with a 'ligand' which binds to that cell using the PSMA receptor/antigen. It then adds the ability to tag that ligand with a highly radioactive molecule capable of delivering a toxic does of radiation but only over a very short distance. This produces a form of high-dose but 'localised radiotherapy'.

	'Localised radiotherapy' can also be produced by Radium 223 but this treatment utilises a different mechanism to target the cancer cell and is only of value in bone metastases. There is an undoubted unmet need for an additional therapy for those patients with both bone and soft tissue metastases. There are no direct comparators for this novel therapy. Some patients could be offered further taxane chemotherapy, but many will not be medically fit for such rigorous treatment or for other reasons may be 'chemotherapy unsuitable'. In addition it has been questioned by some whether further sessions of chemotherapy are always appropriate. It could potentially be argued that cancer cells are now selectively progressing because they are genetically different and are thus not affected by taxane chemotherapy. Their ability to grow has been enhanced by the eradication of chemotherapy sensitive cancer cells. Further taxane chemotherapy may well be illogical and inappropriate. In essence, this is a totally novel treatment and undoubtedly fulfils an unmet need. That need is not just that patients are 'clutching at straws' but that further prolongation of life of good quality can, for them, be a possibility.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Put simply, the advantages are the chance of slower progression of disease and a potential reduction in the onset of adverse events caused by the disease – if they are not present already. It gives those patients with both bone and soft tissue metastases a totally new direction of treatment. Patients know they are not curable – and will not expect it. They purely see this as a way of potentially achieving and increased quality of life for a longer period of time.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients can often be concerned about radiotherapy and the general effects that such treatments can have. The treatment under appraisal is a very localised treatment and, properly managed, side effects can be minimised. It is given by intravenous infusion and will thus requires hospital admission and supervision. As with other forms of nuclear medicine therapy, there is a need for a restriction on contact with others and the need for careful handling of potentially radio-active waste products etc. Side effects can be an issue with any potent therapy. The adverse events reported for 177Lu-PSMA-617 have, in the main, been of low grade. In the VISION trial 12% patients had adverse events that led to discontinuation of therapy. A reduction in dosage or interruption of therapy was noted in 6% and 16% of patients respectively. The patient with whom I spoke had experienced very little side effects and those were relatively transient. Fatigue he put down to his general condition and produced only a minor impact on life overall. The preparation and handling of 177Lu-PSMA-617 carries with it complex logistical problems, but these are not the concern of the patient. These potential problems are not insuperable. Sudden cancellation of a treatment session could potentially occur if there is a problem with supply of the active preparation of 177Lu-PSMA-617 .
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so,	As previously stated, this treatment will particularly benefit patients who have both bone and soft tissue metastases which are progressing despite previous treatment with standard therapies. It could be argued that even for patients with only demonstrable bone lesions 177Lu-PSMA-617 could be a valid alternative. It is recognised that a proportion of patients treated with Radium223 can progress to having visceral / soft tissue metastases. Such metastases could have been present at the time of diagnosis but not identified by the scanning techniques originally used and may well have responded to 177Lu-PSMA-617 had it have been used previously.

please describe them and explain why.	Bone scanning will obviously not identify visceral / soft tissue deposits. PSMA scanning is arguably more sensitive and is a pre-requisite prior to treatment with 177Lu-PSMA-617 .
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There is the potential for inequality in patients who for many reasons have been unable to tolerate taxane chemotherapy or considered 'chemotherapy-unsuitable' for a variety of reasons. Any restrictions on new therapies that require previous use of taxane chemotherapy will exclude this group of patients from potentially beneficial therapy. The restriction on chemotherapy usage that was required by the Covid pandemic will have significantly reduced the numbers of patients having had previous taxane therapy, further increasing the number of patients who might be suitable for 177Lu-PSMA-617 therapy but could be excluded. Such restrictions do not necessarily apply to Radium 223 where a 'chemotherapy-unsutable' population has been identified and accepted.
Other issues	
13. Are there any other issues that you would like the committee to consider?	N / A

Key messages

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

- Patients may reach a stage of progressive disease where all standard therapies have been exhausted. Terminal care may be the only option left along with the significantly poor quality of life that can occur despite all attempts at symptom control.
- 177Lu-PSMA-617 therapy is a combination of 2 innovative techniques – the ability to selectively identify prostate cancer cells and to deliver targeted radiotherapy to those cells. This is a totally new approach to prostate cancer treatment, although it has already been shown to be of benefit in other disease areas such as neuro-endocrine tumours. For prostate cancer there are no direct comparators for this novel treatment.
- There is now the possibility for patients to receive treatment who were previously considered to have no further treatment options left. Those patients with both bone and soft tissue metastases could now be offered life-extending treatment. Patient deemed 'chemotherapy unsuitable' are not excluded from having Radium 223 therapy. It would be illogical if patients were denied 177Lu-PSMA-617 on the grounds of not having previously had taxane chemotherapy.
- Consideration has to be given to the organisational issues of preparing and administering a radio-active substance. However these are not insuperable and this therapy is already in use both in research centres and in private medicine.
- Both *quantity* and *quality* of life have equal importance to patients. This new treatment offers the possibility of extension of life in a clinical situation where previously there was none. Some patients may make the choice not to have further treatment but to choose palliative care, others may choose further treatment. This choice currently does not exist.

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^{177}Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies: A Single Technology Appraisal

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Rider on responsibility for report

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Contributions of authors

Ruth Wong critiqued the company's search strategy. Christopher Carroll summarised and critiqued the clinical effectiveness data reported within the company's submission. Shijie Ren critiqued the statistical aspects of the submission. Sarah Davis and Aline Navega Biz critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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Abbreviations

^{177}Lu	Lutetium-177
ACP	American College of Physicians
ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Akaike Information Criterion
ARPI	Androgen receptor pathway inhibitor
ASCO	American Society of Clinical Oncology
BIC	Bayesian Information Criterion
BNF	British National Formulary
BOR	Best overall response
BPI-SF	Brief Pain Inventory – Short Form
BRCA1/2	Breast cancer genes 1 and 2
BSA	Body surface area
BSC	Best supportive care
BSoC	Best Standard of Care
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
COVID	Coronavirus disease 2019
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible intervals
CODA	Convergence Diagnostic and Output Analysis
CRPC	Castration resistant prostate cancer
cPAS	Comparator Patient Access Scheme
CSR	Clinical study report
CT	Computerised tomography
DARE	Database of Abstracts of Reviews of Effects
DCR	Disease control rate
DIC	Deviance Information Criterion
DID	Diagnostic Imaging Dataset
DOR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
eMIT	Drugs and pharmaceutical electronic market information tool
EQ-5D-5L	EuroQoL-5 Dimension-5 Level
ESMO	European Society for Medical Oncology
FACT-P	Functional Assessment of Cancer Therapy – Prostate

FAS	Full analysis set
FDA	Food and Drug Administration
GBq	Gigabecquerel
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage colony-stimulating factor
HES	Hospital Episode Statistics
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HSPC	Hormone-sensitive prostate cancer
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IPCW	Inverse probability-of-censoring weighting
IRT	Interactive response technology
ITT	Intent to treat
IU	International unit
IV	Intravenous
KM	Kaplan-Meier
KP	Karnofsky performance-status
LDH	Lactate dehydrogenase
LY	Life year
LYG	Life year gained
MBq	Megabecquerel
mCi	Millicurie
MCMC	Markov Chain Monte Carlo
mCRPC	Metastatic castration-resistant prostate cancer
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NAAD	Novel androgen axis drug
NCR	National Cancer Registry
NCRAS	National Cancer Registration and Analysis Service
NCT	National Clinical Trial
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PC	Prostate cancer

PCWG3	Prostate Cancer Working Group 3
PH	Proportional hazards
PD	Progressed disease
PET	Positron emission tomography
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PHE	Public Health England
PR	Partial response
PRO	Patient-reported outcome
PSA	Prostate-specific antigen
PSI	Prostate symptom index
PSMA	Prostate-specific membrane antigen
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QTc	Corrected QT interval
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
rPFS	Radiographic progression-free survival
RTDS	Radiotherapy Dataset
RWE	Real-world evidence
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SPECT	Single photon emission computerised tomography
SRE	Skeletal-related events
SSE	Symptomatic skeletal event
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TOI	Trial outcome index
UK	United Kingdom

1. EXECUTIVE SUMMARY

This External Assessment Group (EAG) report assesses ^{177}Lu vipivotide tetraxetan for treating prostate-specific membrane antigen (PSMA)-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies. This summary provides a brief overview of the key issues identified by the EAG as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, and do not necessarily reflect the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Key issues identified by the EAG that impact on the incremental costs and quality-adjusted life years (QALYs) for ^{177}Lu vipivotide tetraxetan compared with cabazitaxel and ^{177}Lu vipivotide tetraxetan compared with standard of care (SOC) are summarised in Table 1.

Table 1: Overview of the EAG's key issues

ID3840	Summary of issue	Report sections
Issue 1	Broadening of population to include patients who are not medically suitable for taxanes	2.3.1 and 2.3.5
Issue 2	Exclusion of radium-223 as a comparator for people with bone metastases	2.2 and 2.3.3
Issue 3	Concerns regarding company's network meta-analysis	3.3.4.3
Issue 4	Concerns regarding OS estimates for cabazitaxel in the model	4.2.4.2.1, 4.2.4.2.2 and 4.3.4
Issue 5	Use of pre-progression utility values for cabazitaxel that are equivalent to SOC and use of post-progression utility values for cabazitaxel that are lower than for both SOC and ^{177}Lu vipivotide tetraxetan	4.3.4
Issue 6	Exclusion of SOC costs from the ^{177}Lu vipivotide tetraxetan treatment and cabazitaxel treatment arms	4.2.4.5.2 and 4.3.4
Issue 7	Costing of pre-medication and concomitant medications for cabazitaxel	4.3.4
Issue 8	Estimation of SSE incidence	4.3.4

Abbreviations: EAG, External Assessment Group; RWE, real-world evidence; SOC, standard of care; OS, overall survival SSE, symptomatic skeletal event.

The key differences between the company's economic analyses and the EAG's preferred assumptions are as follows:

- The EAG's preferred analysis uses the hazard ratio (HR) estimated from the network meta-analysis (NMA) generated by the EAG (EAG's base case NMA) for overall survival (OS) and radiographic progression-free survival (rPFS), which maintains randomisation of the VISION trial by using data from the subgroup of patients who had androgen receptor pathway inhibitor (ARPI) as part of SOC for both arms of the VISION trial, includes the head-to-head comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel (TheraP trial) for the NMA for rPFS, excludes the following trials: TROPIC, ALYSYMPCA, PROfound, COU-AA-301, AFFIRM and Sun *et al.* 2016, and uses a random effects model. The company's NMA broke the randomisation of the VISION trial, excludes the TheraP trial, includes the six trials excluded in the EAG's base case NMA and uses a fixed effect model;
- The EAG's preferred analysis uses the NMA for OS instead of real-world evidence (RWE) to estimate OS for cabazitaxel;
- The EAG's preferred analysis uses treatment-independent utilities for pre- and post-progression health states estimated from Euroqol 5-Dimensions 5-Level (EQ-5D-5L) data from the VISION trial (mapped to 3L) with treatment specific utility decrements associated with adverse events (AEs) and symptomatic skeletal events (SSEs), instead of utilities by treatment group which are assumed to account for health-related quality of life (HRQoL) losses associated with AEs and SSEs;
- The EAG's preferred analysis includes SOC costs for all treatment groups, instead of excluding these concomitant costs for the ^{177}Lu vipivotide tetraxetan treatment and cabazitaxel treatment arms;
- The EAG's preferred analysis uses alternative assumptions regarding pre-medications and concomitant medications associated with cabazitaxel treatment;
- The EAG's preferred analysis uses the cumulative incidence of symptomatic skeletal events (SSEs) reported from the VISION and CARD trials to estimate costs and HRQoL losses related to SSE, rather than extrapolation of the time-to-first SSE data.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life, using QALYs. An ICER is the ratio of the extra cost for every QALY gained.

Overall, the model suggests that the technology increases QALYs by increasing survival both pre- and post-progression compared to both cabazitaxel and SOC. However, the size of the increase in post-

progression survival for ^{177}Lu vipivotide tetraxetan compared to cabazitaxel is dependent on the company's decision to use RWE to estimate survival for cabazitaxel rather than the NMA.

Overall, the model suggests that the technology affects costs by increasing treatment costs relative to cabazitaxel. When compared to SOC, the technology increases treatment costs, with some of these additional costs being offset, mainly by reduced usage of concomitant medication. However, these cost offsets are dependent on the company's assumption that costs of concomitant medication are incurred for SOC and not for ^{177}Lu vipivotide tetraxetan.

The modelling assumptions that have the greatest effect on the ICER for ^{177}Lu vipivotide tetraxetan versus cabazitaxel are:

- Whether the RWE evidence or the NMA is used to model OS for cabazitaxel,
- The inclusion of evidence directly comparing ^{177}Lu vipivotide tetraxetan and cabazitaxel from the TheraP trial in the NMA for rPFS,
- The utility values applied for the pre-progression and post-progression health states,
- Granulocyte colony-stimulating factor (G-CSF) usage during cabazitaxel treatment.

The modelling assumptions that have the greatest impact on the ICER for ^{177}Lu vipivotide tetraxetan versus SOC are:

- The inclusion of costs for concomitant medications receiving during treatment with ^{177}Lu vipivotide tetraxetan in the VISION trial,
- The utility values applied for the pre-progression and post-progression health states combined with use of cumulative incidence of SSE from trials rather than extrapolating time-to-first SSE data.

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company's submission (CS) is partially in line with the final NICE scope. The target population in the CS is people with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) who have received at least two prior treatments (androgen receptor pathway inhibitor (ARPI) and taxane-based chemotherapy) or who are not medically suitable for taxanes. As part of their submission to NICE, the company submitted an economic analysis which is intended to reflect the population of patients with mCRPC for three subgroups:

(i) Subgroup 1: Patients who have received at least two prior lines of treatment with an ARPI and at least one taxane-based chemotherapy; and who are eligible to receive further taxane treatment with cabazitaxel (third-line positioning of ^{177}Lu vipivotide tetraxetan);

(ii) Subgroup 2: Patients who have received at least two prior lines of treatment with an ARPI and at least one taxane-based chemotherapy and are ineligible to receive further taxanes;

either because they have previously received cabazitaxel (fourth-line positioning of ^{177}Lu vipivotide tetraxetan), or because they are unsuitable for third-line cabazitaxel (third-line positioning of ^{177}Lu vipivotide tetraxetan);

(iii) Subgroup 3: Patients who have received one prior line of treatment, but are unsuitable for treatment with taxanes (second-line positioning of ^{177}Lu vipivotide tetraxetan).

The company presented in their cost-effectiveness analysis a single analysis intended to cover all three subgroups. The CS argues that the main comparator for ^{177}Lu vipivotide tetraxetan is cabazitaxel, and that the comparison against SOC is reserved for patients who are ineligible for treatment with cabazitaxel following treatment with an ARPI and docetaxel or not medically suitable for taxanes (subgroups 2 and 3). Although the company is not specific about the appropriate comparator for patients within subgroup 2 who have previously received third-line cabazitaxel, the EAG believes the appropriate comparator in this group would also be SOC, as they would not be retreated with cabazitaxel. Other comparators listed in the final NICE scope (radium-223 and docetaxel) have not been included in the company's economic analysis.

The key issues related to the decision problem are presented below.

Issue 1: Broadening of population to include patients who are not medically suitable for taxanes

Report section	2.3.1 and 2.3.5
Description of issue and why the EAG has identified it as important	The final scope issued by NICE described the population as patients "*previously treated with an ARPI and taxane based chemotherapy.*" The company has broadened the population to also include those patients who are not medically suitable for taxanes (subgroup 3). The EAG notes that patients who have not received taxane-based chemotherapy are outside of the final scope and there is no evidence presented in the CS that estimates the effectiveness or cost-effectiveness of ^{177}Lu vipivotide tetraxetan in patients who not medically suitable for taxanes. The company estimates that this group will be around 42% of the total population eligible for ^{177}Lu vipivotide tetraxetan.
What alternative approach has the EAG suggested?	Given the lack of information on the effectiveness and cost-effectiveness of ^{177}Lu vipivotide tetraxetan in this subgroup, the EAG would suggest that the estimates of clinical and cost-effectiveness in the company submission are not considered applicable to this group.
What is the expected effect on the cost-effectiveness estimates?	The estimates of cost-effectiveness for this subgroup are informed by evidence from the VISION trial, which relate to populations previously treated with docetaxel. Therefore, the ICER for patients who are not eligible for taxanes is not known and could be higher, lower or similar to that estimated in the CS.
What additional evidence or analyses might help to resolve this key issue?	Evidence from an ongoing study (NCT04689828) may provide information about the clinical effectiveness of ^{177}Lu vipivotide tetraxetan compared with androgen receptor-directed therapy (ARDT) in patients with PMSA-positive mCRPC not previously treated with taxanes (except when treated in the adjuvant or neo-adjuvant setting more than 12 months previously).

Issue 2: Exclusion of radium-223 dichloride as a comparator for people with bone metastases

Report section	2.2 and 2.3.3
Description of issue and why the EAG has identified it as important	The final scope issued by NICE included radium-223 dichloride as a comparator for people with bone metastases. The company excludes radium-223 as a comparator in the submission. The EAG disagrees with this, as patients with bone metastases who do not have visceral metastases, would receive radium-223 in the post-ARPI and taxane setting and post-ARPI where docetaxel is contraindicated or unsuitable setting. However, the EAG recognises that radium-223 would be a relevant comparator only for a minority of patients. The EAG also recognises that there were concerns regarding the generalisability of data from the ALSYMPCA trial to the population with both prior ARPI and taxane treatment. This limits the potential for unbiased indirect comparison between ^{177}Lu vipivotide tetraxetan and radium-223.
What alternative approach has the EAG suggested?	No alternative approach has been suggested given the limited data available to estimate relative treatment effect.
What is the expected effect on the cost-effectiveness estimates?	The ICER for ^{177}Lu vipivotide tetraxetan relative to radium-223 in the subset of patients who have bone metastases without visceral metastases is unknown.
What additional evidence or analyses might help to resolve this key issue?	The EAG did not identify any ongoing studies that would address this uncertainty.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The key clinical evidence presented in the CS and that informs the economic analysis for ^{117}Lu vipivotide tetraxetan is from the Phase III VISION study, which compared ^{177}Lu vipivotide tetraxetan + SOC with SOC alone in pre-treated mCRPC PSMA-positive adults. In the absence of Phase III trial data directly comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel, the CS presented the following evidence for consideration: an NMA comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel and other potentially relevant comparator therapies (seven Phase III RCTs plus VISION), and supporting evidence including a Phase II trial comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel (the TheraP trial) and a RWE analysis on cabazitaxel. The most relevant cabazitaxel trial included in the NMA was the CARD trial, because it included patients who had received both an ARPI and a taxane-based treatment previously. The CARD trial compared cabazitaxel to ARPIs. Therefore, to facilitate an indirect comparison between cabazitaxel and ^{177}Lu vipivotide tetraxetan, the company used data from the subgroup of patients in the SOC only arm of the VISION trial who had received ARPIs as part of SOC in the NMA, but also used data from all patients in the ^{177}Lu vipivotide tetraxetan + SOC arm regardless of whether they had received ARPIs as part of SOC in the NMA.

The EAG's key issues regarding the clinical effectiveness evidence are discussed below.

Issue 3: Concerns regarding company's NMA

Report section	3.3.4.3
Description of issue and why the EAG has identified it as important	The EAG has several concerns with the company's NMA: that data used from the VISION trial broke the randomisation; exclusion of the head-to-head trial (TheraP); inclusion of the TROPIC and ALSYMPCA trials where the population was less heavily pre-treated compared to the VISION trial population; assuming that PSA progression-free survival is the same as the rPFS when analysing rPFS, and the use of a fixed effect model which underestimates the between-study heterogeneity.
What alternative approach has the EAG suggested?	The EAG has provided an alternative NMA using the following methods: maintaining randomisation by using data from the subpopulation who had ARPI as part of SOC for both arms of the VISION trial (note that inclusion of an ARPI as part of SOC is a stratification factor at randomisation); excluding the TROPIC, ALSYMPCA trials (which rendered the inclusion of the PROfound, COU-AA-301, AFFIRM and Sun *et al*. 2016 trials unnecessary so these were also excluded); including the TheraP trial, and employing a random effects model.
What is the expected effect on the cost-effectiveness estimates?	The EAG's exploratory analysis (EA10) demonstrates that incorporating the EAG's preferred NMA does not have a substantial impact on the ICER when continuing to use the RWE for OS. However, comparing EAG analyses EA11 with EA12 shows that the EAG's NMA has a substantial upward impact on the ICER when using the NMA to estimate OS for cabazitaxel instead of the RWE.
What additional evidence or analyses might help to resolve this key issue?	The EAG prefers to use the EAG's alternative NMA to inform the economic analysis. Beyond this, the EAG is not aware of any additional evidence or analyses that would address this issue further.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The company's base case economic analysis compares ^{177}Lu vipivotide tetraxetan versus cabazitaxel and SOC in people with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes. The model adopts a partitioned survival approach, and includes three health states: (i) progression-free; (ii) post-progression and (iii) dead. Health outcomes and costs are evaluated from the perspective of the NHS and Personal Social Services (PSS) over a time horizon of 10 years, which is considered sufficient to capture life-time costs and benefits in this population. OS, rPFS and time-to-first SSE for ^{177}Lu vipivotide tetraxetan and SOC are based on data from VISION. For cabazitaxel, rPFS was estimated by applying HRs from the company's NMA and OS was estimated using the RWE. Health utilities for ^{177}Lu vipivotide tetraxetan and SOC groups were estimated using a generalised linear mixed model fitted to EQ-5D-5L mapped to 3L data collected in VISION. For cabazitaxel it was assumed that the pre-progression utility value would be equivalent to SOC and the post-progression utility value was taken from a previous NICE technology appraisal (TA). Resource use estimates were derived from VISION, previous NICE TA, additional studies, standard costing sources and assumptions.

The deterministic version of the company's base case model suggests that ^{177}Lu vipivotide tetraxetan is expected to generate an additional [redacted] QALYs when compared to cabazitaxel, at an additional cost of [redacted] per patient and corresponding ICER of [redacted] per QALY gained. In the comparison against SOC, the deterministic version of the model suggests that ^{177}Lu vipivotide tetraxetan generates an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is [redacted] per QALY gained.

The EAG's key issues regarding the cost-effectiveness evidence and the company's economic analyses are discussed below.

Issue 4: OS estimates for cabazitaxel

Report section	4.2.4.2.1, 4.2.4.2.2 and 4.3.4
Description of issue and why the EAG has identified it as important	The company has used the RWE to estimate OS for cabazitaxel whereas the extrapolation of OS data for ^{177}Lu vipivotide tetraxetan and SOC were based on survival models fitted to the VISION trial data. The EAG notes that median survival in the RWE analysis of cabazitaxel is lower than median survival in the SOC arm of VISION ([redacted] months vs. 11.3 months). The company's explanation is that this is because patients in trials receive better care than those treated in the real-world. The EAG argues that this introduces a potential bias because patients in the two treatment groups of VISION would also benefit from the better standard of care provided within the study and therefore this could similarly bias the OS estimates for ^{177}Lu vipivotide tetraxetan to be higher than would be expected in clinical practice.
What alternative approach has the EAG suggested?	The EAG prefers to estimate the relative treatment effect from the NMA as this eliminates the impact of any differences in the standard of care provided within the trial and real-world clinical settings. This relative treatment effect is then applied to the trial-based estimates of OS for ^{177}Lu vipivotide tetraxetan to estimate the expected OS for cabazitaxel within a trial setting.
What is the expected effect on the cost-effectiveness estimates?	The EAG's scenario analysis (EA11) shows that estimating cabazitaxel OS using the relative treatment effect from the NMA, instead of the RWE, has a substantial impact on the ICER when using the company's preferred NMA to estimate the HRs. The impact is even greater when combined with the EAG's preferred NMA (see EA12).
What additional evidence or analyses might help to resolve this key issue?	The EAG is not aware of any additional evidence or analyses currently available that might further resolve this issue. The Appraisal Committee may wish to seek further advice from additional clinical experts regarding the expected survival of patients receiving ^{177}Lu vipivotide tetraxetan and cabazitaxel.

Issue 5: Utility values for cabazitaxel

Report section	4.3.4
Description of issue and why the EAG has identified it as important	The company assumed that the pre-progression utility for cabazitaxel would be equivalent to that of SOC from the VISION trial, and applied a post-progression utility value for cabazitaxel that was lower than for both SOC and ^{177}Lu vipivotide tetraxetan. The EAG is concerned that these low utility values for cabazitaxel are not fully justified by the evidence provided. Whilst the EAG accepts that the toxicity profile for cabazitaxel may lead to lower HRQoL for this group compared to ^{177}Lu vipivotide tetraxetan for patients receiving treatment pre-progression, based on comparisons of HRQoL data from the TheraP trial, there is a lack of direct head-to-head evidence quantifying how this would translate to utility differences.
What alternative approach has the EAG suggested?	The EAG prefers the approach used in the company's scenario analysis, whereby treatment-independent utility values are applied to the pre- and post-progression health states, and these are adjusted to account for differences in AEs and SSEs. This allows a consistent approach to be applied across all three treatments being compared. It also has the potential to capture differences between ^{177}Lu vipivotide tetraxetan and cabazitaxel arising from differences in toxicity reflected in AE rates.
What is the expected effect on the cost-effectiveness estimates?	This had significant impact on the ICER for ^{177}Lu vipivotide tetraxetan versus cabazitaxel and versus SOC in the exploratory analysis described as EA6.
What additional evidence or analyses might help to resolve this key issue?	The company could explore mapping from the EORTC QLQ-C30 values for ^{177}Lu vipivotide tetraxetan and cabazitaxel obtained from the TheraP trial to EQ-5D utility values to provide an estimate of the likely size of any utility difference between these treatments.

Issue 6: Exclusion of SOC costs from ^{177}Lu vipivotide tetraxetan and cabazitaxel arms

Report section	4.2.4.5.2 and 4.3.4
Description of issue and why the EAG has identified it as important	The base case analysis in the company's model assumes that the costs for these concomitant therapies are only incurred by patients in the SOC treatment group. The EAG believes this is inappropriate, given that patients in the ^{177}Lu vipivotide tetraxetan arm of the VISION trial also received these treatments and the potential impact of these treatments on study outcomes is uncertain.
What alternative approach has the EAG suggested?	The EAG prefers to include estimates of concomitant therapies for all treatment strategies based on data form VISION for ^{177}Lu vipivotide tetraxetan arm and data averaged across both arms of the VISION trial for cabazitaxel. This is the approach used in a company's scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	This issue mainly affects the comparison between ^{177}Lu vipivotide tetraxetan and SOC, where it underestimates the incremental cost of ^{177}Lu vipivotide tetraxetan. Using the EAG's preferred approach significantly increases the ICER for ^{177}Lu vipivotide tetraxetan versus SOC from [redacted]. This issue has a small impact in the comparison of ^{177}Lu vipivotide tetraxetan and cabazitaxel because both arms are affected similarly.
What additional evidence or analyses might help to resolve this key issue?	The EAG is not aware of any additional evidence or analyses that might further resolve this issue.

Issue 7: Costing of pre-medication and concomitant medications for cabazitaxel

Report section	4.3.4
Description of issue and why the EAG has identified it as important	The company's analysis includes G-CSF costs for 14 days of every 21-day cabazitaxel cycle. The EAG's clinical advisors stated that G-CSF usage varied within current clinical practice, but that when used, it is mainly used for 5 to 7 days only. The EAG also identified some issues with the costing of pre-medications (antihistamines, H2 antagonists, corticosteroids) and prednisolone given alongside cabazitaxel, but these had less of an impact than the G-CSF cost.
What alternative approach has the EAG suggested?	The EAG has reduced the cost of G-CSF to 5 days per 21-day cycle.
What is the expected effect on the cost-effectiveness estimates?	This had significant impact on the ICER for ^{177}Lu vipivotide tetraxetan versus cabazitaxel in the exploratory analysis described as EA3. Although this also included adjustments for other pre-medications, the G-CSF costs were the primary driver of change in this scenario.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert views could be sought on the usage of G-CSF along-side cabazitaxel in clinical practice.

Issue 8: Estimation of SSE incidence

Report section	4.3.4
Description of issue and why the EAG has identified it as important	The company's base case approach used a log-normal survival model to extrapolate the incidence of SSEs from the time-to-first SSE data from VISION. The company assumed that the same survival curve would be applied to both ^{177}Lu vipivotide tetraxetan and cabazitaxel, on the basis that the time-to-first SSE curves from the VISION and CARD trials were similar. However, the extrapolated curves were restricted by OS and this led to different cumulative incidences of SSEs for ^{177}Lu vipivotide tetraxetan and cabazitaxel. The approach used by the company resulted in a cumulative incidence of SSE that is much higher than observed in the trials despite the Kaplan-Meier plot of time-to-first SSE or death being relatively complete by the end of the VISION trial follow-up.
What alternative approach has the EAG suggested?	The EAG prefers the approach used in the company's scenario analysis in which the cumulative incidence of SSEs is based on rates observed in the VISION trial for ^{177}Lu vipivotide tetraxetan and SOC, and rates observed in the CARD trial for cabazitaxel. The timing of SSEs is assumed to follow the timing of radiographic progression. This leads to a cumulative incidence of SSEs which matches the rates observed in the trials but with incorrect timing. However, the EAG believes this is preferable to the approach used by the company which results in a cumulative incidence of SSE that is much higher than observed in the trials and which introduces a difference between SSE rates for ^{177}Lu vipivotide tetraxetan and cabazitaxel which is not supported by the evidence.
What is the expected effect on the cost-effectiveness estimates?	This has a minimal impact on the ICER for either comparison when this was changed in isolation (EA7). However, it has a significant impact on the ICER when combined with the alternative approach to utility values (Issue 6 and EA6) within exploratory analysis EA8.
What additional evidence or analyses might help to resolve this key issue?	The EAG is not aware of any additional evidence or analyses that might further resolve this issue.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 summarises the results of the EAG's preferred analyses for the comparisons of ^{177}Lu vipivotide tetraxetan versus cabazitaxel, and ^{177}Lu vipivotide tetraxetan versus SOC. Each analysis reflects individual model amendments relative to the EAG-corrected version of the model (EA1). The EAG's preferred analysis (EA13) suggests that the deterministic ICER for ^{177}Lu vipivotide tetraxetan versus cabazitaxel and versus SOC is estimated to be [redacted] per QALY gained and [redacted] per QALY gained, respectively. For the comparison of ^{177}Lu vipivotide tetraxetan versus SOC, the probabilistic ICER is similar to the deterministic ICER, but for the comparison of ^{177}Lu vipivotide tetraxetan versus cabazitaxel the probabilistic ICER is higher ([redacted] per QALY) as it incorporates the wide credible intervals around the HRs for OS and rPFS. The EAG's full critique of the company's economic analyses and the EAG's exploratory analyses can be found in Sections 4.3 and 4.4.

Table 2: Summary of results of EAG exploratory analyses, deterministic (unless otherwise stated)

Scenario	^{177}Lu vipivotide tetraxetan versus cabazitaxel			^{177}Lu vipivotide tetraxetan versus SOC		
	Incremental QALYs	Incremental cost	ICER (change from CBC)	Incremental QALYs	Incremental cost	ICER (change from CBC)
Company's base case (CBC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA1: Correction of errors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA2: EAG preferences for unit costs for epoetin alpha and filgrastim	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA3: EAG preferences for cabazitaxel pre-medications and concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA4: Costs for SOC concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA5: Cost of ^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA6: Approach for health-state utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA7: Alternative approach for SSE incidence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA8: Alternative approach for SSE incidence and disutilities (EA6+EA7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA9: EA8 + Alternative source for SSE disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA10: Alternative rPFS and OS HR estimates for cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA11: Use of NMA instead of RWE to estimate OS for cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA12: Alternative rPFS and OS estimates and approach to estimate OS for cabazitaxel (EA10+EA11)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CBC, company's base case; EA, exploratory analysis; EAG, External Assessment Group; N/A, not applicable to this analysis; SOC, standard of care; SSE, symptomatic skeletal event; rPFS, radiographic progression-free survival; OS, overall, survival; HR, hazard ratio; RWE, real-world evidence; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

2 BACKGROUND

This section presents a brief summary and critique of the company's description of the disease and the current treatment pathway for prostate-specific membrane antigen (PSMA)-positive hormone-relapsed metastatic prostate cancer in England.

2.1 Critique of company's description of underlying health problem

Section B.1.3 of the company submission (CS)[1] contains an accurate overview of the health problem. Prostate cancer (PC) is a cancer that starts in the prostate gland. Metastatic PC means the cancer has spread from the prostate to other parts of the body, and it most commonly spreads to lymph nodes in other parts of the body or to the bones.[2] Castration-resistant PC (CRPC), which is also known as hormone-relapsed PC, refers to PC after failure of primary androgen deprivation therapy (ADT).[3] PSMA is a transmembrane glycoprotein that is highly expressed on prostate adenocarcinomas, exhibits only limited expression in benign and extraprostatic tissues and thus makes an ideal target for the diagnosis and management of PC.[4] PSMA-positive patients have been associated with more aggressive disease and poorer outcomes.[5, 6]

PC is the most common cancer in males in the England and Wales, with an incidence of 45,885 cases diagnosed in England and Wales between April 2019 and March 2020, where 13% were presenting with metastatic disease at diagnosis.[7] A systematic review shows that 10%-20% of PC patients develop CRPC within approximately 5 years of follow-up.[8] Metastatic CRPC (mCRPC) is associated with significant negative impacts on health-related quality of life (HRQoL).[9-11] In 2018, PC is the second most common cause of cancer death amongst men in the UK, and accounted for 13% of all cancer deaths in 2018 (11,890 deaths).[12] PC mortality is associated with increasing age and metastatic disease.[12] The CS highlights that patients with PSMA-positive mCRPC have already progressed through multiple lines of prior therapy, and remaining available therapies are often have the same mechanism of action as previously trialled therapies, limiting clinical response due to disease resistance.[1]

2.2 Critique of company's overview of current service provision

Section B.1.3. of the CS details current service provision in the UK.[1] The company notes that PSMA-positivity can be determined using any suitable gamma-emitting radiotracer linked to an appropriate PSMA ligand. The draft Summary of Product Characteristics (SmPC) for ^{177}Lu vipivotide tetraxetan (otherwise known as Lutetium-177 prostate-specific membrane antigen-617[177Lu-PSMA-617]) does not specify the determination method for PSMA-status.[13] Positron emission tomography-computerised tomography (PET-CT) and single-photon emission computerised tomography (SPECT) scans could be used for assessing PSMA-status and currently ^{68}Ga PET-CT scanning is accessible in five cities in England.[1] The company notes that the ^{68}Ga gozetotide is expected to receive an approval from the

Medicines and Healthcare products Regulatory Agency (MHRA) in [redacted] and a technetium-99m[^{99m}Tc]-labelled PSMA radiotracer is currently in development by the University of California. The company highlights that the commercialisation of ^{68}Ga gozetotide and ^{18}F fluorinated PSMA radiotracers for use with PET-CT infrastructure will provide further options for the identification of PSMA-positive patients with mCRPC and that "*expansion of existing services has been addressed through the NHS Levelling Up agenda and the future expansion of PET–CT facilities is eagerly anticipated by the clinical community*".[1]

The company summarises that for mCRPC patients in the pre-chemotherapy setting, patients who have no or mild symptoms after primary failure of ADT may be treated with corticosteroids or an androgen receptor pathway inhibitor (ARPI) (abiraterone or enzalutamide) in combination with prednisone or prednisolone. The CS notes that ARPIs should only be used once within the entire PC treatment pathway according National Institute for Health and Care Excellence (NICE) guidelines.[14] During the COVID-19 pandemic in 2020, NICE rapid guidance on systemic anticancer therapy guidance recommended using an ARPI (enzalutamide) as an alternative to docetaxel in men with newly-presenting hormone-sensitive prostate cancer, given that enzalutamide is less immunosuppressive and can be administrated at home. This resulted in a rapid and marked fall in docetaxel use, and a marked increase in ARPI use.[7]

In mCRPC patients where chemotherapy is clinically indicated, the NICE guideline NG131 recommends docetaxel only if their Karnofsky Performance-Status score is 60% or more. The CS states that "*patients who receive docetaxel in earlier hormone-sensitive disease are highly unlikely to receive repeat treatment with docetaxel in the mCRPC setting*".[1] Clinical advice received by the External Assessment Group (EAG) also confirmed that docetaxel rechallenge was not commonly used.

Cabazitaxel in combination with prednisone or prednisolone is recommended for mCRPC patients whose disease has progressed during or after docetaxel chemotherapy, only if the person has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and has had 225 mg/m^2 or more of docetaxel, or treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first).[15] The CS states that both abiraterone and enzalutamide (an ARPI) may be used following failure of docetaxel or in patients in whom docetaxel was not suitable. The CS also states that "*Radium-223 is recommended in patients with mCRPC who have already received docetaxel and who have symptomatic bone metastases. Its use is precluded in patients with visceral metastases*".[1]

The company's interpretation of the treatment pathway for patients with PSMA-positive mCRPC is provided in Figure 2 of the CS. The company anticipates that ^{177}Lu vipivotide tetraxetan will be positioned as an additional treatment option for:

(i) Subgroup 1: Patients who have received at least two prior lines of treatment with an ARPI and at least one taxane-based chemotherapy; and who are eligible to receive further taxane treatment with cabazitaxel (third-line positioning of ^{177}Lu vipivotide tetraxetan);

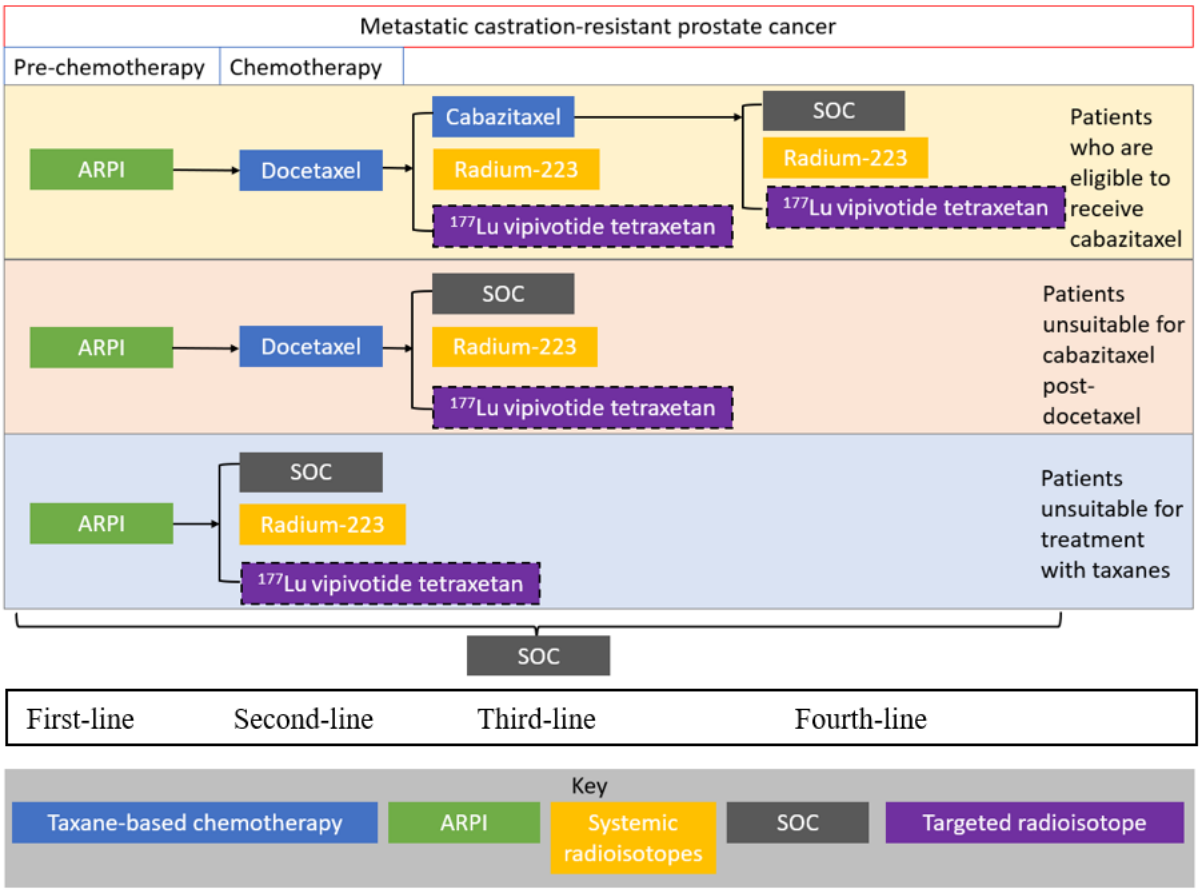
(ii) Subgroup 2: Patients who have received at least two prior lines of treatment with an ARPI and at least one taxane-based chemotherapy and are ineligible to receive further taxanes; either because they have previously received cabazitaxel (fourth-line positioning of ^{177}Lu vipivotide tetraxetan), or because they are unsuitable for third-line cabazitaxel (third-line positioning of ^{177}Lu vipivotide tetraxetan);

(iii) Subgroup 3: Patients who have received one prior line of treatment, but are unsuitable for treatment with taxanes (second-line positioning of ^{177}Lu vipivotide tetraxetan).

The EAG has some concerns around the company's description of existing NHS care pathways. NICE technology appraisal (TA)376 recommends radium-223 for patients in whom docetaxel is contraindicated or unsuitable,[16] which was not described by the company. The company excluded radium-223 as a relevant comparator in this appraisal. In response to clarification question A2 and B1, the company defended their decision to exclude radium-223 on the basis that: (i) there was not sufficient evidence to perform a comparison, and (ii) radium-223 is indicated in patients with symptomatic bone metastases but without any visceral metastases, but ^{177}Lu vipivotide tetraxetan is indicated for use regardless of metastasis site.[17] However, the company notes that further consultation with a clinical expert confirmed that there is a minority of patients who would receive radium-223 in the post-ARPI and taxane setting.[17] Three out of four EAG's clinical advisors also agreed that radium-223 is a relevant comparator in this appraisal.

Given the above considerations, an alternative overview of current clinical care pathways provided by clinical input is depicted in Figure 1.

Figure 1: The treatment pathway for metastatic castration-resistant prostate cancer in the UK



Abbreviations: ARPI: androgen receptor pathway inhibitor; SOC: standard of care.

2.3 Critique of company's definition of the decision problem

This section presents a summary and critique of the decision problem addressed by the CS. A summary of the decision problem as outlined in the final NICE scope[18] and addressed in the CS is presented in Table 3. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 3: The decision problem (reproduced from CS, Table 1 with minor amendments and comments from the EAG)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
Population	Adults with PSMA-positive, hormone-relapsed metastatic PC previously treated with an ARPI and taxane based chemotherapy.	Adult patients with PSMA-positive, mCRPC who have been treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes	The patient population of relevance for this submission is in line with the full anticipated marketing authorisation for ^{177}Lu vipivotide tetraxetan in PSMA-positive mCRPC, focussing on patients who experienced disease progression despite treatment with ARPI and taxane-based chemotherapy, or who are not medically suitable for (or do not tolerate) taxanes.	The population consists of a wider patient population group than that described in the final NICE scope. The CS includes patients who are not medically suitable for taxanes whereas the scope is limited to those how have had both an ARPI and a taxane.
Intervention	^{177}Lu-PSMA-617	As per NICE final scope	In line with NICE final scope	-
Comparator(s)	• Cabazitaxel • Docetaxel (for people who have had docetaxel in combination with ADT previously) • Radium-223 dichloride (for people with bone metastases) • Best supportive care The different positions that these comparators could be used in the treatment pathway will be considered in the appraisal.	The relevant comparators addressed in this submission include: • Cabazitaxel • SOC[a] as defined by the clinical judgement of the treating physician which may include: o Supportive measures (pain medications, hydration, transfusions, erythropoietin stimulation agents, etc.) o Ketoconazole o Androgen reducing agents o ARPIs o Bone-targeted agents (including zoledronic acid, denosumab, and bisphosphonates) o External beam or seeded form radiation therapy	Cabazitaxel is the most relevant comparator in patients who have previously received treatment with an ARPI and docetaxel who are eligible for further taxane treatment. SOC is the most relevant comparator for all other patients eligible for ^{177}Lu vipivotide tetraxetan who would not be eligible for further treatment with taxane therapy. Docetaxel rechallenge was not considered a relevant comparator in this appraisal because (i) in current UK clinical practice docetaxel is generally used early in the treatment pathway, (ii) docetaxel rechallenge likely occurs in as low as 2% of patients,[19, 20] (iii) the systematic literature review (SLR) conducted as part of this appraisal did not identify any evidence to support the use of docetaxel in mCRPC after disease progression on an ARPI, which limits the	Docetaxel rechallenge would be very infrequently used in UK practice. Patients with bone metastases would receive radium-223 in the post-ARPI and taxane setting and post-ARPI where docetaxel is contraindicated or unsuitable setting.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
		• SOC is not considered to include: o Investigational agents o Cytotoxic chemotherapy o Immunotherapy o Systemic radioisotopes (e.g., radium-223) o Semi-body radiotherapy	ability to conduct an indirect comparison, (iv) in the forthcoming NICE appraisal for pembrolizumab in combination with olaparib in patients with progressive mCRPC (ID3814), docetaxel was not considered a relevant comparator by NICE in the published draft scope.[21] Radium-223 is not considered a relevant comparator in this appraisal as it is indicated in patients with symptomatic bone metastases but without any visceral metastases, limiting comparability with ^{177}Lu vipivotide tetraxetan, which is intended for use regardless of metastasis site. The SLR did not identify any evidence to support the use of radium-223 in mCRPC in heavily pre-treated (post-ARPI, post-taxane) patients, which limits the ability to conduct an indirect comparison.	
Outcomes	The outcome measures to be considered include: • progression free survival (rPFS) • overall survival (OS) • time to a first symptomatic skeletal event (SSE) • adverse effects of treatment • health-related quality of life	The outcome measures considered include: • rPFS • OS • Time-to-first SSE • Adverse events of treatment • Health-related quality of life • Additional secondary outcome measures o Overall response rate (ORR) o Disease control rate (DCR) o Duration of response (DOR)	In line with NICE final scope. Whilst not specified in the NICE scope, additional secondary outcomes measures from VISION are presented in this submission to demonstrate the benefit of ^{177}Lu vipivotide tetraxetan as a treatment for mCRPC, but these outcomes do not inform indirect treatment comparisons or health economic modelling.	The company's economic model includes data for all the outcomes listed in NICE final scope. The CS clinical section also presented results for additional outcomes: ORR, DCR and DOR.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
Subgroups to be considered	No subgroup analyses were specified in the NICE final scope	Three patient subgroups may be considered: • Adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy and are suitable for further treatment with taxanes • Adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy and are ineligible for further treatment with taxanes Adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and who are not medically suitable for treatment with taxanes	Limiting the use of ^{177}Lu vipivotide tetraxetan to those patients who have previously received treatment with taxane-based chemotherapy would create inequity biased against those patients who are not medically suitable for treatment with taxanes, but who would be considered medically suitable for treatment with ^{177}Lu vipivotide tetraxetan. Mechanistically, there is no reason that the efficacy and safety of ^{177}Lu vipivotide tetraxetan would be significantly different in patients who have not previously received taxanes unless they had significantly more comorbidities; patients who are not medically suitable to receive taxanes for PSMA-positive mCRPC are still likely to derive clinical benefit from ^{177}Lu vipivotide tetraxetan. Therefore, a small proportion of patients with even fewer treatment options, who have been treated with ARPI and who are not medically suitable for taxanes may be considered appropriate for treatment with ^{177}Lu vipivotide tetraxetan.	The evidence that the company provided for treatment with ^{177}Lu vipivotide tetraxetan is for the first two subgroups only. There were no data available for the third subgroup: • Adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and who are not medically suitable for treatment with taxanes. The company estimates that the third subgroup represents around 42% of the total population eligible for ^{177}Lu vipivotide tetraxetan. The EAG also believes that the second subgroup identified by the company is heterogeneous as it includes those who are ineligible for further treatment with taxanes because they are unsuitable for third-line cabazitaxel and those who are ineligible for further treatment with taxanes because they have previously received third-line cabazitaxel.
Special considerations including issues related to equity or equality	NA	NA	Approximately 50% of patients with mCRPC have been identified as being ineligible for taxane-based chemotherapy.[15] Limiting the scope of ^{177}Lu vipivotide tetraxetan to only those patients who have received a taxane-based chemotherapy would potentially create an inequality.	-

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
			There are a currently a limited number of clinical centres in the UK which would be able to conduct the required assessment for PSMA positivity patients and then subsequently deliver treatment with ^{177}Lu vipivotide tetraxetan. Unless expansion of these existing services is prioritised there may be geographical inequality due to the need for some patients to travel long distances to receive treatment.	

[a]The terminology 'Standard of Care (SOC)' is used throughout this submission to align with the lexicon from the VISION trial. SOC should be considered equivalent to the other widely used terminology of 'Best Standard of Care (BSOC)'.

Abbreviations: EAG, External Assessment Group; ^{177}Lu, Lutetium-177; ARPI, androgen receptor pathway inhibitor; BRCA1/2, breast cancer genes 1 and 2; DCR, disease control rate; DOR, duration of response; HSPC, hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; MHRA, Medicines and Healthcare products Regulatory Agency; mHSPC, metastatic hormone-sensitive prostate cancer; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SOC, standard of care; SSE, symptomatic skeletal event; CS, company submission.

2.3.1 Population

The CS defines the target population for ^{177}Lu vipivotide tetraxetan as being the same as the anticipated UK marketing authorisation for ^{177}Lu vipivotide tetraxetan: "*for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive, metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibition (ARPI) and taxane-based chemotherapy or who are not medically suitable for taxanes*".[1] The EAG notes that it consists of a wider patient population group than that described in the final NICE scope, as it includes patients who are not medically suitable for taxanes whereas the scope is limited to people who have had both an ARPI and a taxane.

2.3.2 Intervention

^{177}Lu vipivotide tetraxetan is a novel targeted radioligand therapy, which consists of three components: an unstable lutetium isotope (^{177}Lu), a ligand that binds to PSMA expressed on the surface of PC cells, and a binder which attaches the PSMA-specific ligand to a cage housing the ^{177}Lu atom. Patients receiving ^{177}Lu vipivotide tetraxetan should have the presence of PSMA-positive lesions confirmed by PSMA imaging prior to receiving treatment with ^{177}Lu vipivotide tetraxetan.

^{177}Lu vipivotide tetraxetan may be administered intravenously as an injection using a disposable syringe fitted with a syringe shield (with or without a syringe pump), as an infusion using the gravity method (with or without an infusion pump), or as an infusion using the vial (with a peristaltic infusion pump).[1] The recommended dose of ^{177}Lu vipivotide tetraxetan is 7,400 MBq (200 mCi) every 6 weeks (±1 week).[1] Treatment with ^{177}Lu vipivotide tetraxetan should be continued until disease progression, unacceptable toxicity, or a maximum of 6 doses.[1] ^{177}Lu vipivotide tetraxetan is administered over a total duration of 30 to 40 minutes, followed by an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution.[1] The company expects the vast majority of administrations to be done on an outpatient or day case basis, with guidance of keeping patients up to 4 hours post-infusion.[1]

The company notes that ^{177}Lu vipivotide tetraxetan is intended for monotherapy use in the population relevant to this appraisal, which is consistent with the indication and SmPC submitted to the MHRA for approval.[1] [redacted].

The company submitted a patient access scheme (PAS) for ^{177}Lu vipivotide tetraxetan in this appraisal, representing a discount to the list price of [redacted] The proposed PAS price of one single dose vial of ^{177}Lu vipivotide tetraxetan is [redacted].

2.3.3 Comparators

The NICE scope lists four comparators: (i) cabazitaxel, (ii) docetaxel (for people who have had docetaxel in combination with ADT previously), (iii) radium-223 dichloride (for people with bone metastases), and (iv) best supportive care.[18] The company's economic analysis only includes cabazitaxel as a relevant comparator in patients who have previously received treatment with an ARPI and docetaxel and who are eligible for further taxane treatment. The company's economic analysis includes best supportive care (referred to as standard of care (SOC) in the CS) as a comparator for all other patients eligible for ^{177}Lu vipivotide tetraxetan who would not be eligible for further treatment with taxane therapy.

As discussed in Section 2.2, the EAG agrees with the exclusion of docetaxel rechallenge as a comparator as it would be very infrequently used in practice. The EAG disagrees with the exclusion of radium-223, as patients with bone metastases would receive radium-223 in the post-ARPI and taxane setting and post-ARPI where docetaxel is contraindicated or unsuitable setting.

2.3.4 Outcomes

The NICE scope lists progression free survival (PFS), overall survival (OS), time-to-first symptomatic skeletal event (SSE), adverse effects of treatment and health-related quality of life (HRQoL) as outcomes to be reported.[18] The company included data on all of these outcomes and presented additional secondary outcomes data including overall response rate, disease control rate and duration of response in the clinical effectiveness section of the CS. The EAG notes that the company presented radiographic progression-free survival (rPFS).

2.3.5 Subgroups

The NICE scope did not list any subgroups that warranted exploration.[18] The company considered three subgroups: (i) patients who have been treated with ARPI and taxane-based chemotherapy and are suitable for further treatment with taxanes; (ii) patients who have been treated with ARPI and taxane-based chemotherapy and are ineligible for further treatment with taxanes; and (iii) patients who have been treated with ARPI and are not medically suitable for treatment with taxanes.[1] The EAG notes that the evidence that the company provided for treatment with ^{177}Lu vipivotide tetraxetan is for the first two subgroups; the company has assumed that the clinical efficacy and safety data from the VISION trial[22] are generalisable to those patients who are medically unsuitable for taxanes.

Based on Figure 2 in the CS, the EAG also believes that the second subgroup identified by the company is heterogeneous as it includes those who are ineligible for further treatment with taxanes because they

are unsuitable for third-line cabazitaxel and those who are ineligible for further treatment with taxanes because they have previously received cabazitaxel third-line.

2.3.6 Special considerations

The NICE scope did not list any special considerations including issues related to equity or equality that should be explored.[18] The company did not claim that special considerations were relevant to this appraisal. However, the company notes that approximately 50% mCRPC patients have been identified as being ineligible for taxanes[15] and the third subgroup considered in this appraisal (patients who have been treated with ARPI and are not medically suitable for treatment with taxanes, but who are eligible for ^{177}Lu vipivotide tetraxetan) represents around 42% of the total population eligible for ^{177}Lu vipivotide tetraxetan (see clarification response,[17] question B3). The company suggests that limiting the scope of ^{177}Lu vipivotide tetraxetan to patients who have received taxane-based chemotherapy would potentially create inequality.

The company also raises an issue that there may be geographical inequality because there are currently only a limited number of clinical centres in the UK which would be able to conduct the required assessment to identify PSMA-positive patients. The EAG's clinical advisors also acknowledged that the diagnostic resources required to identify PSMA-positive patients are not currently available to all patients in the UK.

3 CLINICAL EFFECTIVENESS

This section presents a summary and critique of the clinical evidence reported in the CS for ^{177}Lu vipivotide tetraxetan in adult patients with PSMA positive mCRPC.

3.1 Critique of the methods of review(s)

The clinical evidence submitted by the company comprises:

- A systematic literature review (SLR),
- Network meta-analyses (NMAs) of ^{177}Lu vipivotide tetraxetan + SOC versus cabazitaxel and other treatments for mCRPC.

This section summarises the evidence for the clinical effectiveness of ^{177}Lu vipivotide tetraxetan from the CS including the company's SLR and NMAs, and provides a critique of the methods used to identify and synthesise this evidence. Full details of the process and methods used by the company to identify and select the clinical evidence for this appraisal are presented in CS[1] Appendix D.

3.1.1 Searches

The company performed one search to identify all clinical effectiveness and safety studies of treatments or comparator treatments of adult patients with pre-treated, progressive mCRPC. In summary, the EAG has identified limitations in the company search strategy relating to:

- The sources searched (clinical trials registries)
- Single host platform searching and mapping of MeSH/Emtree terms.

The company searched eight electronic bibliographic databases within a single host platform (via Ovid) in June 2019, April 2021 and November 2021 (CS, Appendix D.1): MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), The Health Technology Assessment (HTA) Database, The Database of Abstracts of Reviews of Effects (DARE) database, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Methodology Register and the American College of Physicians (ACP) Journal Club.[1] It is unclear to the EAG, the company's reason for searching ACP Journal club.

The company did not search clinical trials registries for ongoing or complete and unpublished studies. However, some records in CENTRAL originate from PubMed, Embase, CINAHL and clinical trials registries (which has no inception date). Examples of trials registries include clinictrials.gov, WHO International Clinical Trials Registry Platform (ICTRP) and the EU Clinical Trials Register (EUCTR).[1] It is unclear from the CS, the company's reasons for omitting the search for ongoing or unpublished

trials. Clinicaltrials.gov and ICTRP sources together with CENTRAL should be searched to identify unpublished trials.[23]

The company has also searched two HTA agency sites (date not reported): NICE; and the Scottish Medicines Consortium (SMC). The company searched two key conference abstract websites in the last three years (date not reported): American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO).[1] The search strategies in these websites were not reported in the CS. The company also searched reference lists of selected studies, systematic reviews and meta-analysis.

The company has undertaken simultaneous database searches in a single host platform Ovid. The EAG only has access to two of the eight sources within the Ovid platform. It should be noted that the controlled vocabulary/index terms in MEDLINE and Embase are not identical and that in contrast to MEDLINE, Embase has more indexing terms attached to records. Despite the Medical Subject Headings (MeSH) are mapped to Emtree terms, the reverse does not occur, i.e., from Emtree to MeSH and it is important to include all relevant indexing terminology in the search strings. The company has attempted to identify and include MeSH and Emtree terminology in the Ovid search strategy. It is worth noting that Cochrane Library (CDSR and CENTRAL databases) uses MeSH headings as well.

Having reviewed the search strategies comprising population (mCRPC), intervention and comparator terms and applied search filters (randomised controlled trial (RCT) and reviews), there were no significant and consequential errors found and the EAG considers that search is comprehensive.

3.1.2 Inclusion criteria

The inclusion and exclusion criteria for the systematic review are reported in Table 4. They are slightly different from the NICE scope (Table 3) because the intention was also to identify trials for potential indirect treatment comparisons (e.g., PSMA-positive patient population was not a requirement). Overall, the key differences between the CS and the NICE scope are as follows:

- Unlike the NICE scope, the CS population includes patients who are not considered to be medically suitable for taxanes, either docetaxel or cabazitaxel; these patients comprise two of the potential positionings for ^{177}Lu vipivotide tetraxetan in the proposed treatment pathway (see Figure 1). The NICE scope did not specify any subgroups.[18]
- The NICE scope comparators included docetaxel and radium-223, but the CS argues that the intended population for ^{177}Lu vipivotide tetraxetan would not include eligible patients – or very few eligible patients – for these treatments. Eligible patients for ^{177}Lu vipivotide tetraxetan include those who have already received docetaxel and docetaxel rechallenge is rare; and

radium-223 would not be used for patients with visceral metastases, whereas ^{177}Lu vipivotide tetraxetan is eligible for all patients regardless of site (CS, Table 1). Given the range of potential comparators, and the paucity of head-to-head trials including ^{177}Lu vipivotide tetraxetan, the inclusion criteria included all relevant comparators representing relevant treatments for this population so that indirect comparisons with these strategies could be performed.

Table 4: The inclusion and exclusion criteria for the SLR (reproduced from CS, Appendix D.1.1, Table 2)

Element	Inclusion	Exclusion	Rationale
Population	Adult males (≥18 years old) with pre-treated, progressive mCRPC	Children and adolescents Treatment-naïve mCRPC patients	The population in whom the treatment is being appraised
Intervention / Comparator	No restriction in terms of intervention or comparator	--	All treatments are being considered in this appraisal
Outcomes	**Efficacy** • Objective response rate • Complete response/ remission • Duration of response • Partial response/ remission • OS • PFS • Resistant disease • Time to PSA progression • Time to tumour progression • Time to symptomatic skeletal events • PSA response • Disease control rate • Patients with symptomatic skeletal events • Patients with tumour or PSA progression • Time to first response • Time to remission • Progressive disease • Time to treatment failure • Stable disease • Time to pain progression	Studies not reporting any of the efficacy or safety outcomes of interest	These outcomes were evaluated in key trials for the treatment undergoing assessment
	Safety/tolerability • Adverse events (Grade 3+, all grades) • Hypertension • Diarrhoea • Nausea/Vomiting • Fatigue • Anorexia • Peripheral oedema • Constipation		

Element	Inclusion	Exclusion	Rationale
	• Dehydration/hypotension • Infection • Arthralgia • Decreased weight • Urinary tract infection • Thrombocytopenia • Leukopenia • Febrile neutropenia • Abdominal pain • Anaemia • Leukopenia • Neurotoxicity • Pain • Bleeding • Veno-occlusive disease • Death (30- and/or 60-day, induction death, treatment related, and overall) • Discontinuations due to AEs		
Study Design	RCTs (Phase III) *Reference lists of systematic literature reviews were reviewed with a view of identifying any potential trial not captured through the database searches.	Narrative reviews, editorials, commentary, letters, notes, short survey, case series or reports, animal or in vitro studies, open-label extensions, phase I trials, cross-over studies without relevant data prior to cross-over, observational studies	--
Language	English	Non-English publications	Most, if not all of the relevant evidence will be published in English

Abbreviations: AEs, adverse events; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; RCTs, randomised controlled trials; SLR, systematic literature review.

The SLR criteria included the key effectiveness outcomes from the final NICE scope: OS, PFS, time-to-first SSE, as well as quality-adjusted life year (HRQoL) and safety outcomes (CS, Section B.1.1 and Table 1). The company also presented response outcomes data from the VISION trial, but these were not required by the scope or included in the cost-effectiveness analyses. Finally, the CS only included Phase III RCTs. The distinction between Phase II and Phase III trials was not defined in the CS, and was also not provided in response to a question from the EAG, beyond the statement that Phase III trials provide "*the highest quality evidence*" (see clarification response[17], question A3).

3.1.3 Study selection

Appendix D.1.1 of the CS reports that, for all citations, both the title/abstract and full-text screening stages of study selection were undertaken independently by two reviewers, and any discrepancies reconciled by the third independent reviewer.[1] The EAG considers independent study selection by two or more reviewers to be best practice in systematic reviewing.

3.1.4 Critique of data extraction

Details regarding the company's data extraction methods are reported in Appendix D.1.1 of the CS.[1] Data extracted from included trials and reported in the CS are presented in the results in Sections B.2.3, B.2.5, B.2.8 and B.2.9 of the CS. The CS has inconsistencies in the reported process undertaken for data extraction, but this was clarified in response to EAG's clarification question A4: the process was undertaken by one reviewer and checked by a second.[17] The EAG considers independent study selection by two or more reviewers to be best practice in systematic reviewing.

3.1.5 Quality assessment

No details were provided on the processes followed in the conduct of quality assessment of all trials included the clinical effectiveness review. This was clarified in the company's response to clarification question A5: the process was undertaken by one reviewer and checked by a second.[17] The EAG considers independent study selection by two or more reviewers to be best practice in systematic reviewing.

3.2 Included study for ^{177}Lu vipivotide tetraxetan

The clinical SLR presented in the CS identified one Phase III trial of ^{177}Lu vipivotide tetraxetan, which was relevant to the decision problem: VISION (NCT03511664).[22] This trial compared ^{177}Lu vipivotide tetraxetan + SOC with SOC alone in pre-treated mCRPC PSMA-positive adults. SOC included but was not restricted to: approved hormonal treatments (ARPIs, including abiraterone and enzalutamide), bisphosphonates, radiation therapy, denosumab, or glucocorticoid at any dose. It excluded cytotoxic chemotherapy, systemic radioisotopes (e.g., radium-223), immunotherapy, or drugs that were investigational when the trial was designed (e.g., olaparib).[22]

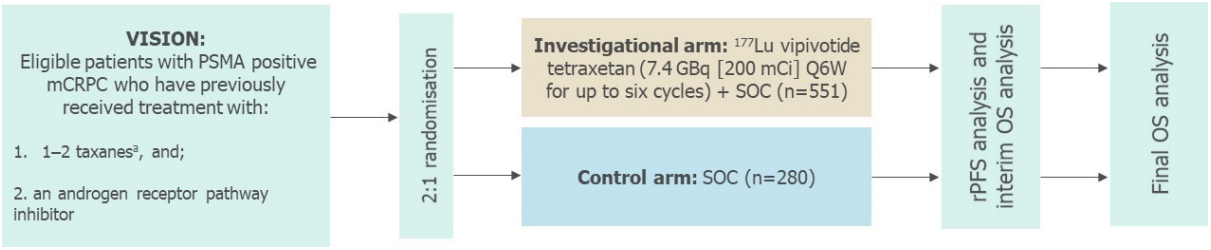
The VISION trial formed the key evidence for clinical effectiveness and safety of ^{177}Lu vipivotide tetraxetan within the CS. One publication was identified and listed for this study (CS, Section B.2.2 and Appendix D.1.2, Table 3).[22] The EAG believes that no relevant published Phase III trials of ^{177}Lu vipivotide tetraxetan that could have provided data on safety and efficacy in the PSMA-positive mCRPC adult population have been omitted from the CS.

3.2.1 Trial design of VISION

VISION is a Phase III, randomised, international, multi-centre, open-label, ongoing, parallel-arm study initiated in May 2018 and conducted in 88 centres across 10 countries (USA, Canada, Belgium, Denmark, France, Germany, Netherlands, Sweden, UK [nine sites] and Puerto Rico) (NCT03511664). The primary completion date was January 2021, but the final completion date is listed on clinicaltrials.gov as November 2022.[24] Overall, 1179 patients were screened, of which 1003 patients received a ^{68}Ga gozetotide PET-CT, and 851 adults with PSMA-positive mCRPC satisfied all eligibility criteria and were randomised.[22]

Details of study location, treatments, inclusion and exclusion criteria, prohibited concomitant medications and relevant outcomes are reported in Table 5. Patients were initially selected based on the eligibility criteria described in Table 5 and assigned in a 2:1 ratio to either the interventional arm (^{177}Lu vipivotide tetraxetan + SOC) or the control arm (SOC only). Randomisation was stratified by baseline lactate dehydrogenase (LDH) [≤260 U/mL or >260 U/mL], presence of liver metastases (yes or no), ECOG performance status (0-1 or 2), and inclusion of an ARPI in protocol-permitted standard care at the time of randomisation (yes or no).[22] The patient cohorts assessed in the clinical effectiveness review are presented in Figure 2.

Figure 2: Overview of trial design for VISION (reproduced from CS, Figure 3)



[a]Patients who had received only 1 prior taxane treatment were eligible only if they were unwilling to receive a further taxane treatment or their physician deemed the patient medically unsuitable to receive a second regimen.
VISION OS data were mature by the time of the first rPFS data analysis.
Abbreviations: ^{177}Lu, lutetium-177; ARPI, androgen receptor pathway inhibitor; mCRPC, metastatic castration-resistant controlled trial; PSMA, prostate-specific membrane antigen; SOC, standard of care.

It should be noted that ARPIs (abiraterone, enzalutamide, apalutamide or any other ARPI) were a required prior treatment for eligibility (Table 5) and permitted as concomitant medications in the trial's SOC (both arms), but clinical advice received by the EAG noted that ARPIs would only be used once in UK clinical practice. The CS states that the following proportions of patients received ARPIs in the ^{177}Lu vipivotide tetraxetan + SOC and SOC only arms, respectively: 34.4% and 47.3% (CS, Table 11).

Patients continued treatment in either arm until one of the following occurred: disease progression based upon radiological assessment as measured by Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria;[25] the investigator felt there was a lack of clinical benefit or unacceptable toxicity; a

prohibited treatment was clinically required; the patient was non-adherent to the trial regimen; consent to continue with treatment was withdrawn; the sponsor's or investigator's discretion.[22] Therefore, the VISION trial evaluated the efficacy and safety of 7.4 GBq (200mCi) of ^{177}Lu vipivotide tetraxetan administered once every 6 weeks for a maximum of 6 cycles in adult patients with PSMA-positive mCRPC.

Table 5: Summary of design of VISION (reproduced from CS, Table 6)

Trial number and ACRONYM	**NCT03511664, VISION**
Location	International multicentre trial conducted across 88 sites in nine countries: Belgium, Canada, Denmark, France, Germany, Netherlands, Sweden, **United Kingdom**, and United States.
Trial design	Prospective, open-label, randomised, controlled, international, Phase III trial.
Eligibility criteria[a]	**Inclusion criteria** • Patients must be ≥18 years of age. • Patients must have an ECOG performance status of 0–2. • Patients must have progressive mCRPC. • Patients must have a positive ^{68}Ga gozetotide PET–CT scan, as determined by the sponsor's central reader. • Patients must have received the following prior treatment: o ADT o At least 1 ARPI o At least 1, but not more than 2, taxane regimens[b] • Patients must have adequate organ function: o Bone marrow o Hepatic o Renal **Exclusion criteria** • Patients must not have received previous treatment with Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223 or hemi-body irradiation within 6 months prior to randomisation. • Patients must not have received previous PSMA-targeted radioligand therapy. • Patients must not be receiving concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy. • Patients must not currently have symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression. • Patients must not have any concurrent, serious (as determined by the investigator) medical conditions that in the opinion of the investigator would impair study participation or cooperation. • Patients must not be diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment.
Method of study drug administration	• Patients randomised to the ^{177}Lu vipivotide tetraxetan arm received protocol-permitted SOC plus a maximum of six cycles of ^{177}Lu vipivotide tetraxetan 7.4 GBq (200 mCi) every six weeks. At the discretion of the investigator, ^{177}Lu vipivotide tetraxetan doses could be delayed by up to 4 weeks or reduced by 20% (without further reduction or re-escalation) to manage toxicity or adverse events. • 7.4 GBq (200mCi) of ^{177}Lu vipivotide tetraxetan administered once every 6 weeks for a maximum of 6 cycles has been used, for a maximum cumulative dose of 44.4 GBq. • ^{177}Lu vipivotide tetraxetan was administered via a slow intravenous injection by a

	qualified healthcare/authorised healthcare professional. • Following ^{177}Lu vipivotide tetraxetan administration, a saline infusion of 500 mL was recommended. • At the investigator's discretion, for patients with high tumour burden or gout, allopurinol could be started within 7 days and up to 10 days following ^{177}Lu vipivotide tetraxetan therapy.
Permitted and disallowed concomitant medication	**Permitted concomitant medications** **SOC:** • SOC treatments were administered based upon the clinical judgement of the treating physician and were optimised for all patients regardless of randomisation arm and disease status. • SOC treatments could be modified over time to suit a patient's evolving clinical needs. • SOC options were predefined in the study protocol and included any, and all, of the following: o Supportive measures (pain medications, hydration, transfusions, etc). o Ketoconazole. o Androgen reducing agents (including any corticosteroid and 5-alpha reductases). o ARPIs: abiraterone, enzalutamide, apalutamide or any other ARPI. o Radiation in any external beam or seeded form (systemic radioisotopes [e.g. radium-223], or hemi-body radiotherapy treatment were not permitted on study). o Bone targeted agents including zoledronic acid, denosumab, and any bisphosphonates. o Blood transfusion or erythropoietin stimulation agents were allowed throughout the study after randomisation. o Routine prophylaxis with G-CSF/GM-CSF and erythropoietin was not recommended. Nevertheless, use was permitted at the investigator's discretion. o Patients had to maintain castrate levels of serum/plasma testosterone either by chemical castration or by previous orchiectomy. **Disallowed concomitant medication** • Investigational agents • Cytotoxic chemotherapy • Immunotherapy • Other systemic radioisotopes (e.g. radium-223) • Hemi-body radiotherapy
Duration of study and follow-up	The data-cut for the final analyses was on 27th January 2021. The median follow-up at this time was 20.9 months.

[a]The inclusion and exclusion criteria presented here represent a summary of the full eligibility criteria, which is presented in CS, Appendix M.
[b]If a patient had only received one taxane regimen, the patient was only eligible if they were not willing to receive a second taxane regimen or the patient's physician deemed him unsuitable to receive a second taxane regimen.
Abbreviations: ^{177}Lu, lutetium-177; ^{68}Ga, gallium-68; ARPI, androgen receptor pathway inhibitor; BPI-SF, Brief Pain Inventory – Short Form; CT, computerised tomography; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQoL-5 Dimension-5 Level; FACT-P, Functional Assessment of Cancer Therapy – Prostate; GBq, gigabecquerel; G-CSF, granulocyte colony stimulating-factor; GM-CSF, granulocyte macrophage colony-stimulating factor; HRQoL, health-related quality of life; ITT, intention to treat; LDH, lactate dehydrogenase; mCi, millicurie; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PET–CT, positron emission tomography – computerised tomography; PFS, progression-free survival; PFS-FAS, progression-free survival full analysis set; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SOC, standard of care; SSE, symptomatic skeletal event.

3.2.2 Quality assessment of VISION

The CS performed a quality assessment of VISION using the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs (as per recommendations in the NICE user guide). The findings were reported in the CS (Appendix D.1.6, Table 2), and are reproduced in Table 6 together with the EAG's judgements.

The CS stated that, "*Overall, VISION is considered to be of high quality with low risk of bias*" (CS, Section B.2.4).[1] The EAG questioned this judgement specifically with reference to the appraisal (clarification response,[17] question A7), given that the CS judged the appropriateness of the randomisation process to be unclear, and noted the presence of imbalances between treatment arms and the open-label nature of the trial (CS, Appendix D.1.6, Table 12). In response to clarification question A7, the company clarified that the process of randomisation was sufficiently clear and that the response could be adjusted accordingly.[17]

The EAG agrees with the company's responses to most of the checklist's other quality assessment criteria, but judged criteria relating to the lack of blinding to present a potential risk of bias for some outcomes, rather than being "*not applicable*" (the CS's judgement). The EAG also conducted a quality assessment using the Cochrane Risk of Bias (RoB) tool (version 2)[26], which is the international standard for quality assessment of RCTs. This assessment is presented in Table 7.

The EAG assessed the VISION trial to be only moderate quality according to the York CRD criteria (Table 6) and as having a high risk of bias according to the Cochrane RoB criteria (Table 7) given the following issues: the failure to control for some known prognostic factors (e.g., tumour volume/burden); imbalances between arms due to withdrawals, even after the implementation of educational measures to reduce drop-out; and the risk of bias potentially affecting one or more outcomes due to the open-label nature of the trial. During the factual accuracy check, the company raised that "*tumour volume/burden was controlled for in VISION through one of the stratification factors for randomisation, lactate dehydrogenase (LDH; (≤ 260 IU/L vs. > 260 IU/L)*" because "*LDH is widely recognised as a representative marker for tumour burden, as it reflects the underlying oncologic cellular turnover, being raised in greater tumour burden*". However, clinical advice to the EAG on this issue suggests that LDH was not viewed as a valid and/or robust prognostic marker and was not routinely collected in prostate cancer in the UK.

Table 6: Quality assessment of the VISION trial with the EAG's critique

Study question	Response (yes/no/not clear/NA) CS / EAG	How is the question addressed in the study? CS / EAG
Was randomisation carried out appropriately?	Not clear* / Yes	No comment / Sartor, *et al*. (2021)[22] Supplement: '*Patients were randomly allocated using an interactive response system. Randomization was stratified by baseline lactate dehydrogenase level (≤260 U/mL or >260 U/mL), presence of liver metastases (yes or no), ECOG Performance Status (0–1 or 2) and inclusion of androgen receptor pathway inhibition in protocol-permitted standard care at the time of randomization (yes or no)'.*
Was the concealment of treatment allocation adequate?	NA / Yes	No comment / '*Patients were randomly allocated using an interactive response system. Randomization was stratified by baseline lactate dehydrogenase level (≤260 U/mL or >260 U/mL), presence of liver metastases (yes or no), ECOG Performance Status (0–1 or 2) and inclusion of androgen receptor pathway inhibition in protocol-permitted standard care at the time of randomization (yes or no)'.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes / Not clear	No comment / Groups were similar across most known prognostic factors, except tumour burden and location (i.e., visceral disease alone, no bone metastases), which are not reported or analysed across groups (Letters and clinical advice received by EAG)
Were the care providers, participants and outcome assessors blind to treatment allocation? **If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?**	NA / No NR / Not clear	No comment / Open-label Phase III trial; unblinded independent central review of imaging outcomes; some patient-reported outcomes, e.g., Quality of life and pain Impact on most outcomes is low, but unblinded central review of imaging outcomes introduces a risk of ascertainment bias
Were there any unexpected imbalances in drop-outs between groups? **If so, were they explained or adjusted for?**	Yes / Yes	No comment / Yes imbalances, yes explained; rPFS outcome adjusted to include only randomised patients after implementation of a different education measures. Sartor, *et al*. (2021)[22]: '*The percentage of patients in the control group who discontinued the trial without receiving the randomly assigned treatment was 56% (47 of 84 patients) before the implementation of these measures and 16.3% (32 of 196 patients) after implementation, as compared with 1.2% (2 of 166 patients) and 4.2% (16 of 385 patients), respectively, in the 177Lu-PSMA-617 group'*. Extensive missing data in control arm for some response outcomes (CS, Table 15)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No / No	No comment / All outcomes listed in protocol (NCT03511664) are reported (limited reporting of Quality of Life outcome data, CS, B.2.5.5 and Sartor, *et al*. (2021)[22], Figure S6), although protocol amendment involved rPFS being listed as a primary rather than a secondary outcome. Sartor *et al*. (2021)[22]: '*A protocol amendment added imaging-based progression-free survival as an alternate primary end point after discussions with the Food and Drug Administration*

Study question	Response (yes/no/not clear/NA) CS / EAG	How is the question addressed in the study? CS / EAG
		(FDA) … At the time of this amendment, a minority of patients had undergone randomization, and no primary endpoint events had occurred'
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes / Yes	No comment / Yes, but with adjustment for drop-outs for key primary and secondary outcomes other than overall survival and safety outcomes. CSR Table 9 and Sartor, 2021: '*All the efficacy outcomes were analyzed in intention- to-treat populations. The analysis of overall survival included all the patients who had undergone randomization, whereas imaging-based progression-free survival and key secondary efficacy outcomes were analyzed in a subgroup of patients who had undergone randomization [due to] a high incidence of withdrawal from the trial … in the control group at certain sites and … attributed principally to patient disappointment … After discussion with regulatory authorities, we implemented enhanced trialsite education measures on March 5, 2019 to reduce the incidence of withdrawal. The high incidence of withdrawal could have affected the interpretability of radiographic end points. Therefore, the primary analysis of imaging-based progression- free survival and the analyses of key secondary end points were amended to include only the patients who had undergone randomization on or after March 5, 2019'*

*Revised to 'Yes' by the company: clarification response, question A7.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EAG, External Assessment Group; CSR, clinical study report; rPFS, radiographic progression-free survival.

Table 7: Cochrane Risk of bias v.2.0: VISION[22]

Author, Year	Bias arising from the randomisation process: sequence generation, allocation concealment, balance between groups)	Bias due to deviations from intended intervention (deviations with likely effect on outcomes)	Bias due to missing data (attrition)	Bias due to measurement of outcome (blinding of assessors, potential for differences between groups)	Bias in selection of reported results (prespecified outcomes, potentially different measures)	Overall risk of bias
Assessment	Some concerns	Low	Some concerns	Some concerns	Low	High risk of bias
Details	'*Patients were randomly allocated using an interactive response system. Randomization was stratified by baseline lactate dehydrogenase level (≤260 U/mL or >260 U/mL), presence of liver metastases (yes or no), ECOG Performance Status (0–1 or 2) and inclusion of androgen receptor pathway inhibition in protocol-permitted standard care at the time of randomization (yes or no)*'.[22] Groups were similar across most known prognostic factors, except tumour burden and location (i.e. visceral disease alone, no bone metastases), which are not reported or analysed across groups ([27] and clinical advice received by EAG)		Potential imbalances across arms due to withdrawals / missing data: the proportions of missing outcome data, and reasons for missing outcome data, differ between intervention groups. rPFS outcome adjusted to include only randomized patients after implementation of a different education measures: '*The percentage of patients in the control group who discontinued the trial without receiving the randomly assigned treatment was 56% (47 of 84 patients) before the implementation of these measures and 16.3% (32 of 196 patients) after implementation, as compared with 1.2% (2 of 166 patients) and 4.2% (16 of 385 patients), respect-ively, in the 177Lu-PSMA-617 group'*. Sartor *et al*. (2021)[22]. Extensive missing data in control arm for some response outcomes (CS, Table 15)	Open-label Phase III trial; independent central review of imaging outcomes, but not blinded so there is a risk of ascertainment bias	All outcomes listed in protocol (NCT03511664) are reported (limited reporting of Quality of Life outcome data, CS B.2.5.5 and Figure S6[22]); protocol amendment involved rPFS being listed as a primary rather than a secondary outcome. Sartor *et al*. (2021)[22]: '*A protocol amendment added imaging-based progression-free survival as an alternate primary end point after discussions with the Food and Drug Administration (FDA) … At the time of this amendment, a minority of patients had undergone randomization, and no primary endpoint events had occurred*'	Multiple 'Some concerns' assessments indicates high risk of bias[26]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EAG, External Assessment Group; CS, company submission; rPFS, radiographic progression-free survival.

3.2.3 Baseline characteristics of VISION

Patients were randomised in a 2:1 ratio between June 2018 and October 2019: 551 patients were assigned to the intervention arm (^{177}Lu vipivotide tetraxetan + SOC) and 280 were assigned to the control arm (SOC only) (total number randomised n=831). However, after initiation of the trial, a high incidence of withdrawal was noted in the control group at certain sites and attributed principally to patient disappointment in not receiving ^{177}Lu vipivotide tetraxetan.[22] In the SOC only group, 47/84 (56%) of patients discontinued the trial without receiving the randomly assigned treatment compared with 2/166 (1.2%) in the ^{177}Lu vipivotide tetraxetan + SOC group. After discussion with the Food and Drug Administration (FDA), the investigators implemented enhanced trial site education measures on 5th March 2019 to reduce the incidence of withdrawal.[22] After implementation, 32/196 (16.3%) of patients discontinued the trial without receiving the randomly assigned treatment in the SOC only group, compared with 16/385 (4.2%) in the ^{177}Lu vipivotide tetraxetan + SOC group.

On account of potential bias due to imbalances between the intervention and control arms (because no treatment had been given and outcome data were missing) before the implementation of new education measures, the trial investigators took a decision to focus on patients prospectively randomised on or after 5th March 2019, when imbalances were smaller. This represented the progression-free survival full analysis set (PFS-FAS), n=581: n=385 in the ^{177}Lu vipivotide tetraxetan + SOC group and n=196 in the SOC only group.

The primary analysis for OS was an ITT analysis that included all randomised patients (i.e., including those randomised before 5th March 2019), n=831. This is the full analysis set (FAS): n=551 in the ^{177}Lu vipivotide tetraxetan + SOC group and n=280 in the SOC group.

The safety analysis used data from all patients randomised and who received treatment, n=734. This is the FAS safety analysis set: n=529 in the ^{177}Lu vipivotide tetraxetan + SOC group and n=205 in the SOC group). Details of the analysis sets are summarised Table 8.

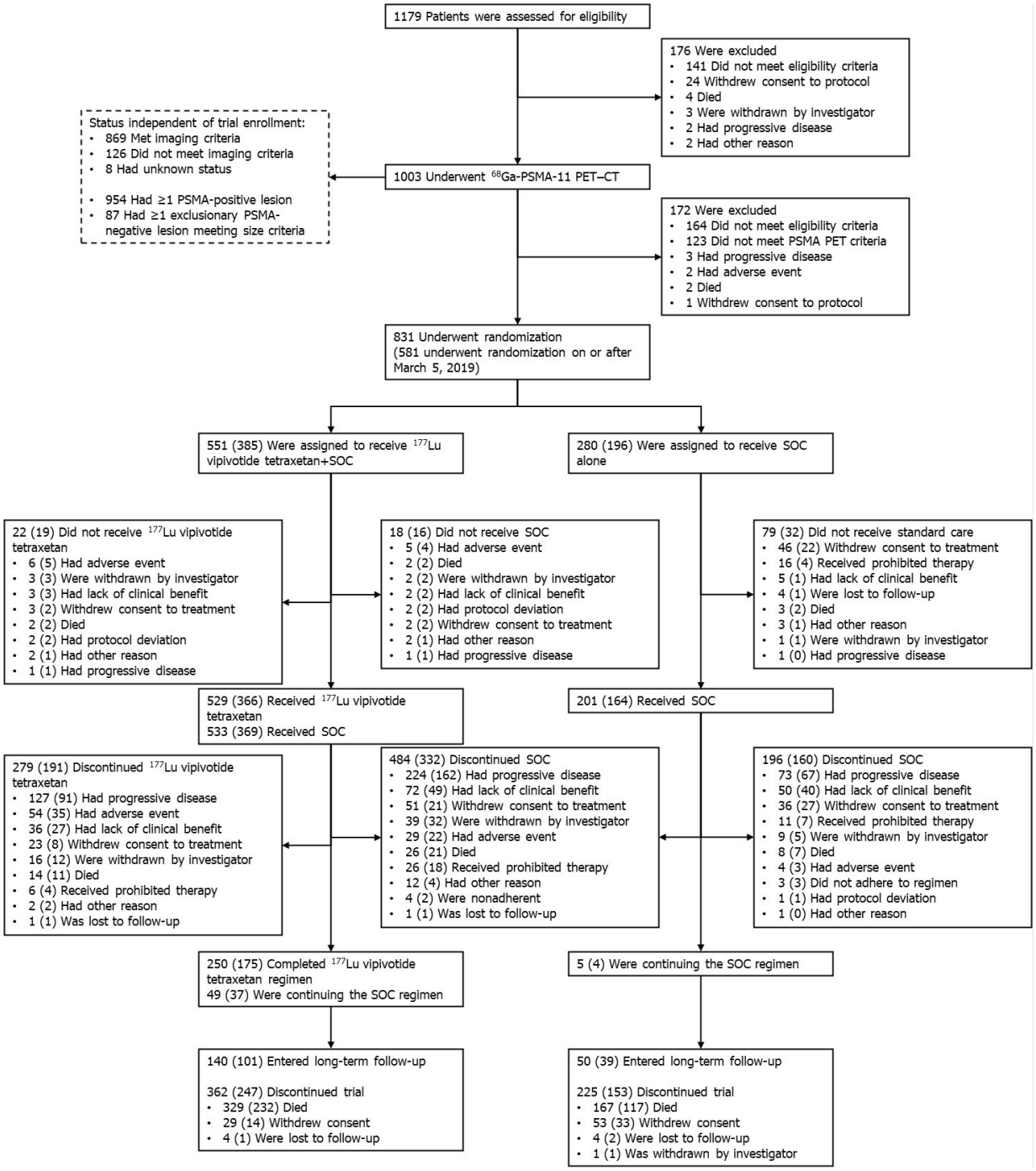
Table 8: Analysis sets used in the analysis of outcomes in VISION (reproduced from CS, Table 6)

Analysis set	Definition
Full Analysis Set (FAS)	• All randomised patients (n=831). • Patients were included in the treatment arm to which they were randomised regardless of actual treatment received. This is an intent to treat (ITT) analysis set. • This analysis set is used for the analysis of OS.
PFS Full Analysis Set (PFS-FAS)	• All patients randomised on or after 5th March 2019 (n=581). • Patients were included in the treatment arm to which they were randomised regardless of actual treatment received. • This analysis set is used for the primary analyses of rPFS and all secondary endpoints except ORR and DCR.
FAS Safety Analysis Set (FAS-SAS)	• The subset of patients in the FAS who received at least one dose of randomised treatment (n=734). • Patients were included in the treatment arm corresponding to the actual treatment received.

Abbreviations: DCR, disease control rate; FAS, full analysis set; ITT, intention to treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; rPFS, radiographic progression-free survival.

A full CONSORT diagram of participant flow in VISION is presented below in Figure 3.

Figure 3: Participant flow in vision (reproduced from CS, Figure 3)



The numbers in parentheses indicate the numbers of patients who underwent randomisation on or after 5th March 2019, which was the date on which trial-site education measures were implemented to reduce the incidence of withdrawal from the trial in the control group (see Document B, Section B.2.3.3 for further details).
Abbreviations: ^{177}Lu, Lutetium-177; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; SOC, standard of care.

The baseline characteristics of each group are reported in Table 9.

Table 9: Baseline demographics and characteristics for the PFS-FAS and FAS groups in VISION (adapted from CS, Table 10)

Characteristic	PFS-FAS (N = 581)		FAS (N = 831)	
	^{177}Lu vipivotide tetraxetan + SOC (N=385)	SOC (N=196)	^{177}Lu vipivotide tetraxetan + SOC (N=551)	SOC (N=280)
Median age (range), years	71.0 (52–94)	72.0 (51–89)	70.0 (48–94)	71.5 (40–89)
ECOG ≤1, n (%)	352 (91.4)	179 (91.3)	510 (92.6)	258 (92.1)
Site of disease, n (%)				
Lung	35 (9.1)	20 (10.2)	49 (8.9)	28 (10.0)
Liver	47 (12.2)	26 (13.3)	63 (11.4)	38 (13.6)
Lymph node	193 (50.1)	99 (50.5)	274 (49.7)	141 (50.4)
Bone	351 (91.2)	179 (91.3)	504 (91.5)	256 (91.4)
Median PSA level (range), ng/ml	93.2 (0–6,988)	90.7 (0–6,600)	77.5 (0–6,988)	74.6 (0–8,995)
Median alkaline phosphatase level (range), IU/litre	108.0 (26–2,524)	96.0 (34–1,355)	105.0 (17–2,524)	94.5 (28–1,355)
Median LDH (range), IU/litre	230.5 (119–5,387)	232.0 (105–2,693)	221.0 (88–5,387)	224.0 (105–2,693)
Median time since diagnosis (range), years	7.3 (0.9–28.9)	7.0 (0.7–26.2)	7.4 (0.9–28.9)	7.4 (0.7–26.2)
Previous prostatectomy, n (%)	159 (41.3)	82 (41.8)	240 (43.6)	130 (46.4)
Previous ARPI, n (%)				
One regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
Two regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
More than two regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Previous taxane therapy, n (%)				
One regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)
Two regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
Docetaxel	377 (97.9)	191 (97.4)	534 (96.9)	273 (97.5)
Cabazitaxel	161 (41.8)	84 (42.9)	209 (37.9)	107 (38.2)

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.

Clinical advice received by the EAG confirmed that the VISION trial population was similar to the likely PSMA-positive mCRPC population who present in UK clinical practice, albeit possibly younger and healthier, like most trial populations. It was also acknowledged that the diagnostic resources required to identify PSMA-positive patients (to be in line with the VISION trial population and the trial's findings) are not currently available to all patients in the UK (CS, Section B.1.3.3 and B.1.4).

Most prognostic factors are balanced across arms and groups, although the following should be noted regarding the prognostic factors of pre-treatment and PSA levels. Patients in the SOC only arm were arguably more heavily pre-treated (a potential prognostic factor): the SOC only arm had a higher

proportion of patients than the ^{177}Lu vipivotide tetraxetan + SOC arm who had received two regimens of ARPIs (PFS-FAS: 43.9 vs. 39.0%; FAS: 45.7% vs. 38.7%) and two taxanes (PFS-FAS: 46.9% vs. 44.9%; FAS: 43.6% vs. 39.9%). The median PSA levels were higher in the PFS-FAS group (^{177}Lu vipivotide tetraxetan + SOC arm: 93.2 ng/ml and SOC only arm: 90.7 ng/ml) than the overall FAS group (^{177}Lu vipivotide tetraxetan + SOC arm: 77.5 ng/ml and SOC only arm: 74.6 ng/ml). The prognostic factor of tumour volume or burden was not recorded, and might moderate outcomes between groups.[27] It should be noted that two or more ARPIs were previously received by approximately half of patients in any arm in any analysis group (range: 44.7%-54.3%), and were permitted as concomitant medications in the trial's SOC (both arms), but clinical advice received by the EAG noted that ARPIs would only be used once in UK clinical practice.

3.2.4 Endpoints

The study endpoints with definitions are presented below (Table 10). The original, only primary endpoint of the study was OS. In a change to the protocol, prompted by discussions with the FDA, the surrogate outcome of rPFS was also designated a primary outcome.[22] This measure was assessed by independent central review.[22] Key secondary outcomes were adverse events, quality of life (including generic and disease-specific measures) and time-to-first SSE, although details of the type of event would not be reported.[28] The VISION trial also reported the surrogate outcome of response, but this was not a designated outcome of the NICE scope. All endpoints except OS were by investigator or patient assessment, or by independent assessment, and there was no blinding.

Table 10: Definitions of key outcome measures in VISION (adapted from CS, Table 7 and NCT03511664[24])

Outcome measure	Definition
Primary outcomes	
OS	OS was defined as the time from randomisation to the date of death from any cause.
rPFS	rPFS was defined as the time from the date of randomisation to the date of radiographic disease progression (as outlined in PCWG3 Guidelines [Scher *et al.* (2016)[25]]) or death from any cause.
Key secondary outcomes	
Time-to-first SSE	Time-to-first SSE was defined as the time (in months) from the date of randomisation to the date of the SSE (first new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic surgical intervention, requirement for radiation therapy to relieve bone pain) or death from any cause.
HRQoL	For HRQoL analyses, patient-reported outcomes (PROs) were assessed using the questionnaires: **EQ-5D-5L** • EQ-5D-5L is a 5-item, self-reported questionnaire comprised of 5 domains of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and

	depression. Patients may indicate impairment in each domain according to five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. **FACT-P** • FACT-P is a 39-item, self-reported questionnaire intended for people with prostate cancer aged 18 years and older. It is composed of 5 subscale domains: physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate cancer subscale. The total score ranges 0–156. **BPI-SF** • BPI-SF is a 9-item, self-reported questionnaire intended to evaluate the severity of a patient's pain and the impact that pain has upon their daily functioning.
Treatment- emergent Adverse Event (TEAEs)	The distribution of adverse events (AE) is done via the analysis of frequencies for treatment emergent Adverse Event (TEAEs), Serious Adverse Event (TESAEs) and Deaths due to AEs, through the monitoring of relevant clinical and laboratory safety parameters, from randomisation til 30 days safety follow-up after the last dose of treatment.
Other secondary outcomes	
ORR	ORR was defined as the proportion of patients with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 response per central review assessment.
DCR	DCR was defined as the proportion of patients with BOR of CR, PR, or Stable disease according to RECIST v1.1 response per central review assessment.
DOR	DOR was defined as the duration between the date of first documented BOR of CR or PR and the date of first documented radiographic progression or death due to any cause.

The following rules were taken into account to define the BOR: CR = at least 2 determinations of CR at least 4 weeks apart; PR = at least 2 determinations of PR or better (i.e. CR) at least 4 weeks apart (and not qualifying for CR); Stable disease = at least 1 Stable disease assessment or better (i.e. CR or PR) > 6 weeks after first dose of randomised treatment (and not qualifying for CR or PR); PD = PD at first evaluable scan after first dose of randomised treatment (and not qualifying for CR, PR or Stable disease).

Abbreviations: AE, adverse event; BOR, best overall response; BPI-SF, Brief Pain Inventory – Short Form; CR, complete response; CT, computerised tomography; EQ-5D-5L, EuroQol 5-dimensions 5-level; FACT-P, Functional Assessment of Cancer Therapy – Prostate; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PD, progressed disease; PR: partial response; PRO, patient reported outcome; PSA, prostate specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS: radiographic progression-free survival; SAE, serious adverse event; SSE, symptomatic skeletal event.

3.2.5 Effectiveness study results of VISION

The data-cut for the final analyses of VISION was 27th January 2021, with a median follow up of 20.9 months.[22] Primary efficacy outcomes were OS and rPFS; secondary efficacy outcomes were time-to-first SSE and HRQoL.

3.2.5.1 Overall survival

The VISION trial reported significantly improved OS for ^{177}Lu vipivotide tetraxetan + SOC compared with SOC only in the FAS population (n=831): median OS was 15.3 months vs. 11.3 months,

respectively (HR 0.62, 95% confidence interval (CI): 0.52 to 0.74, $p<0.001$), an extension of 4 months (Table 11 and Figure 4).

A similar result was reported for the PFS-FAS group (n=581): median OS was 14.6 months vs. 10.4 months, respectively (HR 0.64, 95% CI: 0.51 to 0.80, $p<0.001$) after *ad hoc* adjustment for post-protocol chemotherapy using a time-dependent covariate (Sartor *et al*. [2021][22], Figure S3).

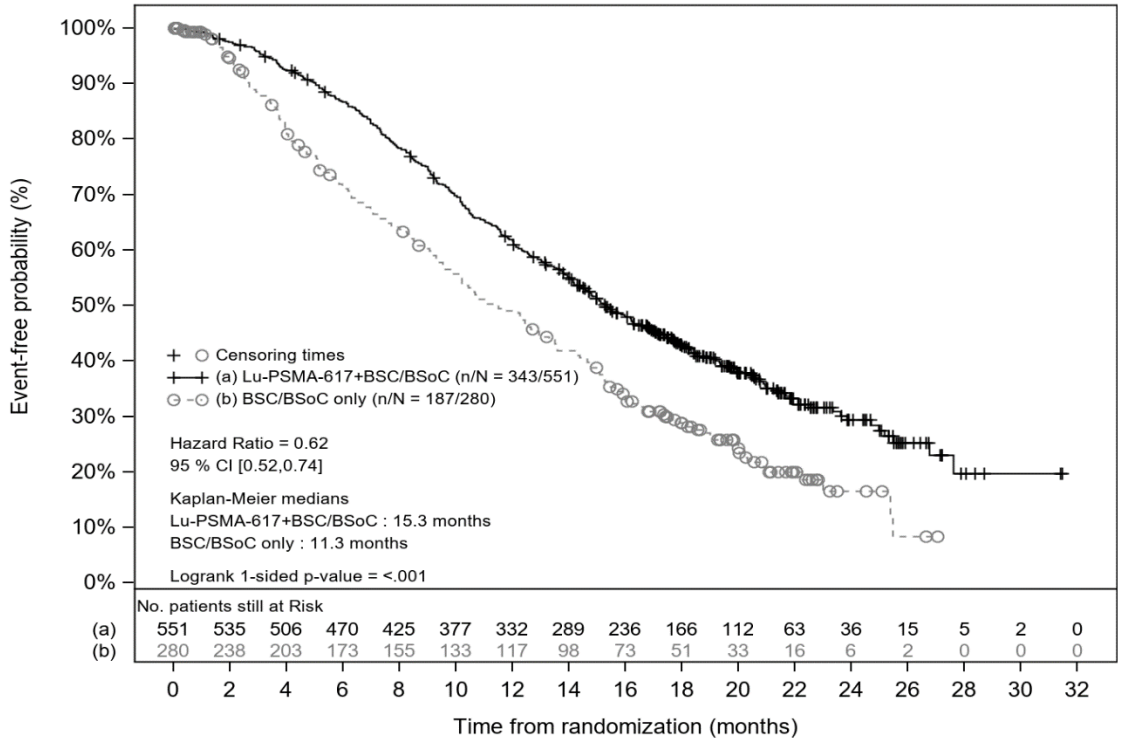
Table 11: OS in VISION (FAS) (reproduced from CS, Table 12)

	^{177}Lu vipivotide tetraxetan + SOC (N=551)	**SOC (N=280)**
Events	343 (62.3)	187 (66.8)
Median OS [95% CI]	15.3 [redacted]	11.3 [redacted]
OS rates (%)		
6 months (SE) [95% CI]	[redacted]	[redacted]
12 months (SE) [95% CI]	[redacted]	[redacted]
18 months (SE) [95% CI]	[redacted]	[redacted]
Log-Rank test and Cox regression model		
HR (95% CI)[a,c]	0.62 (0.52, 0.74)	
p-value[b,c]	<0.001	
Follow-up time (months)[d]		
Median [95% CI]	20.3 [19.8, 21.0]	19.8 [18.3, 20.8]
Minimum, Maximum	[redacted]	[redacted]

[a]Hazard Ratio of ^{177}Lu vipivotide tetraxetan + SOC vs. SOC from stratified Cox PH model. [b]Stratified Log-rank Test one-sided p-value. [c]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. [d]Follow-up time = (Date of event or censoring - randomisation date + 1)/30.4375 (months) censoring for deaths.

Abbreviations: ^{177}Lu, Lutetium-177; HR, hazard ratio; 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 4: Kaplan–Meier plot of OS (FAS) (reproduced from CS, Figure 5)



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.

3.2.5.2 Radiographic progression-free survival

The VISION trial reported significantly improved rPFS for ^{177}Lu vipivotide tetraxetan + SOC compared with SOC only in the PFS-FAS population (n=581): median rPFS was 8.7 months vs. 3.4 months, respectively (HR 0.40, 95% CI: 0.29 to 0.57, p<0.001), an extension of 5.3 months (Table 12 and Figure 5). It has been noted that, "*imaging-based progression-free survival in the current trial dropped sharply at 2 months. This implies that some patients may not benefit from 177Lu-PSMA therapy*".[27]

A similar result was reported for the *ad hoc* FAS group (n=831): median rPFS was 8.8 months vs. 3.6 months, respectively (HR 0.43, 95% CI: 0.32 to 0.58, p<0.001) (Sartor *et al*. [2021][22], Figure S2).

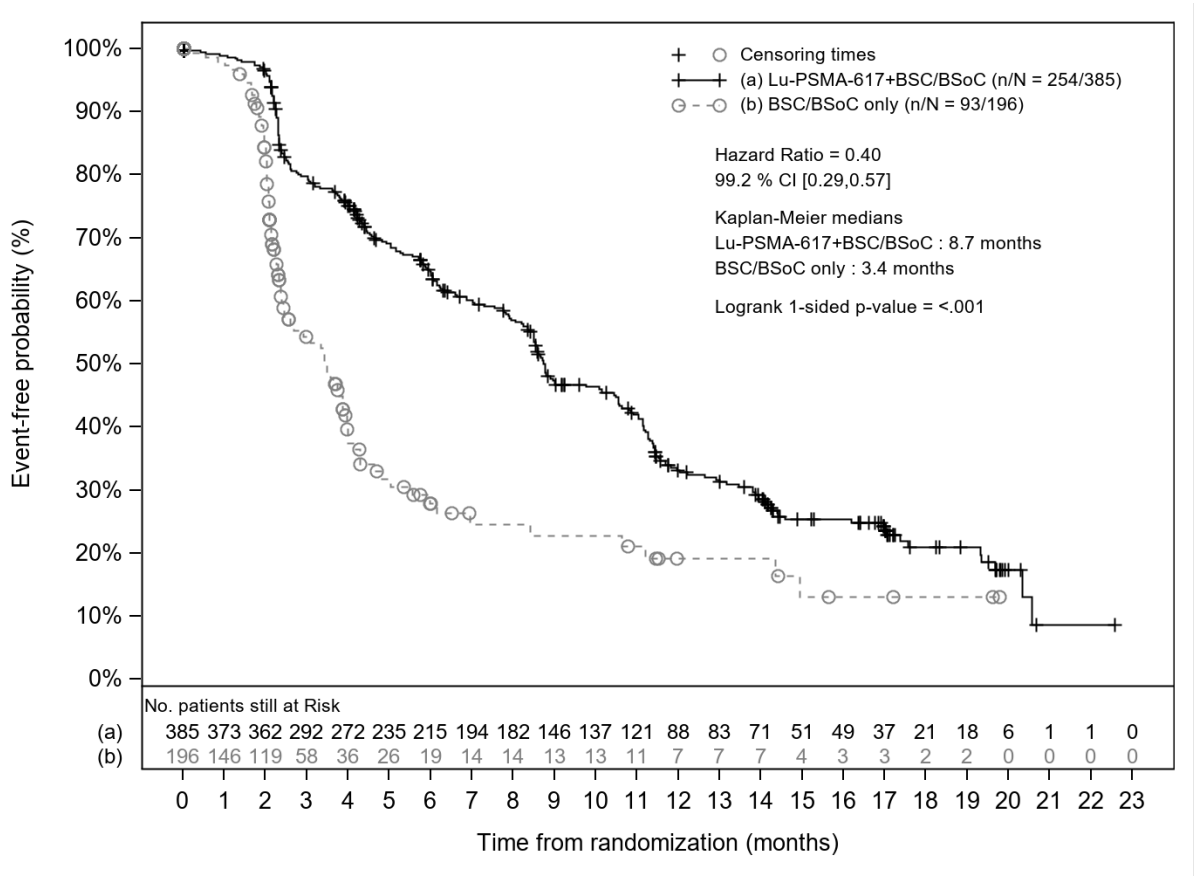
Table 12: rPFS in VISION (PFS-FAS) (reproduced from CS, Table 13)

	^{177}Lu vipivotide tetraxetan + SOC N=385	**SOC N=196**
Events (progression or death)	254 (66.0)	93 (47.4)
Radiographic progressions	171 (44.4)	59 (30.1)
Deaths	83 (21.6)	34 (17.3)
Censored	131 (34.0)	103 (52.6)
Ongoing without event	90 (23.4)	24 (12.2)
Event documented after 2 or more missed tumour assessments	36 (9.4)	44 (22.4)
Adequate assessment not available[c]	5 (1.3)	35 (17.9)
Median rPFS [99.2% CI]	8.7 [redacted]	3.4 [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]	0.40 (0.29, 0.57)	
Stratified Log-rank Test one-sided *p*-value	<0.001	
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; HR, hazard ratio; 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 5: **Kaplan–Meier plot of rPFS (PFS-FAS) (reproduced from CS, Figure 6)**



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.

3.2.5.3 Time-to-first symptomatic skeletal event or death from any cause

The VISION trial reported significantly longer time-to-first SSE or death from any cause for ^{177}Lu vipivotide tetraxetan + SOC than with SOC only in the PFS-FAS population (n=581): median time-to-first event was 11.5 months vs. 6.8 months, respectively (HR 0.50, 95% CI: 0.40 to 0.62, p<0.001), a longer duration of 4.7 months (Table 13 and Figure 6).

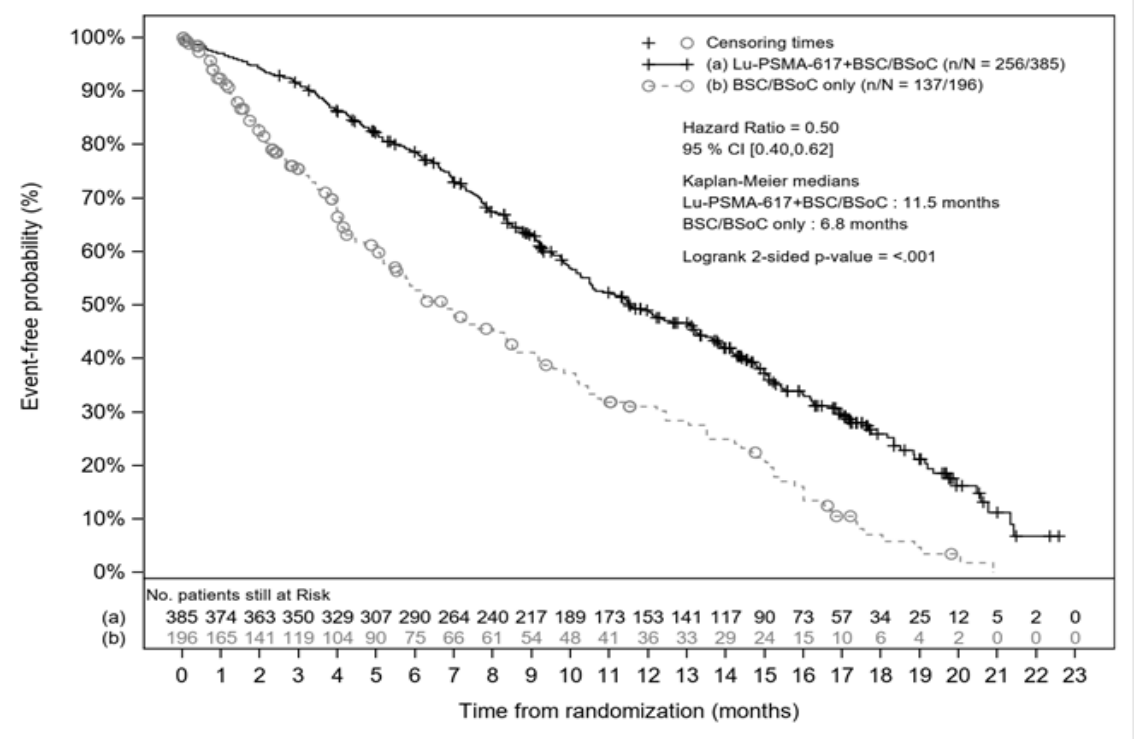
Table 13: Time-to-first SSE or death from any cause (PFS-FAS) (reproduced from CS, Table 14)

	^{177}Lu vipivotide tetraxetan + SOC N=385	**SOC only N=196**
Kaplan–Meier estimates (months)		
Median time-to-first SSE [95% CI]	11.5 [redacted]	6.8 [redacted]
25th percentile [95% CI]	[redacted]	[redacted]
75th percentile [95% CI]	[redacted]	[redacted]

	^{177}Lu vipivotide tetraxetan + SOC N=385	**SOC only N=196**
Log-Rank test and Cox regression model		
Hazard Ratio (95% CI)[a,b]	0.50 (0.40, 0.62)	
Stratified Log-rank Test two-sided *p*-value	<0.001	
Time to first symptomatic skeletal event (SSE), n (%)		
Events (SSE or Death)	[redacted]	[redacted]
SSEs	[redacted]	[redacted]
Deaths	[redacted]	[redacted]
First SSE rates (%)		
3 months (SE) [95% CI]	[redacted]	[redacted]
6 months (SE) [95% CI]	[redacted]	[redacted]
12 months (SE) [95% CI]	[redacted]	[redacted]
Follow-up time (months)[c]		
Median [95% CI]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]

[a]Hazard Ratio of 177Lu vipivotide tetraxetan + BSC/BSOC vs. BSC/BSOC.
[b]Cox PH model is 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 NAAD 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 censoring for death or SSE.
Abbreviations: ^{177}Lu, Lutetium-177; HR, hazard ratio; CI, confidence interval; IRT, interactive response technology; NAAD, novel androgen axis drug; NE, not evaluable; PFS-FAS, progression-free survival full analysis set; PH, proportional hazards; PSMA, prostate-specific membrane antigen; SE, standard error; SSE, symptomatic skeletal event.

Figure 6: Kaplan–Meier plot of time-to-first SSE (PFS-FAS) (reproduced from CS, Figure 7)



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, Easter Cooperative Oncology Group; IRT, interactive response technology; LDH, lactate dehydrogenase; PFS-FAS, progression-free survival full analysis set; PSMA, prostate-specific membrane antigen; SSE, symptomatic skeletal event.

3.2.5.4 Overall response rate (ORR) and disease control rate (DCR)

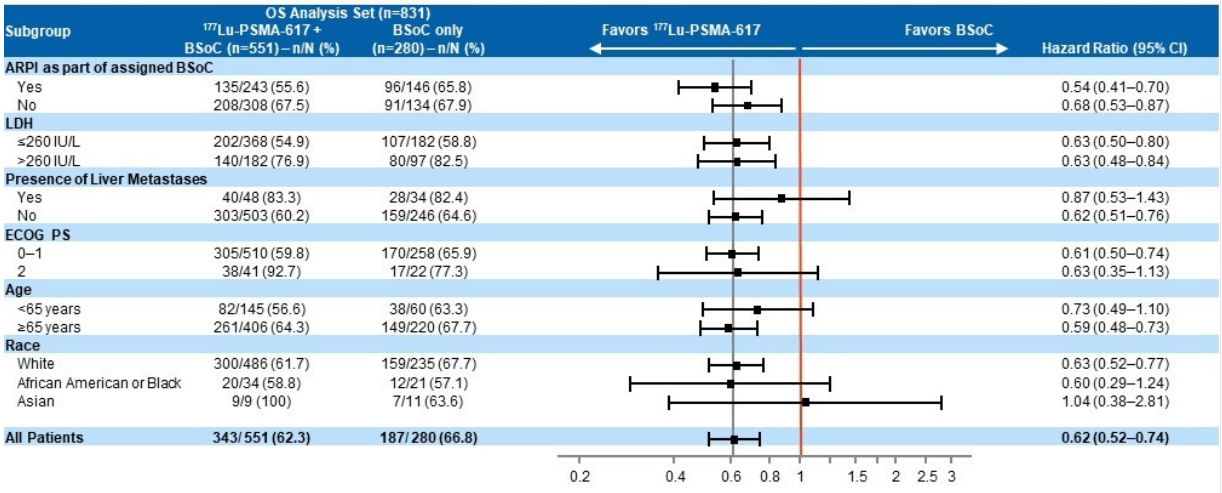
It should be noted that this outcome was not required by the NICE scope[18]. All data collection and analyses were conducted in a subset of the PFS-FAS population (randomised on and after 5th March 2019) with evaluable disease by RECIST at baseline (i.e., at least one target and/or non-target lesion per independent central review radiologist assessment used as the final radiology assessment) (n=439). The VISION trial reported statistically significant improvements in ORR and DCR with ^{177}Lu vipivotide tetraxetan + SOC compared with SOC only (CS, Section B.2.5.6 and Sartor *et al*. [2021][22]). ORR was 29.8% in the ^{177}Lu vipivotide tetraxetan + SOC arm vs. 1.7% SOC only arm, with an odds ratio of 24.99 (95% CI: 6.05 to 103.24). The DCR was also statistically significant in favour of the ^{177}Lu vipivotide tetraxetan + SOC arm (stratified, two-sided Wald's Chi-square test $p<0.001$). DCR was 89.0% in the ^{177}Lu vipivotide tetraxetan + SOC arm vs. 66.7% in the SOC only arm, with and odds ratio of 5.79 (95% CI: 3.18 to 10.55).[22]

3.2.5.5 Subgroups

Pre-specified subgroup analyses were conducted for the primary efficacy outcomes OS and rPFS. The key patient sub-populations included: ARPI as part of assigned SOC at the start of the study, presence of liver metastasis at baseline, baseline LDH level, baseline ECOG score, age, and race.

A forest plot of HRs for the subgroup analyses on OS is presented in Figure 7. For all subgroups, with the exception of non-white patients, which had low patient numbers and thus wide confidence intervals, the analyses showed a favourable trend for the ^{177}Lu vipivotide tetraxetan + SOC arm compared with the SOC only arm. Given the likelihood that ARPI would be used only once in the UK clinical practice, the EAG notes that there is a reduced effect on OS for patients not assigned ARPI as part of SOC compared with those who received an ARPI (HR 0.68 [95% CI: 0.53 to 0.87] vs. 0.54 [95% CI: 0.41 to 0.70], respectively).

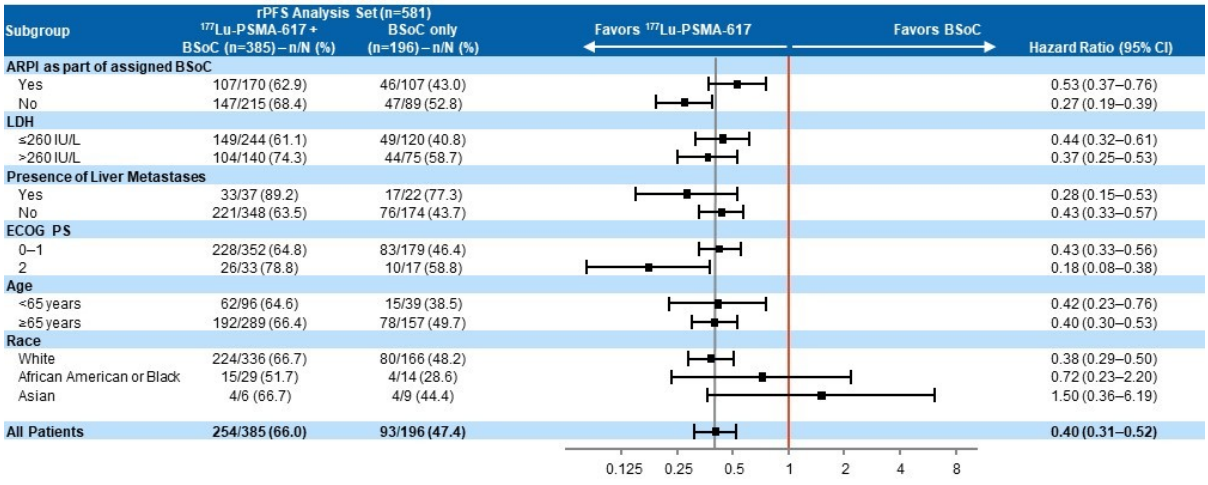
Figure 7: Subgroup analyses of OS per independent central review – Forest plot of HR with 95% CI (FAS) (reproduced from CS, Figure 8)



n/N: number of events/number of patients in treatment arm. Vertical line shows HR for the overall population.
Abbreviations: ^{177}Lu, Lutetium-177; ARPI, androgen receptor pathway inhibition; CI, confidence interval; ECOG, Easter Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; FAS, full analysis set; PS, performance score; PSMA, prostate-specific membrane antigen; SOC, standard of care.

A forest plot of HRs for the subgroup analyses on rPFS is presented in Figure 8. For all subgroups, with the exception of non-white patients, which had low patient numbers and thus had wide confidence intervals, the analyses showed a favourable trend for the ^{177}Lu vipivotide tetraxetan + SOC arm compared with the SOC only arm. Unlike the OS endpoint, there was a greater effect on rPFS for patients assigned an ARPI as part of SOC compared with those who were not assigned an ARPI (HR 0.53 [95% CI: 0.37 to 0.76] vs. 0.27 [95% CI: 0.19 to 0.39], respectively).

Figure 8: Subgroup analyses of rPFS per independent central review – Forest plot of HR with 95% CI (PFS-FAS) (reproduced from CS, Figure 9)



n/N: number of events/number of patients in treatment arm.
Vertical line shows HR for the overall population.
Abbreviations: ^{177}Lu, Lutetium-177; ARPI, androgen receptor pathway inhibition; CI, confidence interval; ECOG, Easter Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; PFS-FAS, progression-free survival full analysis set; PS, performance score; PSMA, prostate-specific membrane antigen; SOC, standard of care.

In *post hoc* analyses, no [redacted] was found for OS between patients who had previously received one rather than two taxanes prior to entry into the VISION trial (Figure 9), although [redacted]. This is consistent with clinical advice to the EAG that number of previous lines of therapy is a prognostic factor.

Figure 9: Survival analysis of patients receiving one vs. two taxanes prior to entry into VISION (reproduced from CS, Appendix M.4, Figure 41)

0 = patients that had received one taxane prior to entry into VISION.
1 = patients that had received two taxanes prior to entry into VISION.

3.2.6 Quality of life study results from VISION

All data collection and analyses were conducted in the PFS-FAS population (n=581): only patients randomised on and after 5th March 2019. As with rPFS, it should be noted that there is a marked drop-off in the number of patients at risk and the event-free probability at 2 months.

3.2.6.1 Time to worsening in Brief Pain Inventory – Short Form (BPI-SF)

Time to worsening in BPI-SF was defined as the earliest occurrence of a ≥30% increase or ≥2 point increase relative to baseline, clinical progressive disease or death. The VISION trial demonstrated a statistically significantly prolonged time to worsening in BPI-SF for patients receiving ^{177}Lu vipivotide tetraxetan + SOC compared with patients receiving SOC only ([redacted]) (see Figure 10). [redacted]. Patients in the intervention arm experienced an increase in median time to worsening in BPI-SF of 3.7, [redacted] months for pain intensity, pain interference, and worst pain intensity, respectively (CS, Section B.2.5.5).

Figure 10: Kaplan-Meier plot of time to worsening in BPI-SF pain intensity scale (PFS-FAS) (reproduced from CS, Appendix M.3, Figure 34)

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 inhibition; BPI-SF, brief pain inventory – short form; IRT, interactive response technology; LDH, lactate dehydrogenase; PFS-FAS, progression-free survival full analysis set; PSMA, prostate-specific membrane antigen.

3.2.6.2 Functional Assessment of Cancer Therapy – Prostate (FACT-P)

Time to worsening in FACT-P was defined as the earliest occurrence of a ≥10 point decrease relative to baseline, clinical progressive disease or death. VISION demonstrated a statistically significantly prolonged time to worsening in FACT-P for patients receiving ^{177}Lu vipivotide tetraxetan + SOC compared with patients receiving SOC only ( ) (see Figure 11). This benefit was demonstrated across FACT-P total score, . Patients in the intervention arm experienced an increase in median time to worsening of 3.5, months for FACT-P total score, PSI-8 score, and TOI score, respectively (CS, Section B.2.5.5).

Figure 11: Kaplan-Meier plot of time to worsening in FACT-P total score scale (PFS-FAS) (reproduced from CS, Appendix M.3, Figure 37)

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 inhibition; BPI-SF, brief pain inventory – short form; FACT-P, Functional Assessment of Cancer Therapy- Prostate; IRT, interactive response technology; LDH, lactate dehydrogenase; PFS-FAS, progression-free survival full analysis set; PSMA, prostate-specific membrane antigen.

3.2.6.3 EuroQoL-5 Dimension-5 Level (EQ-5D-5L)

Time to worsening in EQ-5D-5L was defined as any decrease relative to baseline. VISION demonstrated [redacted] for patients receiving ^{177}Lu vipivotide tetraxetan + SOC compared with patients receiving SOC only [redacted] (see Figure 12). Patients in the intervention arm experienced an increase in median time to worsening in EQ-5D-5L utility scores of [redacted], equivalent to a [redacted] in time to worsening compared with SOC only (CS, Section B.2.5.5).

Figure 12: Kaplan-Meier plot of time to worsening of EQ-5D-5L utility score (PFS-FAS) (reproduced from CS, Appendix M.3, Figure 40)

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 inhibition; EQ-5D-5L, EuroQoL-5 Dimension-5 Level; IRT, interactive response technology; LDH, lactate dehydrogenase; PFS-FAS, progression-free survival full analysis set; PSI-8, prostate symptom index – 8; PSMA, prostate-specific membrane antigen.

3.2.7 Safety study results of VISION

The CS reported the safety data for the VISION trial in Section B.2.9.[1] The data were reported for all randomised patients who had received at least one dose of treatment in either arm: the FAS safety analysis set (SAS) (n=734). Tables and text providing a summary of the data are presented below.

Patients in the ^{177}Lu vipivotide tetraxetan + SOC arm experienced substantially more adverse events (AEs), Serious Adverse Events (SAEs), Grade $\geq$3 AEs, drug-related AEs, drug-related SAEs and drug-related Grade $\geq$3 AEs than patients in the SOC arm. Patients in the ^{177}Lu vipivotide tetraxetan + SOC arm did not experience more AEs leading to reduction, interruption or discontinuation of SOC than the patients in the SOC alone arm (Table 14).

Table 14: Overview of AEs during randomised treatment (FAS-SAS: safety analysis set) (reproduced from CS, Table 23)

Type of AE, n (%)	^{177}Lu vipivotide tetraxetan + SOC N=529	SOC N=205
All AE	519 (98.1)	170 (82.9)
Serious AE	192 (36.3)	57 (27.8)
Grade ≥ 3 AE	[redacted]	[redacted]
Drug-related AE	451 (85.3)	59 (28.8)
Serious drug-related AE	49 (9.3)	5 (2.4)
Drug-related Grade ≥ 3 AE	[redacted]	[redacted]
AE leading to reduction of ^{177}Lu vipivotide tetraxetan	30 (5.7)	0
AE leading to reduction of SOC	[redacted]	[redacted]
AE leading to interruption of ^{177}Lu vipivotide tetraxetan	85 (16.1)	2 (1.0)[a]
AE leading to interruption of SOC	[redacted]	[redacted]
AE leading to discontinuation of ^{177}Lu vipivotide tetraxetan	63 (11.9)	1 (0.5)[a]
AE leading to discontinuation of SOC	[redacted]	[redacted]
Fatal AE	19 (3.6)	6 (2.9)

Drug-related is related to any study drug (^{177}Lu vipivotide tetraxetan or SOC), as assessed by the investigator. [a]Four patients randomised to ^{177}Lu vipivotide tetraxetan + SOC arm received only SOC and therefore contribute to the FAS safety analysis set of the SOC arm

Abbreviations: ^{177}Lu, Lutetium-177; AE, adverse event; FAS-SAS, full analysis set-safety analysis set; PSMA, prostate-specific membrane antigen; SOC, standard of care.

3.2.7.1 Adverse events with a suspected relationship occurring in at least 5% of patients in any arm

No Grade ≥3 AE occurred in >5% of patients in the SOC arm (Table 15). The highest rates of Grade ≥3 AEs in the^{177}Lu vipivotide tetraxetan + SOC arm were [redacted]. The published figures (without the 'suspected relationship' criterion) were: anaemia (12.9%); thrombocytopenia (7.9%); lymphopenia (7.8%); and fatigue (5.9%).[22]

Table 15: AEs occurring in at least 5% of patients in either arm during randomised treatment with suspected relationship by preferred term and maximum grade (FAS-SAS) (reproduced from CS, Table 25)

Preferred term	^{177}Lu vipivotide tetraxetan + SOC N=529		SOC N=205	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Patients with at least one event	**451 (85.3)**	**150 (28.4)**	**59 (28.8)**	**8 (3.9)**
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	^{177}Lu vipivotide tetraxetan + SOC N=529		SOC N=205	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ^{177}Lu, Lutetium-177; AE, adverse event; FAS, full analysis set; PSMA, prostate-specific membrane antigen; FAS-SAS, full analysis set-safety analysis set; SOC, standard of care.

3.2.7.2 Serious adverse events occurring in at least 1% of patients

SAEs occurring in at least three patients in either arm are presented in Table 16. In either arm, [redacted]

Table 16: SAEs occurring in at least 1% of patients in either arm during randomised treatment (FAS-SAS) (reproduced from CS, Table 26)

Preferred term	^{177}Lu vipivotide tetraxetan + SOC N=529		SOC N=205	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Patients with at least one event	**192 (36.3)**	**169 (31.9)**	**57 (27.8)**	**52 (25.4)**
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
Spinal cord compression	[redacted]	[redacted]	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]	[redacted]	[redacted]
Subdural haematoma	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	^{177}Lu vipivotide tetraxetan + SOC N=529		SOC N=205	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Infection	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ^{177}Lu, Lutetium-177; AE, adverse event; FAS-SAS, full analysis set-safety analysis set; PSMA, prostate-specific membrane antigen; SOC, standard of care.

3.2.7.3 Deaths occurring during randomised treatment

SAEs leading to fatal outcome during randomised treatment are presented in Table 17. [redacted].

Table 17: On-treatment deaths during randomised treatment (FAS-SAS) (reproduced from CS, Table 27)

	^{177}Lu vipivotide tetraxetan + SOC N=529 n (%)	SOC N=205 n (%)
Deaths[a]	[redacted]	[redacted]
Reported in patients with primary reason for death = Adverse event	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]
Acute hepatic failure	[redacted]	[redacted]
Bone marrow failure	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Escherichia sepsis	[redacted]	[redacted]
Euthanasia	[redacted]	[redacted]
Haemorrhage intracranial	[redacted]	[redacted]
Hepatic failure	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]
Metastases to central nervous system	[redacted]	[redacted]
Multiple organ dysfunction syndrome	[redacted]	[redacted]
Pneumonia aspiration	[redacted]	[redacted]
Subdural haematoma	[redacted]	[redacted]
Arteriosclerosis	[redacted]	[redacted]
Cardio-respiratory arrest	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

[a]On-treatment deaths are deaths that occurred during randomised treatment or within 30 days of randomised treatment discontinuation.
Abbreviations: ^{177}Lu, Lutetium-177; COVID-19, coronavirus disease 2019; FAS-SAS, full analysis set-safety analysis set; PSMA, prostate-specific membrane antigen; SOC, standard of care.

3.2.7.4 AEs occurring in at least 1% of patients leading to permanent discontinuation of ^{177}Lu vipivotide tetraxetan treatment

AEs leading to dose interruption or reduction of ^{177}Lu vipivotide tetraxetan are presented in Table 18. The most frequent events were anaemia (interruption: [redacted], reduction: [redacted]) and thrombocytopenia (interruption: [redacted] and reduction: [redacted]). All other events that led to dose interruption or reduction were reported for less than [redacted] of the patients. AEs leading to permanent discontinuation of ^{177}Lu vipivotide tetraxetan are also presented in Table 18. The most frequent events were related to cytopenias (ranging from 2.8% for thrombocytopenia and anaemia to 0.6% for pancytopenia). All other events were reported in less than 0.5% of patients.

Table 18: AEs occurring in at least 1% of patients leading to interruption, dose reduction or permanent discontinuation of ^{177}Lu vipivotide tetraxetan during randomised treatment (FAS-SAS) (reproduced from CS, Tables 28 and 29)

Preferred term	^{177}Lu vipivotide tetraxetan + SOC N=529	
	All grades n (%)	Grade ≥ 3 n (%)
Interruption		
Patients with at least one event	85 (16.1)	42 (7.9)
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Dose reduction		
Patients with at least one event	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Discontinuation		
Patients with at least one event	63 (11.9)	37 (7.0)
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]

Abbreviations: ^{177}Lu, Lutetium-177; COVID-19, coronavirus disease 2019; FAS-SAS, full analysis set-safety analysis set; PSMA, prostate-specific membrane antigen; SOC, standard of care; AE, adverse event.

3.2.7.5 Treatment-emergent adverse events of interest

An overview of treatment-emergent adverse events of interest during randomised treatment is presented in Table 19. These events were selected either because of their high likelihood of being associated with active cancer treatment (fatigue, myelosuppression, nausea and vomiting); the known distribution of PSMA in the salivary glands and the proximal tubule and known renal route of excretion (dry mouth and renal effects), or because they are standard safety outcomes (e.g., hepatotoxicity and QTc prolongation).

There were much higher frequencies of fatigue and myelosuppression in the ^{177}Lu vipivotide tetraxetan + SOC arm than the SOC arm, both events of any grade and Grades 3-5. There were much higher rates of dry mouth, nausea and vomiting, and hypersensitivity (which includes rash, stomatitis, pruritus, conjunctivitis, eczema, rash maculo-papular, dermatitis, generalised oedema, scrotal oedema, sneezing, swelling face, acute respiratory failure, blister etc.) in the ^{177}Lu vipivotide tetraxetan + SOC arm than the SOC only arm, though only for Grades 1 and 2.

Table 19: Overview of treatment-emergent adverse events of interest during randomised treatment (FAS-SAS) (reproduced from CS, Table 30 and VISION[22])

Safety topic	^{177}Lu vipivotide tetraxetan + SOC N=529		SOC N=205	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Fatigue	260 (49.1)	37 (7.0)	60 (29.3)	5 (2.4)
Myelosuppression	251 (47.4)	124 (23.4)	36 (17.6)	14 (6.8)
Dry mouth	208 (39.3)	0	2 (1.0)	0
Nausea and Vomiting	208 (39.3)	8 (1.5)	35 (17.1)	1 (0.5)
Hypersensitivity	55 (10.4)	5 (0.9)	7 (3.4)	0
Hepatotoxicity	54 (10.2)	15 (2.8)	16 (7.8)	5 (2.4)
Renal effects	46 (8.7)	18 (3.4)	12 (5.9)	6 (2.9)
Second primary malignancies	11 (2.1)	4 (0.8)	2 (1.0)	1 (0.5)
QT prolongation	9 (1.7)	7 (1.3)	1 (0.5)	1 (0.5)
Intracranial haemorrhage	7 (1.3)	5 (0.9)	3 (1.5)	2 (1.0)

Note: Second primary malignancies includes squamous cell carcinoma, metastases to central nervous system, metastases to meninges, basal cell carcinoma, malignant melanoma, squamous cell carcinoma of skin, extradural neoplasm, squamous cell carcinoma of the tongue.
Abbreviations: ^{177}Lu, Lutetium-177; COVID-19, coronavirus disease 2019; FAS-SAS, full analysis set-safety analysis set; PSMA, prostate-specific membrane antigen; SOC, standard of care.

3.2.7.6 Safety summary

^{177}Lu vipivotide tetraxetan + SOC produces higher frequencies of AEs, Grade 3 AEs, drug-related AEs, and SAEs than SOC alone among patients, especially anaemia, thrombocytopenia, fatigue, dry mouth, myelosuppression, nausea and vomiting, hypersensitivity and leukopenia. Clinical advice received by the EAG suggested that the safety profile was consistent with expectations.

3.2.8 Ongoing studies

The CS stated that there were no relevant ongoing studies due to report within 12 months of the submission (CS, Section B.2.10).[1] There are the following ongoing open-label, Phase III RCTs with later completion dates: NCT04689828 and NCT04720157. PSMAfore (NCT04689828; estimated enrolment, n=450) is investigating ^{177}Lu vipivotide tetraxetan vs. androgen receptor directed therapy

(ARDT) in PSMA-positive mCRPC, who have not been exposed to prior taxanes within the previous 12 months; the primary completion date is October 2022, and the study completion date is August 2023. PSMAddition (NCT04720157; estimated enrolment, n=1,126) is investigating ^{177}Lu vipivotide tetraxetan +SOC vs. SOC alone in PSMA-positive mCRPC, where SOC is defined as a combination of ARDT and ADT; the primary completion date is August 2024, and the study completion date is December 2025.

3.3 Indirect treatment comparisons

Cabazitaxel has been identified as one of the relevant comparators for ^{177}Lu vipivotide tetraxetan (CS, Section B.1.1).[1] Following the criterion applied in the SLR that RCTs had to be designated 'Phase III' to be included in the primary evidence for the clinical effectiveness review, there were no published head-to-head Phase III trials comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel. In the absence of such evidence, the CS presented the following: a Bayesian NMA including VISION plus seven Phase III multicentre RCTs of alternative therapies; and additional supportive evidence including a Phase II trial comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel (the TheraP trial[29]) and a real-world evidence (RWE) analysis from UK clinical practice on cabazitaxel.

3.3.1 Searches

For a full critique of the search, see Section 3.1.1. The original search was used to identify all potential ^{177}Lu vipivotide tetraxetan trials and trials of their comparators for use in the indirect treatment comparisons from a global perspective (CS, Appendix D.1.1).[1] The search results are reported in Appendix D.1.2 and the PRISMA flowchart is presented in Figure 2. Twenty-six publications representing 20 trials satisfied the inclusion criteria (CS, Appendix D.1.1 Table 3): one publication was identified relevant to ^{177}Lu vipivotide tetraxetan (the VISION trial[22]). The following additional inclusion criterion was applied to the included trials for the NMA: Phase III RCTs assessing the efficacy or safety of at least one intervention considered relevant and used in UK clinical practice, including: ARPIs (abiraterone or enzalutamide), radium-223, and cabazitaxel (CS, Section B.2.8.3).

Eight trials (13 publications), including the VISION trial (one publication) satisfied these criteria and were used in the NMA (CS, Appendix, D.1.3, Table 7).[1] The EAG notes that the TheraP trial did not satisfy the company's inclusion criteria for either the clinical effectiveness review or the NMA, and was presented only as "*supporting evidence*" (CS, Section B.2.8.1). The TheraP trial was retrieved by the searches but was excluded from both the review and the NMA. The reasons for excluding the TheraP trial given in the CS were inconsistent: it was excluded either due to its Phase II design (CS, Section B.2.8.1) or due to its population (CS, Appendix D.1.2, Table 4). In response to clarification question A9, the company confirmed that it was excluded on the basis of study design (as a Phase II study).[17]

3.3.2 The TheraP trial

TheraP (NCT03392428) was a multicentre, open-label RCT comparing ^{177}Lu vipivotide tetraxetan (n=99) (6·0–8·5 GBq intravenously every 6 weeks for up to six cycles) with cabazitaxel (n=101) (20 mg/m² intravenously every 3 weeks for up to ten cycles) in PSMA-positive mCRPC.[29] Like the VISION trial, there was a clear imbalance in pre-treatment withdrawals from the cabazitaxel arm compared with the ^{177}Lu vipivotide tetraxetan arm: 16/101 [16%] compared with 1/99 [1%].[29] The primary outcome was PSA response (defined as a reduction of PSA ≥50% from baseline); secondary outcomes included rPFS, response rates, pain and prognostic biomarkers. OS is due to be reported when sufficient events have occurred.

The data cut-off was the 20th July 2020 with a median follow-up of 18.4 months.[29] The patient populations in the VISION trial and the TheraP trail were similar, except that baseline PSA levels were higher in the TheraP trial: 77.5 ng/ml in the FAS population in the VISION trial ^{177}Lu vipivotide tetraxetan + SOC arm vs. 93·5 ng/ml in the TheraP trial for the ^{177}Lu vipivotide tetraxetan arm. The TheraP trial reported a significant more frequent PSA reduction from baseline (defined as a reduction of PSA ≥50% from baseline) in the ^{177}Lu vipivotide tetraxetan group than the cabazitaxel group: 65/95 (66%) compared with 37/101 (37%); difference 29% (95% CI: 16% to 42%; p<0·0001). The HR for rPFS comparing the ^{177}Lu vipivotide tetraxetan group to the cabazitaxel group is also statistically significant 0.64 (95% CI: 0.46 to 0.88). The EAG notes that the confidence interval for this HR was reported incorrectly in the CS.

The safety profile was consistent with the findings of the VISION trial: there was a comparable frequency of AEs and Grade >3 AEs across both arms for those associated with active cancer treatment (e.g., fatigue, pain, nausea and vomiting) and higher frequencies in the ^{177}Lu vipivotide tetraxetan arm compared with the cabazitaxel arm for Grade 1-2 AEs associated with PSMA levels: dry mouth (60% vs. 21%) and dry eyes (30% vs. 4%). Numbers of patients experiencing thrombocytopenia (Grades 1-2: 18% vs. 5%; Grades 3-4: 11% vs. 0%) were higher in the ^{177}Lu vipivotide tetraxetan arm, but diarrhoea (18% vs. 52%), haematuria (Grades 1-2: 3% vs. 14%; Grades 3-4: 1% vs. 6%) and Grade 3-4 neutropenia (4% vs. 13%) were all higher in the cabazitaxel arm. Overall, higher rates of Grade 1-2 AEs were reported for patients on ^{177}Lu vipivotide tetraxetan compared with cabazitaxel (54% vs. 40%), but lower rates of Grades 3-4 AEs were reported for patients on ^{177}Lu vipivotide tetraxetan compared with cabazitaxel (33% vs. 53%).[29]

The CS did not conduct a quality assessment of the TheraP trial, but the company provided this in response to a clarification question from the EAG (see clarification response, question A6).[17] The EAG undertook its own assessment and judged the trial to be at a high risk of bias. This was due to there

being a high risk of bias in at least one domain (due to imbalances and missing data between arms), and some concerns in one domain due to the open-label nature of the trial, potentially affecting some outcomes (Table 20). Neither of these issues was considered a concern in the CS assessment (see clarification response,[17] question A6).

The CS reported that TheraP did not contribute to the efficacy evidence in the economic model due to differences between TheraP and VISION in the diagnostic process, the intervention production and dose, and the stratification of patients (CS, Section B.2.8.1), and TheraP was also not powered to robustly investigate OS and has not yet published any results for this endpoint.

Table 20: Cochrane Risk of bias v.2.0: TheraP[29]

Author, Year	Bias arising from the randomisation process: sequence generation, allocation concealment, balance between groups)	Bias due to deviations from intended intervention (deviations with likely effect on outcomes)	Bias due to missing data (attrition)	Bias due to measurement of outcome (blinding of assessors, potential for differences between groups)	Bias in selection of reported results (prespecified outcomes, potentially different measures)	Overall risk of bias
Assessment	Low	Low	High	Some concerns	Low	High
Details	*Participants were randomly assigned (1:1) via a centralised web-based system that stratified by disease burden (>20 sites vs ≤20 sites by PSMA PET-CT), previous treatment with enzalutamide or abiraterone, and study site using minimisation with a random component*[29]		Potential imbalances across arms due to withdrawals / missing data: the proportions of missing outcome data, and reasons for missing outcome data differ between intervention groups; characteristics of withdrawing patients were not reported; intention-to-treat analysis used for primary outcome only; sensitivity analyses used for per-protocol population.	Open-label phase III trial; review of radiographic outcomes not blinded so there is a risk of ascertainment bias	All outcomes listed in protocol (NCT03392428) are reported except for tertiary outcomes, to be reported elsewhere: '*endpoints related to prognostic and predictive biomarkers await analysis and results will be published separately'* [29]	High risk of bias in at least one domain, and some concerns in one domain[26]

3.3.3 Real-world evidence

The CS reported that a retrospective RWE study was conducted by the company to assess the clinical characteristics, current standard of care, clinical outcomes (survival for patients on cabazitaxel), and healthcare resource usage and associated costs of patients with mCRPC in England.[1] This involved identifying the relevant mCRPC patient population within the UK healthcare system using linked healthcare datasets from Public Health England (PHE) and NHS Digital (CS, Section B.2.8.1). Given problems with identifying relevant mCRPC patients, it was assumed that patients who received cabazitaxel from 1st January 2009 to 31st December 2018 are likely to be those most closely aligned with the relevant population in this submission (post-ARPI, post-taxane). A cohort of [redacted] patients was identified, of which [redacted] patients had no recorded follow-up and hence were censored from further survival analysis (CS, Section B.2.8.1 and Appendix N).[1]

The analysis used combined data from major UK databases including the National Cancer Registry (NCR), the Systemic Anticancer Therapy (SACT) dataset, Hospital Episode Statistics (HES), Diagnostic Imaging Dataset (DID), and Radiotherapy Dataset (RTDS). A comparison of patient characteristics and survival outcomes was made with the VISION patient population. Not all baseline characteristics or prognostic factors were available for comparison across the RWE and VISION datasets, e.g., PSA level and number of prior therapies (and taxanes) at initiation of therapy. Of the characteristics and factors presented for comparison between the VISION trial and the RWE cabazitaxel cohort (CS, Table 16), age and ethnicity had different definitions but were similar, while ECOG status 0-1 and presence of bone metastases were similar (Table 21).

Table 21: Baseline characteristics for the RWE analysis (reproduced from CS, Table 16)

Characteristic	RWE cabazitaxel cohort (n=[redacted])[a]	VISION (FAS) (n=831)
Median age (range), years	[redacted]	[redacted]
Ethnicity, White British %	[redacted]	[redacted]
ECOG ≤1, n (%)	[redacted]	[redacted]
Presence of bone metastases, n (%)	[redacted]	[redacted]

[a][redacted] patients in the RWE cabazitaxel cohort had no recorded follow-up and hence were censored from subsequent survival analysis. [b]Age in the RWE cohort was reported as age at mCRPC diagnosis, not age at cabazitaxel initiation, and thus is not directly comparable to age reported for VISION. [c]Ethnicity in VISION was specified as 'White', not 'White British,[30] [d]ECOG status as reported at the point of cabazitaxel initiation. This data were available for [redacted] patients in total, with [redacted] patients of unknown ECOG status.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; RWE, real-world evidence.

The RWE analysis only analysed OS data, but not rPFS given "*Disease progression, rPFS or PFS, is challenging to capture in database analyses, and often relies on the commencement of a new treatment to act as a proxy for progression. However, in mCRPC that has already progressed despite multiple prior therapies, this proxy becomes inconsistent, especially when patients do not go on to receive*

another therapy leading to high levels of censored data" (CS, Section B.2.8.1). Median OS for RWE study patients receiving cabazitaxel was [redacted], with a restricted mean OS of [redacted]. The CS notes that the median OS for cabazitaxel in the RWE analysis was shorter than the median OS for the SOC only arm of the VISION trial ([redacted] months vs. 11.3 months), but argued that patients in clinical trials receive enhanced monitoring through more frequent visits to physicians and imaging and therefore may have longer OS compared to what would be anticipated in real-world practice. The EAG notes that the same argument applies equally to both the treatment groups in the VISION trial.

3.3.4 Network meta-analysis

As noted above, the NMA contained eight trials, including the VISION trial. These trials are summarised below (see Table 22).

3.3.4.1 Study quality assessment

For the NMA, the company used the NICE methods guide tool, adapted from the CRD guidance for undertaking systematic reviews in health care, to appraise the seven included RCTs that met the inclusion criteria, in addition to the VISION trial. The EAG mostly agrees with the company's responses to the eight quality assessment criteria for these trials (Table 23). However, the EAG's assessments differed from those of the CS principally on allocation concealment, which concerns the randomisation process rather than blinding (and so was frequently considered adequate), and which domain was judged erroneously in the CS as being "*Not applicable*" (Table 6).

Overall, the trials included in the NMA were at low-to-moderate or moderate risk of bias in those instances where the trial was unblinded, which might affect assessment of some outcomes, and where certain key prognostic factors (e.g., tumour burden/volume) were not controlled for. However, this factor was controlled for in the TROPIC trial (stratification by measurable vs. non-measurable disease). In contrast, the VISION trial was at a high risk of bias due to its failure to control for some known prognostic factors (e.g., tumour volume/burden); its unblinded outcome assessment, which might affect some outcomes, and the substantial discontinuation rates.

Table 22: Summary of studies included in the NMA (reproduced from CS, Table 18)

Trial Identifier	Study Population	Intervention (per arm)	Study N (per arm)	Study N (overall)
TROPIC[31] NCT00417079	Patients with mCRPC that are refractory to hormone therapy and previously treated with a docetaxel-containing regimen.	Mitoxantrone + Prednisone	377	755
		Cabazitaxel + Prednisone	378	
COU-AA-301[32] NCT00638690	Patients with mCRPC who had previous treatment with docetaxel	Abiraterone + Prednisone/prednisolone	797	1195
		Placebo + Prednisone/prednisolone	398	
AFFIRM[33] NCT00974311	Patients with mCRPC who had previous treatment with docetaxel	Enzalutamide	800	1199
		Placebo	399	
NR (Sun *et al.* 2016)[34]	Patients ≥ 18 years old with mCRPC	Abiraterone + Prednisone	143	214
		Placebo + Prednisone	71	
ALSYMPCA[35] NCT00699751	Patients ≥ 18 years old with progressive mCRPC	Radium 223 + BSC	352	526
		Placebo + BSC	174	
PROfound [36] NCT02987543 (short-term follow-up)	Patients with mCRPC who have progressed on prior hormonal agent	Olaparib	256	387
		Enzalutamide or abiraterone	131	
PROfound [37] NCT02987543 (long-term follow-up)	Patients with mCRPC who have progressed on prior hormonal agent	Olaparib	256	387
		Enzalutamide or abiraterone	131	
CARD[38] NCT02485691	Patients with progressive mCRPC who had been treated with three or more cycles of docetaxel	Cabazitaxel	129	255
		Enzalutamide or abiraterone + prednisone	126	
VISION[22] NCT03511664	Patients with mCRPC who are pre-treated with taxane regimens	^{177}Lu vipivotide tetraxetan + SOC	551	831
		SOC	280	

Abbreviations: BSC, best supportive care; mCRPC, metastatic castration-resistant prostate cancer; SOC, standard of care; NMA, network meta-analysis.

Table 23: Risk of bias of studies included in the NMA (reproduced in part from CS, Appendix 1.6, Table 12; EAG's differing judgements in brackets)

Study name	Study registration	1. Was randomisation carried out appropriately?	2. Was the concealment of treatment allocation adequate?	3. Were the groups similar at the outset of the study in terms of prognostic factors?	4. Were the care providers, participants and outcome assessors blind to treatment allocation?	5. Were there any unexpected imbalances in drop-outs between groups?	6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
TROPIC[31]	NCT00417079	Yes	Yes	Yes (Not clear)*	No	No	No	Yes, Yes
COU-AA-301[32]	NCT00638690	Yes	Yes	Yes (Not clear)*	Yes[a]	No	No	Yes, Yes
AFFIRM[33]	NCT00974311	Yes	Yes	Yes (Not clear)*	Yes	No	No	Yes, Yes
Sun *et al*. 2016[34]	NCT01695135	Yes	Yes	Yes (No)**	Yes	No	No	Yes, Yes
ALSYMPCA[35]	NCT00699751	Yes	Yes (Not clear)†	Yes (Not clear)*	Yes	No	No	Yes, Yes
PROfound[36, 37]	NCT02987543	Yes	N/A (Yes)‡	Yes (Not clear)*	N/A (No/Yes)§	No	No	Yes, Yes
CARD[38]	NCT02485691	Yes	N/A (Yes)‡	Yes (Not clear)*	N/A	No	No	Yes, Yes
VISION[22]	NCT03511664	Not clear (Yes)†	N/A (Yes)‡	Yes (Not clear)*	N/A (No)	Yes	No	Yes, Yes

*None controlled for the prognostic factor of tumour burden/volume
**Differences between arms: years since diagnosis; Gleason score; evidence of progression; PSA level and pain
[a]Patients and investigators; outcome assessment unclear
†Details not provided ‡Refers to allocation concealment in randomisation process, not blinding so N/A response is not relevant
§rPFS by blinded independent central assessment
Abbreviations: NMA, network meta-analysis; EAG, External Assessment Group.

3.3.4.2 Heterogeneity across included studies

A brief summary of the populations and interventions in the studies considered by the company is presented in Table 24. Given that ARPI was the common comparator in the NMA, a distinct VISION subpopulation of control patients was analysed *post hoc*. This subpopulation included patients in the SOC only arm who received an ARPI as a component of SOC at the time of initial randomisation. This cohort was referred to as 'SOC-ARPI'.

The CS notes that baseline characteristics were relatively similar between trials for median age and ECOG PS 0-1, with reported median PSA levels in PROfound[36, 37], CARD[38], and VISION[22] all being relatively similar and other trials generally reporting higher median PSAs in both intervention and placebo arms (Table 21 and CS, Section B.2.8.4).[1] However, the CS also notes that patient disease characteristics (e.g., PSMA-positivity, genetic characteristics), prior therapies, and trial duration differed substantially between trials (CS, Section B.2.8.4 and Appendix D.1.3, Table 9).[1] Where available, these data have been added to Table 24 by the EAG.

Patients in most comparator trials appear to be less heavily pre-treated than in the VISION trial where 41% had received ≥2 lines of taxane therapy, and 96.9% had received prior docetaxel. In the comparator trials ≤31% of patients in any arm had been pre-treated with ≥2 lines of chemotherapy in three trials, although all patients had had prior docetaxel (TROPIC[31], COU-AA-301[32], AFFIRM[33]), while less than 65% of patients in any arm in two other trials had had docetaxel (ALYSIMPCA[35], PROfound[36, 37]). In the CARD trial, all patients had received prior docetaxel.

Like VISION, patients in two trials had had prior treatment with an ARPI and were being treated with an ARPI (PROfound[36, 37], CARD[38]) and three trials listed prior hormonal treatment therapy (unspecified) (ALSYMPCA[35], TROPIC[31], Sun *et al*. 2016[34]). In four trials, at least one of the interventions being evaluated was an ARPI, but there had been no prior treatment with an ARPI (COU-AA-301[32], AFFIRM[33], Sun 2016, PROfound[36, 37]). PSMA positivity of patients was not reported in any trial other than VISION.

Table 24: Patient baseline characteristics across studies included in the NMA (adapted from CS, Appendix D.1.3, Table 8)

Study name	Intervention	n	Age, median	ECOG 0-1	Gleason score ≥8	Race – White (%)	Prior surgery/ procedures	Baseline PSA levels; median (range) ng/mL	Number of prior lines of chemotherapy (% with ≥2)	Prior treatment with docetaxel (%)	Follow-up, months (median)
TROPIC[31]	Cabazitaxel plus prednisone	378	68	93%	NR	84%	52%	143.9 (51.1–416)	31	100	12.8
	Mitoxantrone plus prednisone	377	67	91%	NR	83%	54%	127.5 (44–419)	29	100	
COU-AA-301[32]	Abiraterone plus prednisone/prednisolone	797	69	90%	57%	NR	54%	129 (0.4–9,253)	30	100	12.8
	Placebo plus prednisone/prednisolone	397	69	89%	59%	NR	49%	138 (0.6–10,110)	31	100	
AFFIRM[33]	Enzalutamide	800	69	91%	55%	NR	66%	108 (0.4–11,794)	27.6	100	14.4
	Placebo	399	69	92%	56%	NR	61%	128 (0.6–19,000)	25.8	100	
Sun *et al*. 2016[34]	Abiraterone plus prednisone	143	68.2*	92%	72%	NR	27%	NR	NR[a]	NR	12.9
	Placebo plus prednisone	71	67.7*	93%	77%	NR	28%	NR	NR[a]	NR	
ALYSYMPCA[35]	Radium-223 dichloride plus BSC	352	68	65%	NR	96%	16%	199 (4–6,026)**	NR	58	36‡
	Placebo plus BSC	174	69	58%	NR	96%	16%	244 (4–14,500)**	NR	58	
PROfound[36, 37]	Olaparib	256	69	94.9%	73%	NR	NR	68.2 (IQR: 24.1-294.4)	NR	65	13.2
	Enzalutamide or abiraterone	131	69	96.9%	75%	NR	NR	106.5 (IQR:	NR	64	

Study name	Intervention	n	Age, median	ECOG 0-1	Gleason score ≥8	Race – White (%)	Prior surgery/ procedures	Baseline PSA levels; median (range) ng/mL	Number of prior lines of chemotherapy (% with ≥2)	Prior treatment with docetaxel (%)	Follow-up, months (median)
								37.2-326.6)			
CARD[38]	Cabazitaxel	129	70	95.3%	56.6%	NR	NR	62 (1.1–15,000)	NR	100	9.2
	Enzalutamide or abiraterone plus prednisone	126	71	94.4%	64.3%	NR	NR	60.5 (1.5–2,868)	NR	100	
VISION[22]	^{177}Lu vipivotide tetraxetan + SOC	551	70	92.6%	66.5%	[redacted]	NR	76.0† (0–6,988)	41% [b]	96.9	
	SOC-ARPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20.9

*=mean value; **=mcg/L which is equivalent to ng/ml †Reported as 77.5 in Table 6 above. ‡Intended, rather than actually reported

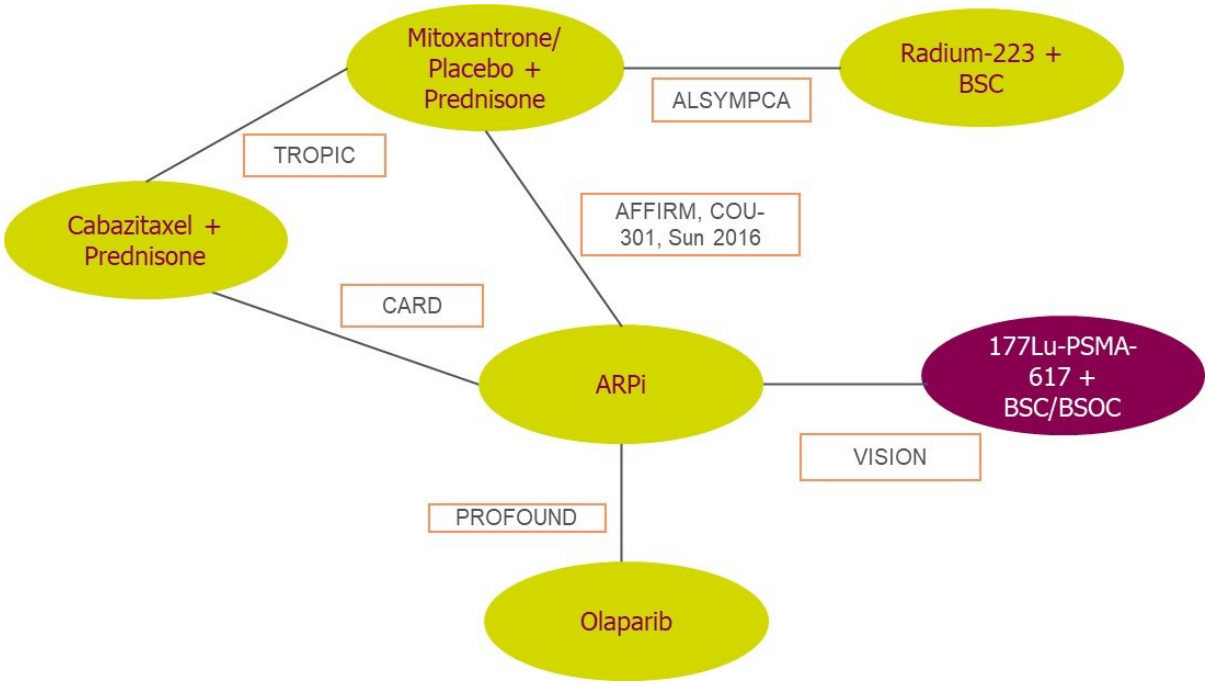
[a]Other therapy including chemotherapy (number of lines not reported) [b]Taxane therapy (including docetaxel) (FAS)

Abbreviations: BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; NR, not reported; SOC, standard of care; NMA, network meta-analysis.

3.3.4.2 NMA methods and results

The NMA was performed using the Markov Chain Monte Carlo (MCMC) approach for OS and rPFS. A linear model with normal likelihood distribution was used to model the time-to-event outcome assuming a constant hazard ratio. The proportional hazards (PH) assumption was tested using the -log(-log(S(t))) vs. log(t) curves and Harrell and Grambsch-Therneau's tests for PH assumption (see clarification response,[17] question A16). The company states that because of the small size of the network and low total number of studies in the network, a fixed effect model was used for both OS and rPFS. The company's OS network is reproduced in Figure 13.

Figure 13: Company's OS network (reproduced from CS, Figure 11)



Abbreviations: ARPI, androgen receptor pathway inhibitor; BSC, best supportive care; SOC, standard of care; OS, overall survival.

In the NMA, a subpopulation of patients in the SOC arm who received an ARPI as a component of SOC at the time of initial randomisation (SOC-ARPI) was used from the VISION trial. For the ^{177}Lu vipivotide tetraxetan + SOC arm in the VISION trial, the whole treatment arm population was used in the NMA. In response to clarification question A14, the company's justification for such an approach was that it connected the VISION trial to the NMA network via the common ARPI comparator, and the pre-specified subgroup analysis on those receiving or not receiving ARPI as a component of SOC provided consistent treatment effects across subgroups (Figure 7 and Figure 8).[17] The company concludes that the NMA results are generalisable to the subgroup of SOC without ARPI based on "*the consistency of treatment effect across subgroups such as those receiving or not receiving ARPI as a component of SOC*", and notes that this generalisability has been confirmed by UK clinicians in an

advisory board meeting (see clarification response,[17] question A14). The clinical advice received by the EAG also confirmed that it is reasonable to assume the generalisability of the treatment effect between SOC-ARPI and SOC without ARPI.

The NMA presented in the CS show a statistically significant benefit in OS [redacted] and in rPFS [redacted] when comparing ^{177}Lu vipivotide tetraxetan to cabazitaxel. When comparing ^{177}Lu vipivotide tetraxetan to ARPI, the benefit associated with ^{177}Lu vipivotide tetraxetan was also statistically significant [redacted].

In response to clarification question A15, the company updated the NMAs only including the subgroup population with ARPI as part of assigned SOC for both treatment arms in the VISION trial.[17] ^{177}Lu vipivotide tetraxetan + SOC-ARPI is associated with statistically significant benefit in OS [redacted] compared against cabazitaxel; [redacted] compared against ARPI). ^{177}Lu vipivotide tetraxetan + SOC-ARPI is associated with greater benefit in rPFS when compared against cabazitaxel ([redacted]); and statistically significant benefit when compared against ARPI ([redacted]).

3.3.4.3 Critique of the company's NMA

3.3.4.3.1 Data used in the NMA

The EAG has some concerns regarding the data used in the company's NMA. Data used from the VISION trial in the company's NMAs broke the randomisation because a subpopulation of patients in the SOC only arm who received an ARPI as a component of SOC at the time of initial randomisation (SOC-ARPI) was used in the NMA, while for the ^{177}Lu vipivotide tetraxetan + SOC arm in the VISION trial, the whole treatment arm population was used in the NMA.

The EAG disagrees with the exclusion of the head-to-head trial (TheraP) comparing ^{177}Lu vipivotide tetraxetan against cabazitaxel on the basis of the design is a Phase II study. Although the Phase II study design was not powered for detecting survival differences between ^{177}Lu vipivotide tetraxetan and cabazitaxel and there are some differences in the trial and patient characteristics between the TheraP trial and the VISION trial, the TheraP trial is highly relevant to this appraisal and should be included in the NMA.

The EAG also disagrees with the inclusion of the TROPIC trial[31] which compared cabazitaxel plus prednisone against mitoxantrone. Clinical advice received by the EAG suggests patients have been more heavily pre-treated in the VISION trial than patients in the TROPIC trial. This is because at the time

the TROPIC trial was recruiting, patients were unlikely to have had ARPIs prior to docetaxel and were therefore unlikely to have had ARPIs prior to recruitment to TROPIC.

In response to clarification question A2, the company clarified that the ALSYMPCA trial[39] which compared radium-223 + SOC against placebo + SOC likely represents a less progressed and less heavily pre-treated population than patients in the VISION trial as only 57% patients in the ALSYMPCA trial had received prior docetaxel and prior use of ARPIs was also not captured.[17] The EAG believes that it is also not appropriate to include ALSYMPCA trial in the NMA.

The company provided the data for the NMAs in response to clarification question A20.[17] The EAG notes that the data from the three trials comparing mitoxantrone/placebo + prednisone against ARPI (COU-AA-301[40], AFFIRM[33] and Sun *et al*. 2016[34]) were combined first before using them in the NMAs. However, the CS does not describe how and why the trial data were combined.

The company's NMA network included olaparib which is not a relevant comparator in this appraisal and does not provide a feedback loop in the network. The EAG believes the NMA should only include the comparators which are not relevant to this appraisal when a feedback loop would be formed.

3.3.4.3.2 rPFS definitions in the NMA

The trials included in the rPFS NMA have different definitions/criteria for rPFS (see Table 25). The TROPIC trial measured PFS which includes PSA progression, tumour progression and pain progression survival.[31] The Sun *et al*. 2016 trial measured PSA progression-free survival[34]. Clinical advice received by the EAG suggests that rPFS is different from PSA progression-free survival. The EAG believes that it is not appropriate to include trials which measured PSA progression-free survival in the NMA for rPFS.

Table 25: NMA trial definitions of (r)PFS

Trial	Definition
TROPIC[31]	The time between randomisation and the first date of progression as measured by PSA progression, tumour progression, pain progression, or death
COU-AA-301[32]	PSA progression: patients in whom the PSA level had not decreased PSA progression was defined as a 25% increase over the baseline and an increase in the absolute-value PSA level by at least 5 ng per millilitre, which was confirmed by a second value; in patients in whom the PSA had decreased but had not reached response criteria [PSA ≤50%], progressive disease would be considered to have occurred when the PSA level increased 25% over the nadir, provided that the increase was a minimum of 5 ng per millilitre and was confirmed; and if at least a 50% decrease in the PSA level had been achieved, PSA progression would be an increase of 50% above the nadir at a minimum of 5 ng per millilitre)

Trial	Definition
	rPFS: defined as soft-tissue disease progression according to modified Response Evaluation Criteria in Solid Tumours [RECIST] [with a baseline lymph node of ≥2.0 cm considered to be a target lesion] or progression according to bone scans showing two or more new lesions not consistent with tumour flare
AFFIRM[33]	Time from randomization to the earliest objective evidence of radiographic progression or death due to any cause. Patients were assessed for objective disease progression at regularly scheduled visits. The consensus guidelines of the PCWG2 were taken into consideration for the determination of disease progression. Radiographic disease progression was defined by RECIST 1.1 for soft tissue disease, or the appearance of 2 or more new bone lesions on bone scan, as per the PCWG2 guidelines. Progression at the first scheduled reassessment at Week 13 required a confirmatory scan 6 or more weeks later; however, time of progression was always determined by initially noted time of progression, regardless of whether confirmation was obtained. A stratified log-rank test was used to compare the enzalutamide-treated and the placebo groups. This comparison was a 2-sided test at the 0.05 level of significance.
Sun *et al*. 2016[34]	The time interval from randomization to the date of PSA progression per PSAWG criteria (unreferenced)
ALYSYMPCA[35]	NR
PROfound[36, 37]	rPFS: imaging-based progression-free survival, assessed by an independent review committee, in patients with at least one alteration in BRCA1, BRCA2, or ATM (cohort A). Imaging-based progression-free survival was defined as the time from randomization until soft-tissue disease progression (by RECIST, version 1.1), bone lesion progression (by Prostate Cancer Clinical Trials Working Group 3 criteria), or death
CARD[38]	rPFS: imaging-based progression-free survival (this is often termed "radiographic" progression-free survival, but the assessment includes nonradiographic measures), which was defined as the time from randomization until objective tumour progression (according to RECIST, version 1.1), progression of bone lesions (according to the Prostate Cancer Working Group 2 criteria), or death (Scher HI, Halabi S, Tannock I, *et al*. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008; 26: 1148-59.)
VISION[22]	The time from the date of randomisation to the date of radiographic disease progression (as outlined in PCWG3 Guidelines[25]) or death from any cause.

Abbreviations: PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; NR, not reported; NMA, network meta-analysis.

3.3.4.3.3 Model used in the NMA

The EAG disagrees with the use of a fixed effect model based on the sparsity of the network and small number included trials. Assuming artificially precise estimates due to the lack of sample data to inform the between-study heterogeneity is not appropriate. The EAG considers that the assumption of zero between-study variation should be treated with caution given the identified differences between trials. An informative prior would be required to inform the between-study heterogeneity and this would lead to more realistic estimates of the uncertainty.

Given the above concerns, the EAG believes that the NMA results should be treated with caution.

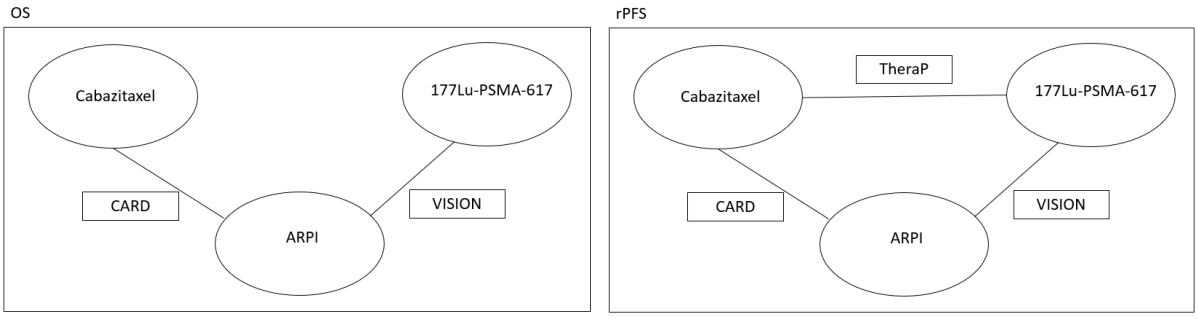
3.4 Additional work on clinical effectiveness undertaken by the EAG

The EAG conducted its own NMA for both OS and rPFS outcomes by incorporating the following changes:

- Exclude TROPIC[31] and ALYSYMPCA[35] as the patients in these two trials have been less heavily pre-treated than patients in VISION.
- Exclude PROfound[36, 37], COU-AA-301[40], AFFIRM[33] and Sun *et al*. 2016[34] because these trials contain treatments are not relevant to this appraisal and do not form a feedback loop in the network after TROPIC[31] and ALYSYMPCA[35] were excluded.
- A subgroup population with ARPI as part of assigned SOC for both treatment arms in the VISION trial was used in the NMAs to preserve the randomisation as ARPI was a stratification factor at randomisation. The EAG notes that the treatment arm became ^{177}Lu vipivotide tetraxetan + SOC-ARPI.
- The TheraP trial was included in the NMA for rPFS. In the TheraP trial, majority of patients in both treatment groups had received ARPIs as previous treatment (92% in the ^{177}Lu vipivotide tetraxetan arm vs. 90% in the cabazitaxel arm). The EAG notes that the study did not report OS results.
- A random effects model with an informative prior[41] (truncated Turner prior assuming that the HR in one study could be no more than 5 times that of the HR in another) was used to inform the estimation of the between-study heterogeneity to allow for more realistic estimates of uncertainty in the presence of heterogeneity.

The EAG's base case NMA includes the VISION, TheraP and CARD trial and the network diagram for OS and rPFS is provided in Figure 14. The EAG notes that the EAG's base case NMA also assumes generalisability of the treatment effect between SOC-ARPI and SOC without ARPI.

Figure 14: EAG's base case NMA network for OS and rPFS



Note: A subgroup population with ARPI as part of assigned SOC for both treatment arms in the VISION trial was used in the NMAs to preserve the randomisation as ARPI was a stratification factor at randomisation.
Abbreviations: OS, overall survival; rPFS, radiographic progression-free survival; ARPI, androgen receptor pathway inhibitor; NMA, network meta-analysis.

The data used for OS and rPFS in the EAG's NMA can be found in Appendix 1. All analyses were performed using the freely available software package WinBUGS and R, using the R2Winbugs interface package.[42] The NMA results were based on 80,000 iterations with a burn-in of 50,000 iterations and thinning every 5 iterations. The EAG's NMA results on ^{177}Lu vipivotide tetraxetan compared against cabazitaxel and ^{177}Lu vipivotide tetraxetan compared against ARPI are presented in Table 26. The EAG's base case NMA shows a benefit for OS (HR 0.84, 95% CrI: 0.37, 1.87) and rPFS (HR 0.74, 95% CrI: 0.47, 1.16) for 177Lu vipivotide tetraxetan compared to cabazitaxel, but the magnitude of the benefit was less than that suggested by the company's NMA and the results were not statistically significant.

Table 26: EAG's NMA results

	SOC-ARPI subgroup		**SOC (with and without ARPI)**	
	Include TheraP	**Exclude TheraP**	**Include TheraP**	**Exclude TheraP**
OS	**HR (95% CrI)**			
^{177}Lu vs. cabazitaxel	NA	0.84 (0.37, 1.87)*	NA	0.98 (0.44, 2.14)
^{177}Lu vs. ARPI	NA	0.54 (0.32, 0.94)	NA	0.63 (0.38, 1.05)
rPFS	**HR (95% CrI)**			
^{177}Lu vs. cabazitaxel	0.74 (0.47, 1.16) *	0.98 (0.43, 2.20)	0.69 (0.46, 1.07)	0.79 (0.37, 1.72)
^{177}Lu vs. ARPI	0.45 (0.28, 0.73)	0.53 (0.29, 0.95)	0.40 (0.26, 0.61)	0.43 (0.25, 0.74)

Note: * indicates the NMA results used in the EAG's base case model.
Abbreviations: OS, overall survival; rPFS, radiographic progression-free survival; ARPI, androgen receptor pathway inhibitor; HR, hazard ratio; NA, not applicable; EAG, External Assessment Group; NMA, network meta-analysis.

3.5 Conclusions of the clinical effectiveness section

The EAG does not believe that there are any published studies relevant to the decision problem, and that could have contributed data on clinical effectiveness, that have been omitted from the CS. The pivotal trial (VISION) was a Phase III, randomised, international (including UK), multi-centre, open-label, ongoing, parallel-arm trial that evaluated the efficacy and safety of 7.4 GBq (200mCi) of ^{177}Lu vipivotide tetraxetan (+ SOC) administered once every 6 weeks for a maximum of 6 cycles in adult patients with PSMA-positive mCRPC. The EAG assessed the VISION trial as being at high risk of bias according to the Cochrane ROB criteria, due to multiple concerns: the failure to control for some known prognostic factors (e.g., tumour volume/burden); imbalances between arms due to withdrawals; and the risk of bias potentially affecting one or more outcomes due to the open-label nature of the trial. Clinical advice received by the EAG confirmed that the VISION trial population was similar to the likely PSMA-positive mCRPC population who present in UK clinical practice, albeit possibly younger and healthier. It should be noted that ARPIs (abiraterone, enzalutamide, apalutamide or any other ARPI) were a required prior treatment for eligibility in the VISION trial and were permitted as concomitant medications in the trial's SOC (both arms), but clinical advice received by the EAG noted that ARPIs

would only be used once in UK clinical practice. The CS stated that the following proportions of patients received ARPIs in the ^{177}Lu vipivotide tetraxetan + SOC and SOC arms, respectively: 34.4% and 47.3%. It was also acknowledged that the diagnostic resources required to identify PSMA-positive patients (to be in line with the VISION trial population and the trial's findings) are not currently available to all patients in the UK.

The VISION trial reported significantly improved OS for ^{177}Lu vipivotide tetraxetan + SOC compared with SOC alone in the FAS population (n=831): median OS was 15.3 months vs. 11.3 months, respectively (HR 0.62, 95% CI: 0.52 to 0.74, p<0.001). A similar result was reported for the PFS-FAS group (n=581): median OS was 14.6 months vs 10.4 months, respectively (HR 0.64, 95% CI: 0.51 to 0.80, p<0.001). The VISION trial reported significantly improved rPFS for ^{177}Lu vipivotide tetraxetan + SOC compared with SOC in the PFS-FAS population (n=581): respectively, median rPFS was 8.7 months vs 3.4 months (HR 0.40, 95% CI: 0.29 to 0.57, p<0.001). It has been noted in a letter to the New England Journal of Medicine concerning VISION that, "*imaging-based progression-free survival in the current trial dropped sharply at 2 months. This implies that some patients may not benefit from 177Lu-PSMA therapy*".[27] The VISION trial reported significantly longer time-to-first symptomatic skeletal event (SSE) for ^{177}Lu vipivotide tetraxetan + SOC than with SOC in the PFS-FAS population (n=581): respectively, median time-to-first event was 11.5 months vs. 6.8 months (HR 0.50, 95% CI: 0.40 to 0.62, p<0.001). Patients receiving ^{177}Lu vipivotide tetraxetan + SOC were also reported to experience significantly longer time to worsening of quality of life across three measures (Brief Pain Inventory – Short Form, Functional Assessment of Cancer Therapy – Prostate, and EQ-5D-5L).

^{177}Lu vipivotide tetraxetan + SOC produces high frequencies of AEs, Grade 3 AEs, drug-related AEs, and SAEs than SOC alone, especially anaemia, thrombocytopenia, fatigue, myelosuppression, dry mouth, nausea and vomiting, hypersensitivity and leukopenia. Clinical advice received by the EAG suggested that the safety profile was consistent with expectations.

In the absence of Phase III trial data directly comparing ^{177}Lu vipivotide tetraxetan with relevant comparator therapies, principally, cabazitaxel, the CS presented the following evidence for consideration: an NMA comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel and other potentially relevant comparator therapies (seven Phase III RCTs plus VISION), and supporting evidence including a Phase II trial comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel (the TheraP trial)[29] and a RWE analysis on cabazitaxel.

The company's NMA showed a significant benefit for OS ([redacted]) and rPFS ([redacted]) for ^{177}Lu vipivotide tetraxetan compared to cabazitaxel. TheraP also reports a statistically significant difference in rPFS (very similar to the rPFS NMA results; OS not assessed) in favour of ^{177}Lu vipivotide tetraxetan + SOC compared with cabazitaxel and the safety

findings were similar to VISION for ^{177}Lu vipivotide tetraxetan. The RWE on cabazitaxel estimated median OS to be [redacted] months, which was lower than the median OS for the SOC only arm of VISION (11.3 months).

The EAG has several concerns regarding the company's NMA: data used from the VISION trial broke the randomisation; exclusion of the head-to-head trial (TheraP); inclusion of the TROPIC and ALSYMPCA trials where the population were less heavily pre-treatment compared to the VISION trial population; assuming the PSA progression-free survival is the same as the rPFS when analysing rPFS; and the use of a fixed effect model which underestimates the between-study heterogeneity. The EAG conducted an alternative NMA analysis. The EAG's base case NMA also shows a benefit for OS (HR 0.84, 95% CrI: 0.37, 1.87) and rPFS (HR 0.74, 95% CrI: 0.47, 1.16) for ^{177}Lu vipivotide tetraxetan compared to cabazitaxel, but the magnitude of the benefit was less than that suggested by the company's NMA and the results were not statistically significant.

4 COST EFFECTIVENESS

This section presents a summary and critique of the company's health economic analyses of ^{177}Lu vipivotide tetraxetan for the treatment of patients with PSMA-positive mCRPC previously treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes. Section 4.1 describes and critiques the company's review of existing economic evaluations. Section 4.2 describes the company's economic model and summarises the company's results. Sections 4.3 and 4.4 present the EAG's critical appraisal of the company's economic model and the additional exploratory analyses undertaken by the EAG, respectively. Section 4.5 presents a discussion of the company's economic analysis.

4.1 EAG's comment on company's review of cost-effectiveness evidence

The company states that a review was conducted to "*identify any relevant economic evaluations for the treatment of adult patients with pre-treated, progressive mCRPC*" (CS, page 86).[1] The company also searched for relevant cost/resource use studies and HRQoL studies but the EAG's main focus in this section is the review of the published economic evaluations.

4.1.1 Summary and critique of the company's search strategy

The company performed two systematic literature searches for: (i) published cost-effectiveness studies of patients who have mCRPC (CS, Appendix G) combined with cost and resource use studies search (CS, Appendix I), and (ii) HRQoL studies (CS, Appendix H). The two searches were undertaken in June 2019, followed by updates in April 2021 and November 2021.

In the combined searches for cost-effectiveness studies and cost and resource use studies, the company searched ten electronic bibliographic databases within a single host platform (via Ovid): MEDLINE, Embase, CDSR, CENTRAL, The HTA Database, DARE, NHS Economic Evaluation Database (NHS EED), EconLit, the ACP Journal Club and Cochrane Clinical Answers. The EAG currently has access to two of the ten databases in the Ovid.com host platform (MEDLINE and Embase). It is unclear to the EAG the reasons for searching ACP Journal Club and Cochrane Clinical Answers. Despite searching numerous electronic sources, the company did not search any conference abstract websites such as American Society of Clinical Oncology (ASCO) or European Society of Medical Oncology (ESMO).

The population terms used for mCRPC are comprehensive and consistent with the clinical effectiveness search strategy (see CS, Appendix D.1). These terms were combined with a highly sensitive economic evaluation search filter. Having reviewed the search, there were no significant and consequential errors found and the EAG considers that the company's search is comprehensive.

Similar to the cost-effectiveness evidence searches, in the HRQoL studies search and cost and resource use searches, the company searched ten databases. The population terms for mCRPC are combined with a HRQoL search filter. There were no consequential errors in the search and the EAG considers that the search is comprehensive.

4.1.2 The inclusion and exclusion criteria used in the study selection

The review of published economic evaluations is targeted at adult males with pre-treated progressive mCRPC (CS, Appendix G, Table 14), but the definition of 'pre-treated' seems to have been applied fairly broadly as it includes chemotherapy-naïve patients, patients pre-treated with docetaxel, patients who have failed ARPI, and for some studies, the population is simply described as mCRPC or 'not reported'. A table of previous NICE TAs is also provided but again the definition of 'pre-treated' appear to have been applied fairly broadly. For the review of economic evaluations, the outcomes of interest were costs, quality-adjusted life year (QALYs), life-years (LYs) and incremental cost-effectiveness ratios (ICERs) and no restrictions were placed on the interventions or comparators or the date of the publication, but studies were restricted to those published in English.

4.1.3 Summary of findings of company's review of existing economic evaluations

The CS states that the review of existing economic evaluations identified of 3,271 citations, of which 26 articles from 20 cost-effectiveness studies (CS, page 86) were included. Details of 17 published studies and 8 NICE TAs are provided in CS, Tables 32 and 33, respectively.[1] None of the included studies evaluated ^{177}Lu vipivotide tetraxetan. The company states that none of the identified analyses included economic comparisons for the specific population of interest for this appraisal submission. However, NICE appraisals which included the population of mCRPC previously treated with a docetaxel-containing regimen (NICE TA391, NICE TA316, NICE TA259), and an ongoing appraisal for olaparib for treating hormone-relapsed mPC after treatment with hormonal therapy (NICE TA ID1640), were considered relevant to inform the development of the *de novo* economic analysis described in the CS.

The EAG agrees that those NICE TAs where the indication was restricted to people previously treated with a docetaxel-containing regimen were more relevant than those appraisals restricted to people not previously treated with chemotherapy, given the company's proposed positioning of ^{177}Lu vipivotide tetraxetan. However, the EAG notes that the TA of radium-223 (TA412) may also be relevant to the subgroup who have bone metastases without any visceral metastases.

CS, Table 33 indicates that the majority of previous appraisals included in the SLR have adopted either a partitioned survival or state transition modelling approaches (Markov or semi-Markov), with health

states defined according to the presence/absence of disease progression and survival; in some instances, occurrence of skeletal-related events have also been included.

4.1.4 EAG critique of the company's review

The EAG identified numerous discrepancies between the details provided in CS, Section B.3.1 and those provided in CS, Appendix G.[1] Firstly, there are 20 included studies described in Appendix G, Table 15, but only 17 studies are presented in CS, Table 32. This may be explained if several papers were considered to be reporting the same study, which the EAG considers to be the likely explanation for the abstracts with accompanying posters described as Li *et al.* (2021)[43] and Barqawi *et al.* (2019),[44] which may duplicate analyses provided in relevant full text publications. In addition, it is possible that the rows with identical titles and similar or identical names are also duplicates (Zhang 2021/Zhang 2021, Ko 2021/Ko 2021 and Ham 2021/Ten Ham 2021).[45-47] If this is the case, then only 15 unique cost-effectiveness analyses would be expected to be presented in the CS. However, two additional budget impact analyses are included in CS, Table 32 (Bui *et al.* [2016] and Flannery *et al.* [2017]),[48, 49] which are not mentioned in CS, Appendix G (or elsewhere in the Appendices).

Furthermore, the combined search for economic evaluations and cost/healthcare resource use studies described in the PRISMA diagram (CS, Appendix G, Figure 8) shows that 74 relevant records were identified as included studies across these two reviews. As 20 of these studies were included in the review of economic evaluations, there should be 54 studies included in the cost/healthcare resource use review described in CS, Appendix I. However, only 36 included studies are presented in Appendix I, Table 24. It is unclear if these additional studies are missing from the review of economic evaluations or the review of cost/healthcare resource use studies. In addition, the reference list of excluded records provided in CS, Appendix G, Tables 16 and 17, cover only the 14 records excluded during updates searches, meaning that the reasons for exclusions are not provided for the majority of the 388 studies excluded at full-text (see CS, Appendix G, Figure 8). No list of excluded studies is provided in Appendix I for the review of cost/healthcare resources use. Given the discrepancies between the main CS and Appendix G and the information missing from Appendix G, the EAG cannot be confident that no relevant published economic evaluations were missed in the company's review.

4.2 Summary of the company's submitted economic evaluation

This section provides a detailed description of the methods and results of the company's health economic analysis. Following the clarification process, the company submitted a revised version of the economic model which included updated estimates of the cost-effectiveness of ^{177}Lu vipivotide tetraxetan (base case only). The changes included the correction of minor errors identified by the EAG in the model originally submitted, related to subsequent treatment administration costs, the number of

weeks and days per year, and formulae related to survival curves for cabazitaxel. For brevity, this report will only refer to the model (and results) received after clarification.

4.2.1 Scope of the company's economic analyses

As part of their submission to NICE,[1] the company submitted an executable model programmed in Microsoft Excel.® The company's base case analysis compares ^{177}Lu vipivotide tetraxetan versus cabazitaxel and SOC for adults with PSMA-positive mCRPC who have received at least two prior treatments (ARPI and taxane-based chemotherapy) or who are not medically suitable for taxanes. The scope of the economic analysis is summarised in Table 27.

Table 27: Scope of the company's economic analyses

Population	Patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes.
Time horizon	10 years, which the company considers sufficient to capture life-time costs and QALY outcomes in this population
Intervention	^{177}Lu vipivotide tetraxetan
Comparator	• Cabazitaxel • SOC
Type of economic analysis	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum
Price year	2019/2020*

*drug acquisition valuated at 2021 prices

Abbreviations: mCRPC, metastatic castration resistant prostate cancer; PSMA, prostate specific membrane antigen; QALY, quality-adjusted life year; NHS, National Health Service; PSS, Personal Social Services; SOC, standard of care.

The economic analysis was undertaken from the perspective of the NHS and PSS over a 10-year horizon. The model assesses the cost-effectiveness of ^{177}Lu vipivotide tetraxetan in terms of the incremental cost per quality-adjusted life year (QALY) gained versus the selected comparator (cabazitaxel or SOC). Unit costs are valued at 2019/20 prices, except for drugs which are valued at 2021 prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

4.2.1.1 Population

The company's presentation of the treatment pathways for mCRPC and their proposed position of ^{177}Lu vipivotide tetraxetan (CS, Figure 2) suggest that ^{177}Lu vipivotide tetraxetan is being proposed for three subgroups (see Section 2.2):

(i) Subgroup 1: Patients who have received at least two prior lines of treatment with an ARPI and at least one taxane-based chemotherapy; and who are eligible to receive further taxane treatment with cabazitaxel (third-line positioning of ^{177}Lu vipivotide tetraxetan);

(ii) Subgroup 2: Patients who have received at least two prior lines of treatment with an ARPI and at least one taxane-based chemotherapy and are ineligible to receive further taxanes; either because they have previously received cabazitaxel (fourth-line positioning of ^{177}Lu vipivotide tetraxetan), or because they are unsuitable for third-line cabazitaxel (third-line positioning of ^{177}Lu vipivotide tetraxetan);

(iii) Subgroup 3: Patients who have received one prior line of treatment, but are unsuitable for treatment with taxanes (second-line positioning of ^{177}Lu vipivotide tetraxetan).

The company presented in their cost-effectiveness analysis a single analysis which they consider to be relevant to all patients covered by their proposed indication for ^{177}Lu vipivotide tetraxetan with only the relevant comparator being considered to differ across the subgroups. The CS claims that the most relevant comparator for ^{177}Lu vipivotide tetraxetan for patients in the first subgroup is cabazitaxel. The company considers SOC as a relevant comparator for ^{177}Lu vipivotide tetraxetan in patients who are not eligible for treatment with cabazitaxel following treatment with an ARPI and docetaxel (subgroup 2), or patients who are medically unsuitable for treatment with taxanes (subgroup 3). The population reflected in the company's economic model is based largely on the characteristics of the FAS population in the VISION trial. Patients included in the trial have received at least one ARPI and at least one (but not more than two) taxane regimens.[1] Therefore information from the VISION trial is not representative of the subgroup who are not medically suitable for taxanes. At model entry, patients are assumed to be approximately [redacted] years of age, and to have a mean weight of [redacted], height of [redacted] and body surface area (BSA) of [redacted].

As noted in Section 2.2, in response to clarification question B3,[17] the company stated that *"Patients medically unsuitable for taxanes having not received prior taxanes, but who are eligible for ^{177}Lu vipivotide tetraxetan (the third subgroup of the target population, as defined in the subgroup row of Table 1 and in Figure 2 of the CS) are expected to represent ~42% of the total patient population eligible for ^{177}Lu vipivotide tetraxetan"*. The EAG notes that this is a large group for which no evidence is available, and the company assumed that the clinical efficacy and safety data from the whole population in the VISION trial[22] is generalisable to all subgroups, including those patients who are medically unsuitable for taxanes.

Clinical advice received by the company considers that there is *"no reason to believe that the efficacy of ^{177}Lu vipivotide tetraxetan should differ in patients suitable or unsuitable for taxanes*" given "*eligibility for taxanes is not based on ability to respond to treatment, but rather on risk of severe side effects limiting treatment tolerability or outweighing any potential benefits of treatment*". They also considered that *"if anything, efficacy may be improved in those patients who have not had prior*

treatment with a taxane", and that *"patients who previously received taxane-based chemotherapy (the VISION trial population) are possibly more likely to experience fatigue, myelosuppression, and dry mouth with ^{177}Lu vipivotide tetraxetan than patients who have not received prior taxane therapy"* (clarification response, question B4).[17] The EAG notes that no clinical data were available that corroborates that data from VISION is generalisable to patients ineligible for taxanes but who are eligible for ^{177}Lu vipivotide tetraxetan (third subgroup in Figure 1), and the evidence for the population in this appraisal is limited to those who have had both an ARPI and a taxane.

4.2.1.2 Intervention

The intervention included in the company's economic analyses is ^{177}Lu vipivotide tetraxetan administered via intravenous (IV) infusions at a dose of 7,400 MBq (200 mCi) once every 6 weeks (QW6) up to a total of 6 doses. This is in line with the draft SmPC for ^{177}Lu vipivotide tetraxetan[13] and the final NICE scope.[18] Treatment duration for patients receiving ^{177}Lu vipivotide tetraxetan in the model is based on mean treatment exposure data from the ^{177}Lu vipivotide tetraxetan + SOC arm of the VISION trial, and patients are assumed to receive further active treatment after disease progression with chemo- and radiotherapies (see Section 4.2.4.5.4).

4.2.1.3 Comparators

The company's analyses include cabazitaxel and SOC as the comparators. This is partially in line with the final NICE scope,[18] which also includes docetaxel and radium-223 as comparators, for patients who have previously received docetaxel in combination with ADT and for patients with bone metastases, respectively. These regimens are not included in the company's economic analyses; the EAG's concerns about the comparators included in the company's economic analyses are discussed in Section 2.3.3.

In the company's model, patients are assumed to receive 25 mg/m2 of cabazitaxel administered via IV every 3 weeks (Q3W) for a maximum of 10 doses. Cabazitaxel is considered by the company to be the most relevant comparator for the group of patients who are eligible to receive further chemotherapy treatment following treatment with an ARPI and docetaxel (CS, Section B.3.2.3).[1] Treatment duration for patients receiving cabazitaxel is based on median treatment exposure data from the CARD trial. Pre-medications associated with cabazitaxel are assumed to be antihistamines, H2-antagonists, corticosteroids and G-CSF.

SOC is considered by the company to be a relevant comparator in the group of patients who are ineligible for treatment with cabazitaxel or unsuitable for treatment with taxanes (subgroups 2 and 3). Patients receiving either ^{177}Lu vipivotide tetraxetan or cabazitaxel are assumed to receive SOC alongside these treatments. SOC includes concomitant medications such as antiemetics, antifungals,

bisphosphonates, corticosteroids, erythropoietin stimulating agents, granulocyte-macrophage colony-stimulating factor (GM-CSF) and opioid analgesics (see Section 4.2.4.5).

Treatment exposure data from VISION for each component of SOC (e.g., antiemetics, antifungals, etc.) were used to inform treatment duration for SOC in the model. These were based on the relevant trial arm of VISION for ^{177}Lu vipivotide tetraxetan and SOC, but were based on the average across both trial arms for cabazitaxel. In the base case analysis, ARPIs received during VISION were excluded for all treatment options and SOC costs were excluded for cabazitaxel and ^{177}Lu vipivotide tetraxetan (see Section 4.2.4.5). As with the intervention group, the model assumes that patients in the cabazitaxel and SOC groups receive following disease progression subsequent treatment with chemo- and radiotherapies.

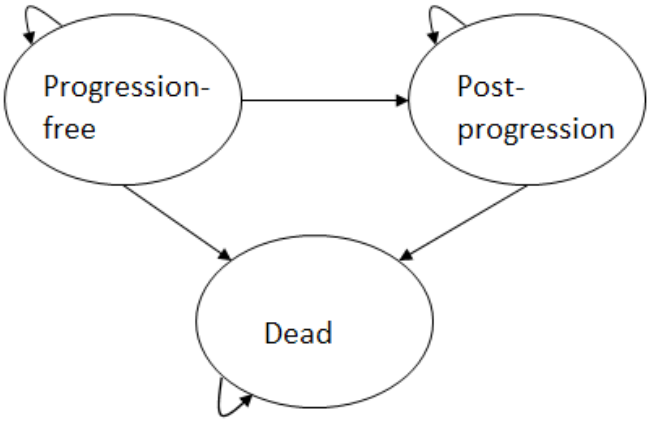
Following a request for clarification from the EAG (see clarification response,[17] question B1), the company stated that *"radium-223 is not considered a relevant comparator in this appraisal as it is indicated in patients with symptomatic bone metastases but without any visceral metastases, limiting comparability with ^{177}Lu vipivotide tetraxetan, which is intended for use regardless of metastasis site*", and that the data available for radium-223 from the ALSYMPCA study are not generalisable to the population considered in the CS (post-ARPI, post-taxane treatments, whilst the population of the trial differed from the VISION trial), and did not report rPFS outcomes. Clinical advice received by the company suggested that only a minority of patients would receive radium-223 in the post-ARPI and taxane setting.[17]

The EAG notes that radium-223 should be considered a comparator for the subgroup of patients with bone metastasis, for whom ^{177}Lu vipivotide tetraxetan would still be considered a treatment option. However, the lack of studies evaluating this treatment option and the uncertainty around the generalisability of the data from the ALSYMPCA study to the population of interest precludes the comparison between ^{177}Lu vipivotide tetraxetan and radium-223 and any further analyses by the EAG.

4.2.2 Model structure and logic

The general structure of the company's economic model is described in Section B.3.2.2 of the CS1 as a partitioned survival model based on three health states: (i) progression-free and alive; (ii) progressed disease and alive, and (iii) dead (see Figure 15).

Figure 15: Company's model structure (drawn by the EAG reproduced from CS, Figure 16)



Abbreviations: EAG, External Assessment Group.

The model logic operates as follows. Patients enter the model in the progression-free state and receive treatment with either ^{177}Lu vipivotide tetraxetan or one of the comparators (cabazitaxel or SOC). Health state occupancy is determined by the cumulative probabilities of OS and rPFS, whereby for any time *t*, the probability of being alive and progression-free is given by the cumulative probability of rPFS, the probability of being alive following disease progression is calculated as the cumulative probability of OS minus the cumulative probability of rPFS, and the probability of being dead is calculated as one minus the cumulative probability of OS.

The cumulative probabilities of OS and rPFS in each time interval for patients receiving ^{177}Lu vipivotide tetraxetan and SOC are modelled using standard parametric distributions or flexible spline models fitted to time-to-event data from the ITT population from VISION trial. The survival functions for patients receiving cabazitaxel are informed by the NMA conducted by the company for rPFS (see Section 3.3.4) and directly by RWE data for OS for patients who received cabazitaxel in UK clinical practice. The survivor functions and the evidence sources to derive these functions are summarised in Table 28, with further detail provided in Section 4.2.4.2. The model applies two structural constraints: (i) within each treatment group, PFS must be less than or equal to OS; and (ii) the predicted incidence of SSE at any timepoint incidence does not exceed the proportion of patients surviving. The model does not include any additional constraints to ensure that the mortality risks for patients with mCRPC must be at least as high as those for the age- and sex-matched general population of the UK. However, modelled mortality rates never fell below age- and sex-matched estimates for the general population of the UK.

HRQoL is assumed to be determined according to the presence/absence of disease progression and, in the base case analysis, treatment group (see Section 4.2.4.4). The utility values applied in the base case analysis for the progression-free and progressed states for patients receiving ^{177}Lu vipivotide tetraxetan or SOC are based on a generalised linear mixed regression model fitted to pooled EQ-5D-3L (mapped from 5L data) from patients in the ITT population of VISION trial. The model assumes that HRQoL for patients who are progression-free and receive cabazitaxel is equivalent to that for patients receiving SOC. The utility value applied for cabazitaxel following disease progression, based on a previous NICE technology appraisal (TA391), is lower than the values applied post-progression for either ^{177}Lu vipivotide tetraxetan or SOC.[15] The company's base case analysis does not explicitly include any QALY losses associated with the incidence of Grade 3/4 AEs as these are assumed to be already captured in the treatment-specific utility values, or any decrements related to SSEs or to reflect the terminal phase of the disease. Health utilities are not adjusted by age.

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) concomitant treatments (SOC therapies and therapeutic interventions); (iv) health state resource use; (v) post-progression (subsequent) treatments; (vi) the management of SSEs; (vii) the management of AEs, and (viii) end-of-life care. These are detailed in Section 4.2.4.5.

The incremental health gains, costs and cost-effectiveness for ^{177}Lu vipivotide tetraxetan versus cabazitaxel or SOC are estimated over a 10-year time horizon using a weekly cycle duration. The company's model does not include half-cycle correction. Although the company states that the comparison against cabazitaxel and the comparison against SOC are relevant to different subgroups of patients (see section 4.2.1.1), both these comparisons are informed by a single model using data and assumptions that are not specific to any subgroup of the population covered by the anticipated marketing authorisation.[1]

4.2.3 Key assumptions employed in the company's model

The company's model employs the following key assumptions:

- The characteristics of patients in the VISION trial (e.g., start age, mean weight, height and BSA) are assumed to represent those of patients who will potentially receive the treatment in the NHS.
- The modelled comparison against cabazitaxel is assumed to be generalisable to patients who have received prior treatment with ARPI and at least one taxane-based chemotherapy, and who are eligible to receive third-line cabazitaxel (subgroup 1).
- The modelled comparison against SOC is assumed to be generalisable to (i) patients who have received one prior line of treatment, but are unsuitable for treatment with taxanes (subgroup 3)

and (ii) those who have had prior taxane-based chemotherapy but are unsuitable for further treatment with taxanes (subgroup 2) either because they are unsuitable for third-line cabazitaxel or because they have already received third-line cabazitaxel.

- Treatment costs for ^{177}Lu vipivotide tetraxetan and cabazitaxel are estimated from the treatment durations reported in the VISION and CARD trials, respectively, and are applied as a one-off cost in the first cycle (time-to-event discontinuation data are not reported or directly used).
- Stratified flexible Weibull (2 knots) distributions are used to model rPFS and OS for ^{177}Lu vipivotide tetraxetan and SOC; all parameters were allowed to vary by treatment which means this was equivalent to fitting separate models by treatment with the only commonality being that the knot positions were the same for both curves; proportional hazards between the ^{177}Lu vipivotide tetraxetan arm and SOC arm are not assumed.
- OS for cabazitaxel is modelled by using the Kaplan-Meier (KM) estimates of the OS from the RWE cabazitaxel cohort directly, whilst rPFS for cabazitaxel is modelled by applying the HR from the NMA to the rPFS survival curve for ^{177}Lu vipivotide tetraxetan.
- The model includes constraints to ensure that: (i) the predicted rPFS and OS are logically consistent; (ii) the predicted SSE incidence does not exceed the proportion of patients surviving. Aside from these constraints, the risks of progression and death are structurally unrelated.
- Log-normal distributions are used to extrapolate the incidence of SSEs beyond the time-frame of the VISION trial for ^{177}Lu vipivotide tetraxetan and SOC (base case analysis). SSE incidence for cabazitaxel is assumed to be the same as for ^{177}Lu vipivotide tetraxetan.
- SSEs result in additional costs but are structurally unrelated to disease progression and QALY losses related to SSEs are only included in scenario analysis.
- HRQoL is determined by the presence/absence of disease progression and treatment group (base case analysis). Utility values are not age-adjusted or capped by general population values.
- HRQoL for progression-free patients receiving cabazitaxel is assumed to be the same as that for SOC, whilst patients with progressed disease are assumed to experience a lower utility value than patients receiving either SOC or ^{177}Lu vipivotide tetraxetan.
- The model assumes that patients receive further active treatment following disease progression; the costs of subsequent treatment are calculated using data observed in VISION on use of these therapies. The durations of treatment with subsequent therapies were assumed to be the same for all treatment groups.
- The model assumes vial sharing and does not include any drug wastage.
- The model includes the weekly costs associated with disease management which were assumed to be the same for all treatment groups.

- Disease management costs are estimated separately for patients within the first three months of the progression-free survival and for all other patients (including post-progression and progression-free beyond four months).
- Within the base case analysis, SOC costs are not included for patients receiving ^{177}Lu vipivotide tetraxetan or cabazitaxel.
- AEs, which are assumed to last one month, result in additional costs, but QALY losses related to AEs are only included in a scenario analysis.

4.2.4 Evidence used to inform the company's model parameters

Table 28 summarises the evidence sources used to inform the model parameters in the company's base case analysis. The derivation of the model parameter values is discussed in detail in the subsequent sections.

Table 28: Summary of evidence used to inform the company's base case analyses

Parameter / group	**^{177}Lu vipivotide tetraxetan**	**SOC**	**Cabazitaxel**
Patient characteristics (age, BSA and mean weight)	Based on characteristics of participants in the ITT population from VISION trial[30]		
rPFS	Stratified flexible Weibull model with 2-knots fitted to unadjusted KM data for rPFS from the ITT population in VISION (N=831)*[1, 30]		HRs from the NMA (HR=[redacted] for cabazitaxel with prednisone relative to ^{177}Lu vipivotide tetraxetan applied to the rPFS survival curve for ^{177}Lu vipivotide tetraxetan[1]
OS	Stratified flexible Weibull model with 2-knots fitted to unadjusted KM data for OS from the ITT population in VISION (N=831)[a 1, 30]		KM OS from the UK RWE analysis for the cabazitaxel cohort used directly[1]
SSE	Log-normal model fitted to KM data for time-to-first SSE from the ITT population in VISION[b];[1, 30] distribution of different types of SSEs included from VISION		Time-to-first SSE for cabazitaxel assumed to be the same as for ^{177}Lu vipivotide tetraxetan; distribution of different types of SSEs based on NICE ID1640[50]
Health state utility values	Treatment-specific utilities value for PF and PD states based on generalised linear mixed model fitted to EQ-5D-5L data from VISION (mapped to 3L); treatment-independent utilities used in scenario analysis		Utility value for PF state assumed to be the same as for SOC; utility value for progressed disease state based on value used in NICE TA391
AE frequencies	Grade 3+ AEs reported by ≥2% of patients in either arm of VISION trial[30]		Grade 3+ AEs reported by ≥2% of patients treated with cabazitaxel in the CARD trial[38]
AE duration	Based on assumptions		
QALY loss resulting from AEs	Not included in the base case analysis; in scenario analysis utility decrements from Doyle *et al*,[51] Swinburn *et al*,[52] Lloyd *et al*,[53] Nafees *et*		

Parameter / group	^{177}Lu vipivotide tetraxetan	SOC	Cabazitaxel
	al,[54] Bermingham *et al.*,[55], NICE TA316,[14] TA259,[56] TA391,[15] NICE DG37[57] and assumptions		
QALY loss resulting from SSEs	Not included in the base case analysis; in scenario analysis utility decrements from Fassler *et al.*[58]		
Drug acquisition costs (excluding SOC)	Unit costs from the company;[1] treatment schedule and mean duration from VISION[22]	-	Unit costs from BNF;[59] schedule and median treatment duration from CARD trial;[38] and mean BSA from patients in the VISION trial[22]. Unit costs for premedication drugs from BNF,[59] eMIT[60] and NICE TA391[15]
Drug administration costs (excluding SOC)	NHS Reference Costs 2019/20[61]	-	NHS Reference Costs 2019/20,[61] PSSRU[62] and additional assumptions.
SOC (drug acquisition and administration)	Not included in the base case; scenario analysis uses data for ^{177}Lu vipivotide tetraxetan arm in VISION[30] and unit costs from BNF[59] and eMIT[60]	Proportion of patients receiving treatment and mean treatment duration from SOC treatment arm in VISION;[30] unit costs from BNF[59] and eMIT[60]	Not included in the base case; scenario analysis assumes proportion of patients receiving interventions and mean treatment duration to be equivalent to overall resource usage from VISION[30]
Concomitant therapeutic resource use	Proportion of patients receiving intervention and duration of treatment interventions from VISION[30]		Proportion of patients receiving interventions and mean number of interventions are assumed to be equivalent to overall resource usage from VISION
Concomitant therapeutic unit costs	NHS Reference Costs 2019/20.[61]		
Disease management costs	Frequency and proportion of patients receiving intervention from NICE TA259[56] and clinical expert opinion; unit costs from NHS Reference Costs 2019/20[61]		
SSE management costs	Distribution of individual SSEs from the VISION trial;[30] unit costs from NHS Reference Costs 2019/20[61]		Distribution of individual SSEs from NICE ID1640;[50] unit costs from NHS Reference Costs 2019/20[61] and clinical expert opinion
AE management costs	Unit costs from NHS Reference Costs 2019/20[61] and assumptions		
End-of-life care costs	Abel *et al*,[63] NICE TA412[64] and NHSCII and HCHS from PSSRU 2020[62]		

[a] The company states that the approach used is equivalent to fitting separate models to each treatment arm (clarification response, question B8)[17]

[b]The EAG believes that the Kaplan-Meier data used to populate the model for time-to-first SSE are based on the full ITT dataset from VISION

Abbreviations: KM, Kaplan-Meier; AE, adverse event; BNF, British National Formulary; BSA, body surface area; CS, company's submission; EQ-5D-3L, Euroqol 5-Dimensions (3-level); NHSCII, NHS Cost Inflation Index; NICE, National Institute for Health and Care Excellence; OS, overall survival; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; rPFS, radiographic progression-free survival; SOC, standard of care; TA, Technology Appraisal.

4.2.4.1 Patient characteristics

At model entry, patients are assumed to have a mean age of [redacted] years, a body surface area (BSA) of [redacted] m^2, and mean weight of [redacted] kg. These values were based on the ITT population in VISION and are used to determine, respectively, the start age of the model; the cost per dose of cabazitaxel, carboplatin, and docetaxel; and the cost per dose for radium-223, epoetin alpha, and filgrastim.

4.2.4.2 Time-to-event parameters

To extrapolate OS, rPFS and time-to-first SSE in the VISION trial for both ^{177}Lu vipivotide tetraxetan + SOC and SOC arms, the CS fitted a range of standard parametric distributions (including exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) and flexible natural cubic spline models by Royston and Parmar (2002)[65] using the *flexsurv* package[66] in R. Royston and Parmar spline models were fitted on the log-cumulative hazard scale with 1, 2 or 3 knots. The company named these spline models as flexible Weibull models (clarification response,[16] question B8 and CS,[1] Section B.3.3.2).

For each model used, the company fitted both unstratified and stratified versions of the model. An unstratified model has the treatment as a covariate and only allows the intercept parameter to vary by treatment (see clarification response,[16] question B8). It is equivalent to fitting a parametric model including treatment as a covariate. A stratified model allows all model parameter to vary by treatment, which is equivalent to fitting a parametric model independently to the two treatment groups (see clarification response,[16] question B8).

The company determined its base case survival model by assessing the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), visual inspection of the fit within the observed period and clinical plausibility for both short- and long-term estimates of survival. In the economic model, adjustments were applied to ensure that rPFS and time-to-first SSE were bounded by OS as a minimum. In each model cycle, the rPFS health state occupancy was capped so that it did not exceed OS, and the incidence of SSEs in each cycle was capped to not exceed the number of patients surviving to that cycle.

The company also conducted additional exploratory survival analysis adjusting for informative censoring for both OS and rPFS (CS, Appendix J) and presented some scenario analyses to explore the impact of these on the cost-effectiveness estimates.[1] The methods used include multiple imputation, inverse probability of censoring weighting (IPCW) for OS; and multiple imputation, IPCW and interval

imputation for rPFS. The company concludes that the unadjusted data are associated with some bias with patients who dropped out were less severe comparing to those who remained in the study given that the HRs obtained from adjusting for dropouts were closer to 1 than those from the unadjusted data for both OS and rPFS. The differences are small for OS ([redacted]) but moderate for rPFS ([redacted]).

4.2.4.2.1 Extrapolating OS

The company fitted various parametric survival functions to the unadjusted OS data from the VISION trial. The fit of all parametric models to the VISION trial data for OS can be found in Figure 25 to Figure 28 of the CS. The model fit statistics (AIC and BIC) for the models fitted to the OS data can be found in Figure 29 of the CS. The company's base case and scenario analysis results for OS are presented in Table 29 and the company's base case extrapolation is plotted in Figure 16.

Table 29: Predicted mean base case and scenario OS for ^{177}Lu vipivotide tetraxetan, SOC (VISION) and cabazitaxel (adapted from CS, Table 39 and Table 40)

Scenario	Model selected for ^{177}Lu vipivotide tetraxetan +SOC and SOC alone	Mean OS, months			Source/assumption for cabazitaxel OS
		^{177}Lu vipivotide tetraxetan +SOC	SOC alone	Cabazitaxel[a]	
Base case	Stratified flexible Weibull (2 knots)	[redacted]	[redacted]	[redacted]	UK RWE Kaplan–Meier data
Scenario	Gamma	[redacted]	[redacted]	[redacted]	HR applied to the reference ^{177}Lu vipivotide tetraxetan curve: stratified flexible Weibull (2 knots)

[a]The mean rPFS for cabazitaxel has been determined from the area under curve of the model trace (assuming a 10-year time horizon).
Abbreviations: HR, hazard ratio; OS, overall survival; SOC, standard of care; RWE, real-world evidence.

In the base case analysis, the OS extrapolation is based on fitting the stratified flexible Weibull (2 knots) model for both ^{177}Lu vipivotide tetraxetan + SOC and SOC alone arm to the unadjusted data from the ITT population (FAS, N=831), shown in CS, Figure 5. A scenario analysis is presented using the gamma model as an alternative survival function for OS extrapolation for ^{177}Lu vipivotide tetraxetan + SOC and SOC alone arm. A scenario analysis is also presented in which survival models have been fitted to the OS data from VISION that have been adjusted for informative censoring using IPCW. In this scenario, the curve selected for implementing OS is again the stratified flexible Weibull (2 knots) model. The reason given is that this is consistent with the choice in the base case and that it had the lowest AIC.

The CS provides long-term data from external sources to validate the predicted OS for SOC. Figure 23 of the CS provides data from Mehtala *et al*. (2020)[67] which has been adjusted by an acceleration factor to fit the OS data from the SOC alone arm of VISION. This shows that OS of SOC is predicted to fall to zero at around 5 years.

For the cabazitaxel arm, the KM estimate of the OS from the RWE cabazitaxel cohort is used directly and the company considers that there is no need for extrapolation as the OS KM curve reaches zero within the follow-up period provided (CS, page 116). Therefore, in the base case analysis the NMA does not inform the OS estimates for any of the treatments modelled. The company states that this approach provides the most relevant evidence relating to UK patients currently treated with cabazitaxel, who would be considered eligible for ^{177}Lu vipivotide tetraxetan.

Figure 16: Company's base case OS extrapolation (reproduced from CS, Figure 32)

Note: This figure shows the intended implementation and does not show the error introduced in the cabazitaxel extrapolation described in Section. 4.3.4 The Markov trace based on the actual implementation within the company model which includes this error is shown in the Appendix of this report (Appendix 2, Figure 24).
Abbreviations: ^{177}Lu, Lutetium-177; OS, overall survival.

A scenario analysis is also presented in which the HR from the fixed effect NMA for cabazitaxel versus ^{177}Lu vipivotide tetraxetan (HR=) has been applied to the OS from the ^{177}Lu vipivotide tetraxetan arm to generate an OS curve for cabazitaxel (NB: the HR used is equivalent to the inverse of the HR for ^{177}Lu vipivotide tetraxetan vs. cabazitaxel as per CS, Figure 12).

The EAG broadly agrees with the company's base case model choice for OS for ^{177}Lu vipivotide tetraxetan +SOC and SOC alone arm, but notes that there are a few other models for which the AIC and BIC values are within 3 points differences from the AIC and BIC given by the base case model (stratified flexible Weibull 2 knots), which means that there are no differences in terms of goodness of fit among these models[68]. The EAG notes that the stratified flexible Weibull (2 knots) implemented in the base case for extrapolating OS for SOC does provide a low probability of survival by 5 years ([redacted]) and appears to match the time accelerated adjusted data from Mehtala *et al*. (2020)[67] up to 2 years (CS, Figure 23). However, the probability of surviving to 3 years appears much lower in the extrapolated data than would be expected based on the prediction from Mehtala *et al*. (2020)[67] ([redacted] versus approximately [redacted]). Furthermore, the data in Figure 24 of CS based on the original data from Notohardjo *et al*. (2021)[69] suggest a 3-year survival of approximately [redacted]. The EAG notes that the 3-year extrapolated OS data for SOC given by the stratified flexible Weibull (2 knots) falls within the range provided by the EAG's clinical advisors.

4.2.4.2.2 Extrapolating rPFS

The company has fitted various survival models to the rPFS data from VISION using the unadjusted ITT dataset (n=831). This differs from the PFS-FAS dataset used to analyse rPFS in the clinical effectiveness section, which included all patients randomised after 5th March 2019. Median survival for rPFS when using the ITT data set is 8.8 months for ^{177}Lu vipivotide tetraxetan and 3.6 months for SOC (Sartor *et al.* [2021][22], Supplementary appendix Figure S2). The fit of all parametric models to the VISION trial data for rPFS can be found in Figure 15 to Figure 18 of the CS. The model fit statistics (AIC and BIC) for the models fitted to the rPFS data can be found in Figure 19 of the CS. The company's base case and scenario analysis results for rPFS are presented in Table 30 and Figure 17.

Table 30: Predicted mean base case and scenario rPFS for ^{177}Lu vipivotide tetraxetan, SOC (VISION) and cabazitaxel (adapted from CS, Table 36 and Table 37)

Scenario	Model selected for ^{177}Lu vipivotide tetraxetan +SOC and SOC alone	Mean rPFS, months			Source/assumption for cabazitaxel rPFS
		^{177}Lu vipivotide tetraxetan +SOC	SOC alone	Cabazitaxel[a]	
Base case	Stratified flexible Weibull (2 knots)	[redacted]	[redacted]	[redacted]	HR applied to the reference ^{177}Lu vipivotide tetraxetan curve: stratified flexible Weibull (2 knots)
Scenario	Stratified flexible Weibull (1 knot)	[redacted]	[redacted]	[redacted]	HR applied to the reference ^{177}Lu vipivotide tetraxetan curve: stratified flexible Weibull (1 knot)

[a]The mean rPFS for cabazitaxel has been determined from the area under curve of the model trace (assuming a 10-year time horizon).
Abbreviations: HR, hazard ratio; rPFS, radiographic progression free survival; SOC, standard of care, ^{177}Lu, Lutetium-177.

In the base case analysis, the rPFS extrapolation is based on the stratified flexible Weibull (2 knots) model for both ^{177}Lu vipivotide tetraxetan + SOC and SOC alone arm. It should be noted that in the economic model the rPFS curves for SOC have been adjusted so that the hazards in the SOC arm are always greater than or equal to the hazards in the ^{177}Lu vipivotide tetraxetan arm at time points beyond the maximum rPFS follow-up (months), to ensure that the rPFS in the SOC arms does not cross to being higher than the rPFS in the ^{177}Lu vipivotide tetraxetan arm, which would otherwise occur at 67 months.

Figure 17: Company's base case rPFS extrapolation (reproduced from CS, Figure 21)

Abbreviations: ^{177}Lu, Lutetium-177; rPFS, radiographic progression free survival.

In order to estimate rPFS for the cabazitaxel arm, the HR from the fixed effect NMA for cabazitaxel relative to ^{177}Lu vipivotide tetraxetan (which is equivalent to the inverse of the HR of for cabazitaxel vs. ^{177}Lu vipivotide tetraxetan reported in CS, Figure 13) has been applied to the rPFS survival curve for ^{177}Lu vipivotide tetraxetan. The HR from the NMA has been applied as a constant HR throughout the whole modelled timeframe (10 years).

A scenario analysis is provided using the stratified flexible Weibull model (1 knot) with the same constraint applied to ensure that the hazards in the SOC arm always remain equal to or above the hazards in the ^{177}Lu vipivotide tetraxetan arm beyond the maximum duration of rPFS follow-up. A scenario analysis is also presented in which survival models have been fitted to the rPFS data from VISION that have been adjusted for interval censoring using interval imputation. Although CS Appendix J.6 states that both the flexible Weibull model with 2 knots and the stratified flexible Weibull model with 2 knots provided the best fit,[1] for the scenario analysis presented in CS Table 71 the flexible Weibull model with 2 knots was implemented in the comparison against SOC and the stratified flexible Weibull model with 2 knots was implemented in the comparison against cabazitaxel.

The EAG broadly agrees with the company's base case and scenario analysis model choice for rPFS for ^{177}Lu vipivotide tetraxetan +SOC and SOC alone arm and also agrees with applying a HR from the NMA for rPFS to the extrapolated ^{177}Lu vipivotide tetraxetan arm to obtain the extrapolated cabazitaxel arm. However, the EAG notes the issues raised previously in the EAG's critique of the company's NMA (see Section 3.3.4 for details).

4.2.4.2.3 Time-to-first systemic skeletal events

In the company's base case analysis for time-to-first SSE, parametric extrapolation is used to estimate the incidence of SSEs over the timeframe of the model. For the ^{177}Lu vipivotide tetraxetan and SOC treatment arms, the unstratified log-normal model fitted to the time-to-first SSE data has been applied directly to estimate the incidence of SSE each month. The incidence of SSEs each month is capped so it cannot exceed the number of patients surviving. Overall, this results in a cumulative incidence of [redacted] for ^{177}Lu vipivotide tetraxetan and [redacted] for SOC over the 10-year model horizon (CS, Table 41). These are much higher than the cumulative incidences observed during trial follow-up of [redacted] and [redacted] respectively for ^{177}Lu vipivotide tetraxetan and SOC within the VISION trial (CS, Table 42).

It should be noted that the KM data for the time-to-first SSE outcome to which the parametric survival models are fitted (CS, Figure 33) are different from the outcome of time-to-first SSE presented in the clinical section (CS, Figure 7). Time-to-first SSE presented in the clinical section of the CS used the PFS-FAS dataset and the definition of an SSE event also includes death (clinical study report (CSR),[30] Table 11-5 reports both deaths and SEEs and events as the total of these). The EAG believes that the KM data used to populate the model for time-to-first SSE are based on the full ITT dataset from VISION (but does not include death). This is based on the description of the SSE data in CS, Appendix J, Table 29, which relates to the full ITT dataset.

For the cabazitaxel arm, the company compared the reconstructed time-to-first SSE KM curve for cabazitaxel arm from the CARD trial and the time-to-first SSE KM curve from the VISION trial (CS, Figure 40) and concluded that the results were very similar. Based on this finding, the company assumed the rate of SSEs was the same in the cabazitaxel arm as in the ^{177}Lu vipivotide tetraxetan arm from VISION. This is implemented by applying the survival curve for time-to-first SSE estimated from the ^{177}Lu vipivotide tetraxetan arm of the VISION study to the cabazitaxel arm in the model. However, the capping of the SSE incidence, to ensure it does not exceed the proportion surviving in the model, results in a lower cumulative incidence of [redacted] for cabazitaxel versus [redacted] for ^{177}Lu vipivotide tetraxetan.

A scenario analysis is provided in which the SSE rate for cabazitaxel is estimated from the SOC arm of VISION instead of from the ^{177}Lu vipivotide tetraxetan arm. The CS also provides a scenario analysis in which the total cumulative incidence of SSEs, taken from VISION for the ^{177}Lu vipivotide tetraxetan and SOC arms, and from CARD for the cabazitaxel arm, is applied across the modelled time horizon, assuming that SSEs occur at the time of progression. The cumulative incidences of SSE are [redacted], [redacted] and 36.5% for ^{177}Lu vipivotide tetraxetan, SOC and cabazitaxel respectively, when using this approach (CS, Table 42).

The EAG notes that the company's base case analysis for time-to-first SSE data (without death) using a log-normal model does not fit the tail of the KM curve for ^{177}Lu vipivotide tetraxetan + SOC and SOC only arm very well, and the extrapolations were heavily influenced by the adjustment applied to cap the incidence of SSEs not exceeding the number of patients surviving.

4.2.4.3 Treatment safety

The CS states that the AEs included in the model were Grade ≥ 3 AEs with an incidence of at least 2% of patients in each of the arms of the VISION trial. Table 31 presents the AE incidences used in the model for each intervention, which were based on the relevant arms of VISION for SOC and ^{177}Lu vipivotide tetraxetan, whereas for cabazitaxel they were based on the CARD trial. The EAG notes that some of the AEs included in the model are not described in CS, Table 44. These were abdominal pain, dyspnoea, and muscular weakness; therefore, the EAG extracted the incidence for these AEs from the submitted model.

Table 31 Adverse events included in the economic model (adapted from CS, Table 44 and supplemented with model data)

	AE incidence			Notes
	^{177}Lu	**SOC**	**Cabazitaxel**	
Abdominal pain	[redacted]	[redacted]	0.8%	Not reported in CS, Table 44 so incidence based on 'Default Data' model sheet
Anaemia	[redacted]	[redacted]	7.9%	-

	AE incidence			Notes
	^{177}Lu	SOC	Cabazitaxel	
Asthenia	[redacted]	[redacted]	4.0%	-
Back pain	[redacted]	[redacted]	0.0%	-
Dyspnea	[redacted]	[redacted]	0.0%	Not reported in CS, Table 44 so incidence based on 'Default Data' model sheet; not included in AE costs
Fatigue	[redacted]	[redacted]	0.0%	-
Hypokalaemia	[redacted]	[redacted]	3.2%	Not included utility decrements
Muscular weakness	[redacted]	[redacted]	0.0%	Not reported in CS, Table 44 so incidence based on 'Default Data' model sheet
Musculoskeletal pain	[redacted]	[redacted]	1.6%	-
Neutropenia	[redacted]	[redacted]	43.7%	-
Thrombocytopenia	[redacted]	[redacted]	3.2%	-
Lymphopenia/ lymphocytopenia	[redacted]	[redacted]	0.0%	-
Leukopenia	[redacted]	[redacted]	31.7%	-
Urinary tract infection	[redacted]	[redacted]	0.0%	-
Haematuria	[redacted]	[redacted]	0.0%	-
Acute kidney injury	[redacted]	[redacted]	0.0%	-
Hypertension	[redacted]	[redacted]	0.0%	-

Abbreviations: ^{177}Lu, Lutetium-177; AE, adverse event; SOC, standard of care.

4.2.4.4 Health-related quality of life

In response to clarification question B14, the company confirmed that the full analysis set (FAS) was used to generate the dataset used for the EQ-5D analysis.[17] A generalised linear mixed model was used to generate health state utility values using the full analysis set using *xtmixed* in Stata. The full model included the following covariates as fixed effects: planned treatment, time of visit (since randomisation), age, baseline utility, baseline ECOG status, ARPI, health state, and an interaction term between planned treatment and health state; and patient as a random effect (see clarification response,[17] question B16). A stepwise approach was used to obtain the final model, although there was no description on the detail of the stepwise approach. The final model included the following covariates as fixed effects: utility at baseline, ECOG status, treatment, health state and the interaction between health state and treatment (see clarification response,[17] question B16).

As part of the clarification process, the EAG requested the data and code used by the company for the utility analysis which would have allowed the EAG to check and/or reanalyse the utility data using a mixed effect model (clarification question,[17] question B18). Whilst the company provided the code for the reduced and full models, the individual patient data has not been shared due to confidentiality issues. Therefore, the EAG was unable to run any further analyses.

Health state utility values used in the model are presented in Table 32. The EAG agrees with the use of a mixed effect model for analysing utility values, since it allows accounting for repeated measures in the same patient. The EAG notes that Table 9 in the company's response to clarification question B15 shows that in both treatment groups, patients who dropped out had higher baseline utilities than those who continued in the study.[17] This result is consistent with conclusion from the analysis which adjusts for informative censoring in OS and rPFS, which also suggest that the patients who dropped out were less severe compared to those who remained in the trial. Because the dropouts were less severe in both treatment groups, it is unclear what the impact might be if the analysis for adjusting for informative censoring was conducted.

Table 32: Utility values for pre- and post-progression health states (adapted from CS, Table 46)

Treatment	Progression-free	Post-progression	Sources	
Company base case				
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]	Analysis of VISION EQ-5D data with treatment as coefficient	
SOC	[redacted]	[redacted]		
Cabazitaxel	[redacted]	0.627	Assumed equal to SOC	Utility value from TA391
Scenario analysis				
All treatments [a]	[redacted]	[redacted]	Analysis of VISION EQ-5D data without treatment as coefficient	

[a] treatment specific QALY losses attributable to SSEs and AEs were applied in this scenario but not in the base case; see Table 33 and Table 34 for details.
Abbreviations: ^{177}Lu, Lutetium-177; SOC, standard of care.

In clarification questions B19 and B20, the EAG asked for justification for the assumptions that: (a) the pre-progression health state utility for cabazitaxel is aligned with the utility value for the SOC treatment arm from the VISION trial, rather than closer to the HRQoL for patients receiving ^{177}Lu vipivotide tetraxetan, and (b) that patients receiving cabazitaxel would incur a lower utility value whilst in post-progression state than patients receiving SOC or ^{177}Lu vipivotide tetraxetan. The company replied that these assumptions were validated by clinical expert opinion, which advised that the likely lower pre-progression utility value for cabazitaxel in relation to ^{177}Lu vipivotide tetraxetan was related to patients experiencing a negative psychological response to being offered cabazitaxel, if they previously had a poor experience with docetaxel, with many opting not to receive cabazitaxel despite its potential to extend life.[17] In addition, the company stated that their clinical advisors supported a lower post-progression utility score for cabazitaxel in relation to ^{177}Lu vipivotide tetraxetan and SOC due to the substantial toxicity associated with cabazitaxel treatment, particularly in the post-docetaxel setting. The

EAG notes that the company's estimate of 0.627 for the post-progression utility in patients receiving cabazitaxel was based on data from the UK Early Access Programme (EAP) that was summarised in the committee papers for TA391.[15] Furthermore, the company proposed that the post-progression utility values in the population relevant to this appraisal could be lower than this value given that the UK EAP cohort were less heavily pre-treated than patients in VISION.[17]

No constraints or adjustments for sex and age-matched general population HRQoL were included in the model. In response to clarification question B29, the company justified its exclusion based on poor survival outcomes in mCRPC, where adjusting utilities would be anticipated to only minimally impact results.[17]

4.2.4.4.1 QALY losses associated with AEs

The company's model does not include utility decrements for AEs in the base case analysis, with the justification that their base case includes treatment specific utility values for each health state which assumes to already include the effects of AEs on HRQoL. The company presents a scenario analysis (CS, page 171) which uses treatment-independent health state utility values from VISION and includes utility decrements associated with AEs and SSEs. The utility decrements for AEs applied in this scenario analysis are summarised in Table 33. The mean duration of all AEs was assumed to be one month in the company's scenario analysis which incorporated utility decrements for AEs. In response to clarification question B11, the company justified that *"data for the duration of individual AEs was not available from the VISION study and published data were not identified for all AEs included in the model"* and that this assumption was likely to be overestimating the impact of AEs, since the majority of AE durations in previous NICE appraisals (TA391, TA580, TA316 and ID1640) were between 7 and 14 days.[17] All QALY losses related to AEs were applied in the first cycle of the model. The QALY losses attributable to AEs were estimated to be [redacted] for ^{177}Lu vipivotide tetraxetan and [redacted] for SOC. The QALY loss due to AEs for cabazitaxel was identical to that for SOC due to an error further described in Section 4.3.4; but when corrected by the EAG it was estimated to be [redacted].

Table 33: AE frequencies, disutility values and durations applied in the company's base case model

AE	Frequency	Disutility - value	Disutility - source	Duration (days) - value	Total QALY loss		
					^{177}Lu	SOC	Cabazitaxel
Abdominal pain	See Table 31	0.069	Doyle *et al*. (2008)[51a]	30.44	[redacted]	[redacted]	0.0000
Anaemia		0.119	Swinburn *et al*. (2010)[52]		[redacted]	[redacted]	0.0008
Asthenia		0.115	Lloyd *et al*. (2006)[53a]		[redacted]	[redacted]	0.0004
Back pain		0.069	Doyle *et al.* (2008)[51]		[redacted]	[redacted]	-
Dyspnea		0.050	NICE TA316[14a]		[redacted]	[redacted]	-
Fatigue		0.115	Lloyd *et al*. (2006)[53]		[redacted]	[redacted]	-
Muscular weakness		0.115	Assumed to be the same as Asthenia[a]		[redacted]	[redacted]	-
Musculoskeletal pain		0.069	Doyle *et al* (2008)[51a]		[redacted]	[redacted]	0.0001
Neutropenia		0.090	Nafees *et al*. (2008)[54]		[redacted]	[redacted]	0.0033
Thrombocytopenia		0.090	NICE TA391[15b] (assumed to be equal to neutropenia)		[redacted]	[redacted]	0.0002
Lymphopenia/lymphocytopenia		0.090	NICE TA259[56] (assumed equal to neutropenia)[c]		[redacted]	[redacted]	-
Leukopenia		0.090	NICE TA259[56]		[redacted]	[redacted]	0.0024
Urinary tract infection		0.019	Bermingham *et al*. (2012)[55]		[redacted]	[redacted]	-
Haematuria		0.019	Assumed equal to UTI[c]		[redacted]	[redacted]	-
Acute kidney injury		0.110	NICE DG37[57]		[redacted]	[redacted]	-
Hypertension		0.153	NICE TA259[56]		[redacted]	[redacted]	-
Net lifetime QALY loss per patient					[redacted]	[redacted]	**0.0072[d]**

[a] Source not reported in CS, so source here is as reported on 'Default Data' sheet in the submitted economic model.
[b] Assumed equal to neutropenia in TA391.
[c] the utility decrement associated with haematuria was assumed by the company to be equal to urinary tract infection, and lymphopenia/lymphocytopenia to be equal to neutropenia. (clarification response, question B13).[17]
[d] QALY loss for cabazitaxel when correctly applying AE frequency for cabazitaxel rather than AE frequency for SOC as per company error
Abbreviations: AE, adverse event; TA, Technology Appraisal; QALY, quality-adjusted life year.

4.2.4.4.2 QALY losses associated with SSEs

Similarly to the utility decrements for AEs described in the previous section, the company's base case analysis does not include any utility decrements related to SSEs, where treatment specific utility values for each health state are assumed to incorporate differences in SSEs experienced. A scenario analysis which uses treatment-independent health state utility values from VISION and includes utility decrements associated with SSEs and AEs is presented in CS, page 171. The utility decrements associated with SSEs included in the company's scenario analysis were informed by Fassler *et al*. (2011).[58] The company clarified that utility decrements associated with SSEs were not analysed in the VISION utility analysis (clarification response, question B12), and that the company validated the utility decrements (from Fassler *et al.* [2011] and used in previous NICE TA ID1640) and duration of SSEs (determined based on estimates provided by clinical experts) used in the model through clinical expert opinion.[17] The associated disutilities and the durations they are applied for are summarised in Table 34 (reproduced from CS, Table 45).

Table 34: Utility decrements associated with SSEs (reproduced from CS, Table 45)

SSE	Utility decrement	Duration[a]	Source
Radiation to bone	−0.07	1 month (4 cycles)	Fassler *et al*. (2011)[58]
Pathological fracture	−0.13	2 month (8 cycles)	
Surgery to bone	−0.13[a]	3 month (12 cycles)	
Spinal cord compression	−0.555[b]	6 months (24 cycles)	

[a] the decrement for surgery to bone was assumed by the company to be equal to the decrement for pathological fracture (clarification response, question B12)[17]
[b] the decrement for spinal cord compression was determined by the average from the values reported by (0.50–0.61) (clarification response, question B12)[17]
Abbreviations: SSE, symptomatic skeletal event.

4.2.4.5 Resource use and unit costs

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) concomitant treatments (SOC therapies); (iv) health state resource use; (v) post-progression (subsequent) treatments; (vi) the management of SSEs; (vii) the management of AEs, and (viii) end-of-life care. The costs applied in the company's model are summarised in Table 35, and described in further detail below.

Table 35: Summary of cost parameters used in the model

Cost component	^{177}Lu vipivotide tetraxetan	SOC	Cabazitaxel
Drug acquisition costs (once-only)	[redacted]	£0.00	£31,561.62*
Drug administration costs (once-only)		£0.00	£2,870.69
SOC acquisition costs (once-only)	£0.00 (base case); [redacted] (scenario analysis)	[redacted] (base case and scenario analysis)	£0.00 (base case); [redacted] (scenario analysis)
SOC administration costs (once-only)	£0.00 (base case); [redacted] (scenario analysis)	[redacted] (base case and scenario analysis)	£0.00 (base case); [redacted] (scenario analysis)
Therapeutic concomitant interventions (once-only)	[redacted]	[redacted]	[redacted]
Health state costs – progression-free (per weekly cycle)	£55.81 (months 1-3); £23.51 (months 4+)	£55.81 (months 1-3); £23.51 (months 4+)	£55.81 (months 1-3); £23.51 (months 4+)
Health state costs – progressed disease (per weekly cycle)	£23.51	£23.51	£23.51
Subsequent treatment costs (once-only, includes admin costs)	[redacted]	[redacted]	[redacted]
AE management costs (once-only)	[redacted]	[redacted]	£973.39
SSE costs (once-only)	[redacted]	[redacted]	£2,254.48
End-of-life care (once-only)	£2,299.00	£2,299.00	£2,299.00

***** includes premedication for cabazitaxel.
Abbreviations: ^{177}Lu, Lutetium-177; wk, week; AE, adverse event; SOC, standard of care, SSE, symptomatic skeletal event.

4.2.4.5.1 Drug acquisition and administration costs

The drug acquisition and administration costs for ^{177}Lu vipivotide tetraxetan and cabazitaxel are summarised in Table 36, whilst the costs related to SOC are detailed in a following section. Drug acquisition costs for ^{177}Lu vipivotide tetraxetan are modelled as a function of the mean duration of treatment exposure and treatment schedules based on VISION trial,[30] and unit costs provided by the company.[1]

The list price for ^{177}Lu vipivotide tetraxetan is [redacted] per vial containing 7.40 GBq. The company has proposed a PAS which takes the form of a simple price discount of [redacted]%; including this discount results in a cost per vial of [redacted]. ^{177}Lu vipivotide tetraxetan is assumed to be administered via IV injection or infusion Q6W for a maximum of 6 doses, with a mean treatment duration of 6.26 months.[22]

Cabazitaxel is assumed to be given via IV Q3W at the dosage of 25 mg/m^2 for a maximum of 10 doses. Each pack of cabazitaxel contains one vial of 60mg at a cost per pack of £3,696.00.[59] The acquisition costs for cabazitaxel are calculated as a function of the unit cost per pack taken from the British National Formulary (BNF), the median duration of treatment exposure, the treatment dosing schedule based on the CARD trial,[38] and mean BSA from patients in the VISION trial.[22] The costs for cabazitaxel also include premedication drugs, which are 12mg of dexamethasone, 4mg of chlorpheniramine, 300mg of ranitidine, and 0.5million units/kg ([redacted] million units) of filgrastim. All these drugs are assumed to be administered orally daily for the duration of cabazitaxel treatment (5.06 months), with exception of filgrastim, which is assumed to be given by home injection for 14 days each 3 weeks.

Within the economic model, the acquisition costs of ^{177}Lu vipivotide tetraxetan and cabazitaxel are applied as a one-off cost to all patients in the first cycle. The model does not include relative dose intensity (RDI) estimates from the trials or any consideration of wastage for any of the drugs included in the model. As part of the clarification process, the company stated that *"Costs associated with drug acquisition and administration were based on mean treatment exposures, which accurately capture the number of doses received. Treatment exposure data already account for treatment discontinuation due to any reason so there is no need to link to survival or disease progression"*, and that, given the maximum duration of these treatments being less than one year, discounting of these costs would not be applicable (clarification response,[17] question B22).

Administration costs for ^{177}Lu vipivotide tetraxetan and cabazitaxel were based on NHS Reference Costs 2019/20,[61] PSSRU[62] and additional assumptions. The model applies a cost of £1,254.25 for each IV infusion of ^{177}Lu vipivotide tetraxetan, based on the administration of radionucleotide therapy from NHS Reference Costs 2019/20[61] (RN52Z - delivery of other radionucleotide therapy; total). Administration costs for cabazitaxel are assumed to include the cost of delivering chemotherapy from NHS Reference Costs 2019/20[61] (SB13Z - deliver more complex parenteral chemotherapy at first attendance; outpatient setting) and an additional hour of pharmacists' time from PSSRU 2020,[62] in line with NICE TA391.[15] The model assumes no further administration costs associated with cabazitaxel premedication drugs.

Table 36: Dosing, treatment schedules and drug cost per cycle for treatments included in the company's model

Regimen	Regimen component	Admin route	Dosing schedule	Mean duration of treatment (months)	Drug costs per dose	Admin cost - NHS Reference Cost code	Admin cost per dose	Total acquisition costs	Total admin costs	Total drug costs
^{177}Lu vipivotide tetraxetan		IV	Q6W	6.26	[redacted]	delivery of other radionucleotide therapy; total (RN52Z)	£1,254.25	[redacted]	£5,690.08	[redacted]
Cabazitaxel	Cabazitaxel	IV	Q3W	5.06	£3,199.13	deliver more complex parenteral chemotherapy at first attendance; outpatient setting (SB13Z) plus 1 hour of pharmacist time from PSSRU (derived from NICE TA391)	£391.46	£23,460.32	£2,870.69	£26,331.01
	Antihistamine (chlorphenamine)	oral	daily		£0.03			£4.40	-	£4.40
	H2 antagaonist (ranitidine)	oral	daily		£0.42			£64.83	-	£64.83
	Corticosteroid (dexamethasone)	oral	daily		£0.77			£119.29	-	£119.29
	G-CSF (filgrastim)	Subcutaneous infusion	14 days in every 3W		£77.07			£7,912.78	-	£7,912.78
	Total	-	-	-	-	-	-	**£31,561.62**	**£2,870.69**	**£34,432.31**
SOC		See SOC treatment group in Table 37.								

*assumed by the company.

Abbreviations: ^{177}Lu, Lutetium-177; Admin, administration; Q3W, every 3 weeks; Q6W, every 6 weeks; IV, intravenous; SOC, standard of care; PAS, patient access scheme.

4.2.4.5.2 SOC resource usage (concomitant treatments)

Costs related to standard of care treatment (concomitant drug therapy) are assumed to include the costs of: antiemetics; antifungals; bisphosphonates; corticosteroids; erythropoietin stimulating agents; GM-CSF and opioid analgesics (see Table 37). Unit costs were taken from BNF[59] and eMIT,[60] whilst the proportion of patients receiving each treatment and mean treatment duration were informed by data for the ITT population in the VISION trial.[30] For the cabazitaxel treatment group, the proportion of patients receiving these therapies and mean treatment duration are based on the 'overall' resource usage, estimated as the weighted average for the two treatment arms, from the VISION study (clarification response,[17] question B6). Administrations costs were obtained from NHS Reference Costs 2019/20[61] and additional assumptions.

The company's base case analysis assumes that the costs for these concomitant therapies are only incurred by patients in the SOC treatment group; a scenario analysis is presented whereby the costs of SOC treatment are also included for patients receiving ^{177}Lu vipivotide tetraxetan and cabazitaxel (see Section 4.3). The total costs of SOC treatments were re-estimated by the EAG after an error was identified in the distribution of opioids by type, which had a minimal impact on the costs of SOC (see Section 4.3.4 and 4.4.1). After this correction, the total costs of SOC were estimated to be [redacted] for SOC and £0.00 for the other two treatment groups in the base case analysis (see Table 37). In the scenario analysis which includes SOC costs for all treatment groups, the total costs of SOC treatments are estimated to be [redacted] for ^{177}Lu vipivotide tetraxetan and [redacted] for cabazitaxel. All SOC costs are applied as a once-only cost in the first model cycle.

The EAG notes that ARPIs are not included as part of SOC in the base case analysis despite these being used in a proportion of patients in the VISION trial. The company's rationale was that patients in the UK clinical practice would have received them in previous lines of therapy and would not be eligible to receive them again. Nonetheless, the company presents a scenario analysis in which this group of drugs is included as part of SOC for the SOC treatment group.

Table 37: SOC resource use and costs applied in the company's model

Treatment group	Treatment regimen	Proportion of patients receiving treatment			Mean treatment exposure (months)			Split between drugs in the same category (if applicable)	Unit costs (per dose)	Admin route	Admin costs	Total costs (administration plus acquisition)		
		^{177}Lu + SOC‡	SOC‡	Caba* + SOC	^{177}Lu + SOC‡	SOC‡	Caba* + SOC					^{177}Lu + SOC‡	SOC‡	Caba* + SOC
ARPIs†	abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£97.68	Oral***	£207.79	[redacted]	[redacted]	[redacted]
	enzalutamide								£97.67					
Antiemetics	prochlorperazine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£0.04	Oral	£207.79	[redacted]	[redacted]	[redacted]
Antifungals	ketoconazole								£0.21	Oral	£207.79			
Bisphosphonates	zoledronic acid								£10.31	IV	£302.53			
Corticosteroids	dexamethasone								£0.77	Oral	£207.79			
	prednisolone								£0.18					
Erythropoietin stimulating agents	Epoetin alpha	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		£1,314.23	SubCI	£221.35	[redacted]	[redacted]	[redacted]
GM-CSF‡	pegfilgrastim	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£411.83	SubCI	£221.35	[redacted]	[redacted]	[redacted]
Opioid analgesics	morphine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1.28	Oral	£207.79	[redacted]	[redacted]	[redacted]
	oxycodone								£0.15					
	tramadol								£0.08					
Total												[redacted]	[redacted]	[redacted]

*Estimates for cabazitaxel are based on the overall resource usage from the VISION study (Clarification response, question B6).[17]
† ARPIs were not included in the base case, but the company presents a scenario analysis using the ARPI-group included for SOC.
‡GM-CSF use is assumed to include only pegfilgrastim.
[a] corrected by EAG from 0.54; [b] corrected by EAG form 0.37.
Abbreviations: ^{177}Lu, Lutetium-177; SOC, standard of care; Caba, cabazitaxel; ARPIs, androgen receptor pathway inhibitors.

4.2.4.5.3 Health state resource use

Health care resource use related to the disease management include the costs associated with medical visits (consultants and nurses), blood tests and imaging (computerised tomography [CT], magnetic resonance image [MRI], electrocardiogram, ultrasound, bone scan, full blood count liver and kidney function tests and prostate-specific antigen). The model includes three different sets of costs associated with the management of the disease: (i) ongoing follow-up and monitoring costs of patients in the progression-free state in the first four months of treatment; (ii) lower ongoing follow-up and monitoring costs of patients in the progression-free state after four months or patients who have progressed, and (iii) costs associated with therapeutic interventions received by patients as concomitant treatment.

The first two sets of costs are assumed to be independent of treatment group and are applied in every weekly cycle. These disease management costs were based on NICE TA259,[56] NHS Reference Costs 2019/20[61] and clinical expert opinion. Table 38 presents the per-cycle costs for the progression-free and progressed disease health states applied in the company's model. The reduction in costs after the first 3 months appears to relate to monitoring requirements for abiraterone (see discussion in Section 4.3.2).

The last set of costs includes blood transfusions and radiotherapy, is applied as one-off cost in the first model cycle, and is based on the proportion of patients receiving each intervention and the mean number of interventions per patient for each treatment group from the VISION trial[30] and assumptions. Table 39 summarises the costs related to concomitant therapeutic interventions applied in the company's model.

Table 38: Health state resource use and costs applied in the company's model

Resource item	Frequency per 4 weeks		Unit cost	Proportion of Patients	Total cost per 7-day cycle	
	PF (0-3 months)	PF (4 months+) and PP			PF (0-3 months)	PF (4 months+) and PP
Outpatient visit (consultant)	2	1	£144.61	0.5	£36.15	£18.08
Outpatient visit (nurse)	2	1	£43.46	0.5	£10.86	£5.43
Computed tomography scan	0.67	0	£120.55	0.05	£1.00	£0.00
Radiographic scan/magnetic resonance imaging	0.67	0	£211.33	0.05	£1.76	£0.00
Electrocardiogram	0.67	0	£147.15	0.05	£1.23	£0.00
Ultrasound	0.67	0	£16.75	0.05	£0.14	£0.00
Bone scan	0.67	0	£256.29	0.05	£2.14	£0.00
Full blood count	0.67	0	£2.53	1	£0.42	£0.00
Liver function test	2	0	£2.53	1	£1.27	£0.00

Resource item	Frequency per 4 weeks		Unit cost	Proportion of Patients	Total cost per 7-day cycle	
	PF (0-3 months)	PF (4 months+) and PP			PF (0-3 months)	PF (4 months+) and PP
Kidney function test	1	0	£2.53	1	£0.63	£0.00
Prostate-specific antigen	0.67	0	£1.20	1	£0.20	£0.00
Total (per weekly cycle)					**£55.81**	**£23.51**

Abbreviations: PF, progression-free; PP, post-progression.

Table 39: Therapeutic interventions included in the model as concomitant treatment resource utilisation and costs applied in the company's model

	Proportion of patients receiving the therapeutic intervention			Therapeutic intervention use (mean number of administrations)			Unit costs	Total costs		
	^{177}Lu	SOC	Caba	^{177}Lu	SOC	Caba		^{177}Lu	SOC	Caba
Radio-therapy (local external beam)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£739.30	[redacted]	[redacted]	[redacted]
Blood transfusions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£221.46	[redacted]	[redacted]	[redacted]
Total								**£247.75**	**£194.59**	**£229.82**

Abbreviations: ^{177}Lu, Lutetium-177; SOC, standard of care; Caba, cabazitaxel.

4.2.4.5.4 Post-progression treatment costs

The model includes the costs of subsequent treatment following ^{177}Lu vipivotide tetraxetan, cabazitaxel or SOC as third or fourth-line therapies. These costs are based on the subsequent therapies received and the mean duration of use observed in VISION for patients receiving ^{177}Lu vipivotide tetraxetan and SOC, and in the CARD study for patients receiving cabazitaxel (see Table 40). Drug acquisition and administration costs were taken from eMIT, BNF and NHS Reference Costs 2019/20.[59-61] The EAG notes that the CS does not explicitly mention the inclusion of vial sharing for any of the IV drugs or drug wastage for oral drugs; however, vial sharing is implicitly assumed in the model for therapies administered via IV, whilst no wastage is included for oral therapies. Some oncologic drugs (pembrolizumab, olaparib, and bevacizumab) present in the model are not included by the company in the calculations of costs with the argument that they are not used in the UK clinical practice for this population. The EAG's clinical experts agreed that this was appropriate.

The CS (page 138) states that the cost of subsequent treatments was applied within the model as a one-off cost at the time of disease progression. However, these costs are in fact applied at the first cycle of

the model as a fixed sum cost, and are therefore not related to the time of progression or subject to appropriate discounting. The EAG notes that, although the impact of this issue may be small given that they are based on subsequent treatments received within the trail follow-up of either VISION or CARD, it creates a disconnection between modelled outcomes and modelled costs.

The company's clarification response[17] to question B21 states that the administration costs for radium-223 as a subsequent treatment were assumed to be equal to an IV infusion based on NICE TA412, but these may be underestimating the costs associated with the preparing and administering radium-223, as they do not include, "*for example, resourcing for radiopharmacy, radiation protection and training*".

Table 40: Post-progression (subsequent) treatment costs applied in the company's model, ^{177}Lu vipivotide tetraxetan and comparators

	Subsequent Cancer Related Therapy Use			Total Doses*	Unit drug costs	Unit admin costs	Total costs		
	^{177}Lu	SOC	Cabazitaxel				^{177}Lu	SOC	Cabazitaxel
Cabazitaxel	[redacted]	[redacted]	0.14	7.33	£3,199.13	£391.46	[redacted]	[redacted]	£3,581.02
Carboplatin	[redacted]	[redacted]	0.07	[redacted]	£289.97	£302.53	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	0.05	10.00	£155.80	£302.53	[redacted]	[redacted]	£215.41
Radium-223	[redacted]	[redacted]	0.14	6.00	£3,259.67	£302.53†	[redacted]	[redacted]	£2,949.50
Radiotherapy (local external beam)	[redacted]	[redacted]	0.10	1.21	£739.30	£0.00†	[redacted]	[redacted]	£86.12
Total							[redacted]	[redacted]	[redacted]

***** Derived from the mean duration of treatment in months, which have been converted to number of doses by multiplying by the number of days in a month and then by dividing it by the frequency: every 3 weeks for cabazitaxel, docetaxel, every 4 weeks for carboplatin and radium-223 (CS, Table 57).[1]

† The company assumed that the admin costs for radium-223 would be the same as for intravenous infusion (clarification response, question 21)[17] and that radiotherapy (local external beam) does not incur in any administration costs.

Abbreviations: ^{177}Lu, Lutetium-177; SOC, standard of care; Caba, cabazitaxel.

4.2.4.5.5 SSE management costs

Costs related to the management of SSEs were based on the distribution of individual SSEs observed in the ^{177}Lu vipivotide tetraxetan and SOC treatment arms from the VISION trial,[30] whilst the distribution of SSEs for the cabazitaxel treatment group were based on the current NICE appraisal for olaparib for previously treated mPC (ID1640).[50] Unit costs were taken from NHS Reference Costs 2019/20[61] and clinical expert opinion. SSE management costs for ^{177}Lu vipivotide tetraxetan, SOC and cabazitaxel are estimated to be [redacted], [redacted] and £2,254.48, respectively. These costs are applied in every cycle to patients experiencing their first SSE in each of the treatment groups (see Table 41 and Section 4.2.4.2.3).

Table 41: SSE event management costs used in the company's model, ^{177}Lu vipivotide tetraxetan and comparators

	SSE distribution			Unit costs	Total costs		
	^{177}Lu	SOC	Cabazitaxel		^{177}Lu	SOC	Cabazitaxel
Radiation to bone	[redacted]	[redacted]	69.3%	£739.30	[redacted]	[redacted]	£512.42
Pathological fracture	[redacted]	[redacted]	12.7%	£4,168.52	[redacted]	[redacted]	£529.34
Surgery to bone	[redacted]	[redacted]	2.6%	£4,694.93	[redacted]	[redacted]	£124.20
Spinal cord compression	[redacted]	[redacted]	15.3%	£7,094.16	[redacted]	[redacted]	£1,088.52
Total					[redacted]	[redacted]	**£2,254.48**

Abbreviations: ^{177}Lu, Lutetium-177; SOC, standard of care; SSE, symptomatic skeletal event.

4.2.4.5.6 AE management costs

Costs related to the management of AEs were based on the frequency of individual Grade 3/4 AEs with an incidence ≥2% observed in either the ^{177}Lu vipivotide tetraxetan and SOC arms of the ITT population of VISION, and in the cabazitaxel arm in the CARD trial.[30, 38] Unit costs were taken from NHS Reference Costs 2019/20[61] and assumptions. AE frequencies, unit costs and total costs used in the model are summarised in Table 42. AE management costs per patient for ^{177}Lu vipivotide tetraxetan, SOC and cabazitaxel are estimated to be [redacted], [redacted] and £973.39, respectively. These costs are applied once-only during the first model cycle for each of the treatment groups.

Table 42: Adverse event costs assumed in the company's model, ^{177}Lu vipivotide tetraxetan and comparators

	AE incidence	Unit costs	Total costs		
			^{177}Lu	SOC	Cabazitaxel
Abdominal pain	See Table 31	£649.11	[redacted]	[redacted]	£5.15
Anaemia		£672.11	[redacted]	[redacted]	£53.34
Asthenia		£595.43	[redacted]	[redacted]	£23.63
Back pain		£1,059.74	[redacted]	[redacted]	£0.00
Fatigue		£595.43	[redacted]	[redacted]	£0.00
Hypokalaemia		£1,059.74	[redacted]	[redacted]	£33.64
Muscular weakness		£1,059.74	[redacted]	[redacted]	£0.00
Musculoskeletal pain		£1,059.74	[redacted]	[redacted]	£16.82
Neutropenia		£1,082.72	[redacted]	[redacted]	£472.61
Thrombocytopenia		£770.92	[redacted]	[redacted]	£24.47
Lymphopenia/ lymphocytopenia		£1,082.72	[redacted]	[redacted]	£0.00
Leukopenia		£1,082.72	[redacted]	[redacted]	£343.72
Urinary tract infection		£1,724.59	[redacted]	[redacted]	£0.00
Haematuria		£1,274.27	[redacted]	[redacted]	£0.00
Acute kidney injury		£1,961.20	[redacted]	[redacted]	£0.00
Hypertension		£638.81	[redacted]	[redacted]	£0.00
Total			[redacted]	[redacted]	**£973.39**

Abbreviations: AE, adverse event; SOC, standard of care; ^{177}Lu, Lutetium-177; SOC, standard of care.

4.2.4.5.7 End-of-life care costs

The cost of end-of-life care was estimated to be £2,299.00 per patient (see Table 43), which was assumed to include the costs of care in the last three months of life of patients with mPC. This cost is based on weighted mean annual costs related to hospital and hospice care costs based on Abel *et al.* (2013)[63] and NICE TA412[64] The reported values were uplifted to 2019/20 costs using the NHS Cost Inflation Index (NHSCII) and Hospital and Community Health Services (HCHS) indices.[62] This cost is applied as a once-only cost to patients at the point of death.

Table 43: End-of-life costs assumed in the company's model

Terminal care costs	Annual costs	Proportion of patients	Weighted 3-month cost (2013 values)	3-month cost (2020 values)
Hospital	£11,298.00	0.173375	£489.70	£539.40
Hospice	£7,730.00	0.826625	£1,597.45	£1,759.60
Total				**£2,299.00**

4.2.5 Model evaluation methods

The CS presents the results of the base case analyses in terms of incremental cost-effectiveness ratios (ICERs) using pairwise comparisons for ^{177}Lu vipivotide tetraxetan versus cabazitaxel and SOC.[1] The company's base case results were generated using the deterministic and probabilistic versions of the

model; the probabilistic ICERs are based on 1,000 Monte Carlo simulations. The distributions used in the probabilistic sensitivity analysis (PSA) are summarised in Table 44. The EAG notes that the company's model samples independently from the HR for ARPI versus ^{177}Lu vipivotide tetraxetan and the HR for cabazitaxel versus ^{177}Lu vipivotide tetraxetan and does not use the convergence diagnostic and output analysis (CODA) samples from the NMA. The results of the PSA are additionally presented as a cost-effectiveness plane and as cost-effectiveness acceptability curves (CEACs) for ^{177}Lu vipivotide tetraxetan versus cabazitaxel and versus SOC.

Table 44: Summary of distributions used in company's PSA

Parameter group	Parameter	Treatment group	Distribution applied in PSA	EAG comments
Patient characteristics	Start age	-	Normal	-
	Mean weight	-	Normal	-
	Mean height	-	Normal	Used to calculate BSA using the Mosteller method
rPFS	Distribution parameters	177-Lu and SOC	Multinormal	Not mentioned in the CS, obtained by the EAG from the model
	HR	cabazitaxel	Log-normal	-
		ARPI	Log-normal	-
OS	Distribution parameters	177-Lu and SOC	Multinormal	Not mentioned in the CS, obtained by the EAG from the model
	HR	cabazitaxel	Log-normal	-
		ARPI	Log-normal	-
SSE	SSE Incidence	-	Beta	company assumed the rate of SSEs for cabazitaxel to be the same as ^{177}Lu
	SSE distribution	-	Dirichlet	-
AE	AE incidence	-	Beta	-
	AE duration	-	Fixed	-
HRQoL	Utility value (Progression-free state)	-	Beta	-
	Utility value (Post-progression state)	-	Beta	-
	SSE disutility	-	Beta	[redacted]
	AE disutility	-	Beta	[redacted]
Resource use and costs	Drug acquisition costs	-	Fixed	-
	Drug administration costs	-	Gamma	[redacted]
	Treatment duration	-	Gamma	[redacted]
	SOC (proportion of patients)	-	Beta	[redacted]

Parameter group	Parameter	Treatment group	Distribution applied in PSA	EAG comments
	SOC (distribution within drug categories)	-	Dirichlet	-
	SOC (treatment exposure, individual components)	-	Gamma	[redacted]
	Subsequent therapies (proportion of patients)	^{177}Lu and SOC	Beta	[redacted]
		cabazitaxel	Normal	[redacted]
	Subsequent therapies (treatment duration)	-	Gamma	[redacted]
	Concomitant therapeutic interventions (unit costs)	-	Gamma	[redacted]
	Concomitant therapeutic interventions (proportion of patients)	-	Beta	[redacted]
	Concomitant therapeutic interventions (Treatment duration)	-	Normal	[redacted]
	Health state costs (individual interventions and total costs)	-	Gamma	[redacted]
	AE unit costs	-	Gamma	[redacted]
	SSE unit costs	-	Gamma	[redacted]
	End of life costs	-	Gamma	[redacted] Not mentioned in the CS, obtained by the EAG from the model

Abbreviations: PSA, probabilistic sensitivity analysis; EAG, Evidence Review Group; BSA, body surface area; AE, adverse event; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PF, progression-free; PD, progressed disease; HR, hazard ratio; SE, standard error; 3L+, third- and subsequent-line; HRQoL, health-related quality of life; ^{177}Lu, Lutetium-177; PSA, probabilistic sensitivity analysis.

Deterministic sensitivity analyses (DSAs) are presented for ^{177}Lu vipivotide tetraxetan versus cabazitaxel and versus SOC using tornado plots. Some of these analyses involve varying parameters according to their 95% CIs where available, or using +/- 10% of the expected value where 95% CIs were not available.

The CS also reports the results of 12 scenario analyses undertaken to explore the impact of: using a limited set of alternative parametric distributions for OS and rPFS; applying alternative approaches to SSE modelling (using total incidence to model SSEs and applying the SOC SSE rate to the cabazitaxel treatment group); including SOC treatment costs to the ^{177}Lu vipivotide tetraxetan and cabazitaxel treatment groups; assuming the cabazitaxel treatment group has the same concomitant therapeutic intervention usage as the SOC treatment group; applying a similar approach to subsequent treatments

for cabazitaxel as the other treatment groups, and using alternative assumptions and approaches regarding HRQoL.[1]

4.2.6 Company's model validation and face validity check

The CS (pages 171 and 172) briefly describes the company's model validation activities, which involved checking for errors and inconsistencies in all model inputs and programming validation (including *"checks of the model results, calculations, data references, model interface, and Visual Basic for Applications code"),* but no further details were provided about these activities.[1] Validation also included checking by an independent health economist. The use of clinical opinion during the conceptualisation stage of the model is also mentioned; however, it is not clear if it included any additional validation exercise comparing model predictions against efficacy outcomes from VISION and CARD trials, or from other literature sources.

4.2.7 Company's model results

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted in response to the clarification process. The results presented in this section include the proposed discount for ^{177}Lu vipivotide tetraxetan but exclude price discounts available for any other drugs used as comparators or subsequent treatments. The results with comparator Patient Access Scheme (cPAS) discounts incorporated into the analysis are provided in a confidential appendix to this EAG report.

4.2.7.1 Central estimates of cost-effectiveness

The CS presents pairwise ICERs for ^{177}Lu vipivotide tetraxetan versus each of the comparators (cabazitaxel and SOC – see Section 4.2.1 for details on which subgroups these separate analyses are intended to represent).[1] Table 45 presents the central estimates of cost-effectiveness generated using the company's model for the comparison against cabazitaxel, whilst Table 46 presents the results for the comparison versus SOC.

The probabilistic version of the model suggests that ^{177}Lu vipivotide tetraxetan is expected to generate an additional [redacted] QALYs when compared to cabazitaxel, at an additional cost of [redacted] per patient; the corresponding ICER is [redacted] per QALY gained. The deterministic version of the model produces a slightly higher ICER of [redacted] per QALY gained. In the comparison against SOC, the probabilistic version of the model suggests that ^{177}Lu vipivotide tetraxetan is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is [redacted] per QALY gained. The deterministic version of the model produces a slightly lower ICER of [redacted] per QALY gained.

Table 45: Company's central estimates of cost-effectiveness, ^{177}Lu vipivotide tetraxetan versus cabazitaxel, generated by the EAG using the company's model

Options	LYGs*	QALYs	Cost	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic model							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Undiscounted.
Abbreviations: Inc, incremental; LYG, life year gained; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; ^{177}Lu, Lutetium-177; EAG, External Assessment Group.

Table 46: Company's central estimates of cost-effectiveness, ^{177}Lu vipivotide tetraxetan versus SOC, generated by the EAG using the company's model

Options	LYGs*	QALYs	Cost	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic model							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Undiscounted.
Abbreviations: Inc, incremental; LYG, life year gained; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; ^{177}Lu, Lutetium-177; SOC, standard of care; EAG, External Assessment Group.

4.2.7.2 Company's probabilistic sensitivity analysis results

The company presented scatterplots and CEACs for ^{177}Lu vipivotide tetraxetan versus SOC and versus cabazitaxel in the CS[1] (pages 159 and 160); however updated results for these were not presented in its clarification response. The EAG has generated the scatterplots and CEAC using the updated company's model; however, the EAG identified additional errors in the updated model, and therefore the results of the PSA presented in this section should be interpreted with caution (see Section 4.3.4).

Assuming willingness-to-pay (WTP) thresholds of £30,000 and £50,000 per QALY gained, the company's model suggests that the probability that ^{177}Lu vipivotide tetraxetan generates more net benefit than cabazitaxel is [redacted], and [redacted] respectively (see Figure 18). The probability that ^{177}Lu vipivotide tetraxetan generates more net benefit than SOC at WTP thresholds of £30,000 and £50,000 per QALY gained is approximately [redacted] (see Figure 19).

Figure 18: Company's base case cost-effectiveness acceptability curve, ^{177}Lu vipivotide tetraxetan versus cabazitaxel (adapted from the company's updated model)

Abbreviations: ^{177}Lu, Lutetium-177.

Figure 19: Company's base case cost-effectiveness acceptability curve, ^{177}Lu vipivotide tetraxetan versus SOC (adapted from the company's updated model)

Abbreviations: ^{177}Lu, Lutetium-177; SOC, standard of care.

4.2.7.3 Company's one-way sensitivity analyses

Following the clarification process, the company did not present revised results for the deterministic univariate sensitivity analyses. The results for the model originally presented at the submission stage are presented in Sections B.3.8.2 of the CS (pages 160 to 164).[1] The EAG has produced equivalent tornado diagrams using the model submitted post-clarification (see Figure 20 and Figure 21), although these should be interpreted with caution due to the presence of additional errors identified by the EAG (see Section 4.3.4).

In the comparison against cabazitaxel, the most influential model parameters relate to the mean exposure treatment duration for ^{177}Lu vipivotide tetraxetan (by over [redacted]), followed by the pre-progression utility values for ^{177}Lu vipivotide tetraxetan, mean exposure treatment duration for cabazitaxel and BSA.

In the comparison with SOC, the most influential parameters were those related to the pre- and post-progression utility values for ^{177}Lu vipivotide tetraxetan and SOC, and the mean exposure treatment duration for ^{177}Lu vipivotide tetraxetan.

Figure 20: Company's updated results, deterministic sensitivity analyses, ^{177}Lu vipivotide tetraxetan versus cabazitaxel (extracted by the EAG from the company's updated model)

[redacted]

Abbreviations: ^{177}Lu, Lutetium-177.

Figure 21: Company's updated results, deterministic sensitivity analyses, ^{177}Lu vipivotide tetraxetan versus SOC (extracted by the EAG from the company's updated model)

Abbreviations: ^{177}Lu, Lutetium-177; SOC, standard of care.

4.2.7.4 Company's scenario analyses

Updated results for scenario analyses of ^{177}Lu vipivotide tetraxetan versus cabazitaxel and, ^{177}Lu vipivotide tetraxetan versus SOC were not provided in the company's clarification response. Since the EAG spotted additional errors in the updated version of the model, some of which specifically affected key scenario analyses, results for these scenarios using the updated model are not considered meaningful, and therefore are not presented here. For results using the original model presented at the submission stage, see Section B.3.8.3 of the CS (pages 164 to 171).[1] The EAG presents the results of alternative approaches to the company's modelling in the EAG's exploratory analyses in Section 4.4.3.

4.3 Critical appraisal of the company's health economic analysis

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which these are based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the EAG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the model reported in the CS and the company's executable model.

- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS using the company's model.
- Where possible, checking of key parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

4.3.1 Model verification by the EAG

The EAG rebuilt the deterministic version of the company's original and updated base case model in order to verify its implementation. During the process of rebuilding the original version of the model, the EAG has identified programming errors which were resolved by the company during the clarification process.[17] Additional programming errors were identified by the EAG after the clarification stage; these are described in Section 4.3.4. The EAG believes the company's updated version of the model to be generally well programmed despite these errors, and that the version of the model used by the EAG after correcting these errors are appropriate for the decision problem.

4.3.2 Correspondence of the model inputs and the original sources of parameter values

Where possible, the EAG checked the model input values against their original sources including published sources and additional sources provided by the company such as the CSR of the VISION trial. The EAG noted several inconsistencies, which are detailed below.

<u>Cabazitaxel OS from RWE</u>

The company's model includes what appears to be the cumulative probabilities from the KM function from the RWE analysis but which does not exactly match that shown in CS, Figure 10 as the changes in OS in Figure 10 are more stepped with fewer points of change than the data presented in the model. A visual inspection shows that modelled OS and the KM function are close but not identical. For example, at [redacted] months the cumulative OS for cabazitaxel is [redacted] despite it not showing as reaching its minimum point until [redacted] months in CS, Figure 10. Due to these slight differences between the original KM and the extracted KM used in the model, the restricted mean OS calculated by the company in the model is slightly lower than reported in CS, Table 17 (13.30 months versus [redacted] months). However, any error introduced by differences between the KM function in the model and that presented in CS, Figure 10 is likely to have a small impact on the ICERs.

<u>Credible intervals for HR</u>

The HR for rPFS for ^{177}Lu vipivotide tetraxetan versus cabazitaxel from the company's NMA is reported in CS, Figure 13 as [redacted]. Based on this, the HR for cabazitaxel vs. ^{177}Lu vipivotide

tetraxetan (calculated by taking the inverse) is estimated to be [redacted]. However, the CS reports this HR as "[redacted]" and the lower 95% CrI limit reported in the model is [redacted]. The EAG believes that this is a transcription error and the actual lower limit of the 95% CrI should be [redacted].

Incidence for acute kidney injury

The EAG was also unable to verify the source of the incidence rate for acute kidney injury in the ^{177}Lu vipivotide tetraxetan arm. The data in CS, Table 44 appear to match those in the CSR, Table 12-5 for the other AEs, but acute kidney injury is not included in CSR, Table 12-5. Instead, the incidence for acute kidney injury, for SOC appears to match that in CSR, Table 12-9 (2.4%) but the incidence data for ^{177}Lu vipivotide tetraxetan in this table is 1.5%, rather than the 3.0% reported in CS, Table 44. No changes were made to the model by the EAG, as it was unclear which data source the company had been intending to use, but the EAG anticipates that any error introduced is likely to be small.

Duration of treatment

Duration of treatment for ^{177}Lu vipivotide tetraxetan (6.26 months) is based on the VISION trial (CS, Table 53). From this, the company estimated a mean number of doses of 4.54 doses, by assuming exactly 1 dose every 6 weeks. The EAG notes that it is the mean number of doses and not the mean duration of treatment that determines the treatment cost and that CSR, Table 10-17, presents the distribution of number of doses received by patients in VISION. Therefore, the mean number of doses was estimated by the EAG to be 4.46, which is close to the value used by the company in the model.

For cabazitaxel, the duration of treatment is based on a median duration of treatment of 22 weeks reported in the CARD trial, which is converted to 5.06 months (CS, Table 53). However, the cost is estimated by assuming that each dose is exactly 3 weeks apart, giving a median number of doses 7.33. The EAG recognises that the mean number of doses cabazitaxel would be a better predictor of expected costs than the median duration of treatment, but this is not reported by de Wit *et al*. (2019)[38]

Although the VISION CSR, Table 10-20 reports the mean duration of SOC, the model instead uses data on the number of days for each class of concomitant treatment to calculate the costs for SOC. These are provided in CS, Table 54, but they appear to be additional data sourced from VISION for the purposes of modelling as they are not reported in the CSR, and therefore could not be cross-checked by the EAG.

Health state resource use for pre-progression and post-progression states

The CS states that the frequency of resource use for the pre- and post-progression health states was based on assumptions from TA259, which was an appraisal of abiraterone acetate for the treatment of mCRPC. The CS does not specify why the resource use reduces from month 3, but from a brief

examination of documents from TA259, the EAG believes that this relates to the reduced requirements for monitoring for abiraterone beyond the first 3 months of treatment. The EAG is unclear why this pattern of resource use that is specific to the monitoring requirements for abiraterone is relevant to the population being modelled. However, the EAG notes that the model is not particularly sensitive to the costs associated with the pre- and post-progression health states and that the costs of any subsequent therapies required post-progression, which may have a larger impact on cost-effectiveness, are captured separately.

The other model parameters appear to be consistent with their original sources.

4.3.3 Adherence of the company's model to the NICE Reference Case

The extent to which the company's submission adhere to the NICE Reference Case[70] is summarised in Table 47. The company's economic analysis is partially in line with the Reference Case; the main deviations relate to issues already raised in Section 2 which were: (i) the population included in the CS is wider that the population defined in the final NICE scope; (ii) the exclusion of radium-223 as a comparator despite this being listed in the final NICE scope.[18]

Table 47: Adherence of the company's economic analysis to the NICE Reference Case

Element	Reference case	EAG comments
Defining the decision problem	The scope developed by NICE	The company's economic analysis is broadly in line with the final NICE scope, with the exception of the patient population group included in the company's submission being wider then in the final NICE scope (see Section 2.3) and discrepancies regarding the comparators as detailed in the next row.
Comparator(s)	As listed in the scope developed by NICE	The NICE scope[18] specifies four comparators: (a) cabazitaxel (b) docetaxel (for people who have had docetaxel in combination with ADT previously) (c) radium-223 dichloride (for people with bone metastases) (d) best supportive care However, the economic analysis includes only cabazitaxel and best supportive care as comparators. As discussed in Section 2.2, the EAG agrees with the exclusion of docetaxel rechallenge as a comparator as it would be very infrequently used in practice. The EAG disagrees with the exclusion of radium-223 as patients with bone metastases would receive radium-223 in the post-ARPI and taxane setting and post-ARPI where docetaxel is contraindicated or unsuitable setting.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are valued in terms of QALYs gained. Health impacts on caregivers were not included in the analysis.
Perspective on costs	NHS and PSS	The analysis adopts an NHS and PSS perspective.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The results of the analyses are presented in terms of the incremental cost per QALY gained for ^{177}Lu vipivotide tetraxetan versus cabazitaxel and versus SOC, as pairwise comparisons. A full incremental analysis was not presented. This is considered reasonable by the EAG because SOC would only be a relevant comparator in those unable to receive cabazitaxel or unsuitable for taxanes (see Figure 1).
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 10-year time horizon. Approximately all patients in the ^{177}Lu vipivotide tetraxetan, SOC and cabazitaxel groups ([redacted], respectively) have died by the end of the modelled time horizon.

Element	Reference case	EAG comments
Synthesis of evidence on health effects	Based on systematic review	Time-to-event outcomes (rPFS, OS and time-to-first SSE), HRQoL estimates, treatment duration and AE frequencies for patients receiving ^{177}Lu vipivotide tetraxetan and SOC are based on data from the ITT population from the VISION trial.[30] Health outcomes for patients who receive cabazitaxel are based on the results of a fixed effect NMA for rPFS, data from a retrospective RWE study for OS (see Section 3.3.3), previous TAs (ID1640) and assumptions. The EAG has several concerns on the company's NMA (see Section 3.3.4); however, the EAG considers it more appropriate to use data from the NMA generated by the EAG than the RWE for generating survival estimates for OS for cabazitaxel.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health gains are valued in terms of QALYs and were directly reported by patients, using EQ-5D-5L data (mapped to 3L) collected in the VISION study, to which a generalised linear mixed regression model was fitted, and utilities were valued based on the UK population.[71] The company's base case analysis uses treatment-specific utility values based on disease progression status, and assumes that the values for the progression-free state already incorporate effects related to AEs and SSEs experienced. The progression-free utility value for patients receiving cabazitaxel is assumed to be equivalent to patients receiving SOC, whist the post-progression utility value for these patients is assumed to be lower than for patients receiving ^{177}Lu vipivotide tetraxetan or SOC, based on value taken from NICE TA391. The EAG considers that using treatment-independent utilities incorporating separately any QALY losses related to AE or SSE events, is more appropriate than the company's base case approach.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource costs include those which are relevant to the NHS and PSS. Unit costs were valued at 2019/20 prices with drug costs set at 2021 prices. The company's base case analysis does not include the costs of SOC therapies for patients receiving ^{177}Lu vipivotide tetraxetan and cabazitaxel, which the EAG believes is inappropriate, given that the health outcomes for patients in the ^{177}Lu vipivotide tetraxetan trial arm of VISION study received these treatments and the potential impact of these treatments on study outcomes is uncertain.

Element	Reference case	EAG comments
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum.

Abbreviations: EAG, External Assessment Group; EQ-5D-3L, Euroqol 5-Dimensions 3-Level; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; QALY, quality-adjusted life year.

4.3.4 Key issues identified from the EAG's critical appraisal

Following the clarification round, the company submitted an updated version of their model which addresses some of the errors identified by the EAG which impacted the company's base case (clarification response,[17] questions B21, B23 and B28) and some which impacted only on the scenario analyses including utility decrements for AEs and SSEs (clarification response,[17] questions B24 and B25). The EAG has identified additional errors after the clarification letter was submitted, which are included in the description of model errors in this section.

The main issues identified from the EAG's critical appraisal are summarised in Box 1. These are discussed in further detail in the subsequent sections.

Box 1: Summary of main issues identified within the EAG's critical appraisal

(1) Model errors
(2) Applicability of cost-effectiveness estimates to those who are ineligible to receive taxanes
(3) Issues relating to company's survival modelling
(4) Uncertainty surrounding relative treatment effects (see Section 3.4)
(5) Issues relating to HRQoL
    a. Assumptions for cabazitaxel progression-free and post-progression utilities
    b. SSE disutilities
(6) Issues relating to costs
    a. Exclusion of SOC costs for cabazitaxel and ^{177}Lu vipivotide tetraxetan
    b. Pre-medication and concomitant G-CSF costs for cabazitaxel
    c. Administration costs for concomitant oral medications as part of SOC
    d. Concerns regarding unit costs for epoetin alpha and filgrastim
    e. Estimation of the mean number of doses for ^{177}Lu vipivotide tetraxetan
(7) Concerns regarding the estimates of SSE incidence

(1) Model errors

The EAG identified the following errors in the company's original submitted economic model:

(i) *Programming error in implementation of the RWE KM OS data for cabazitaxel*

The EAG identified an error, in that when using the RWE KM data for cabazitaxel, the OS KM data selected for use in the health-state occupancy calculation is from a table where the number of rows is not equal to the number of model cycles. This means that data from the OS table is not being applied

to the corresponding time cycle within the health-state occupancy calculation. A consequence of this is that whilst the OS in the RWE KM data reaches zero at week 325, which is row 170 of the KM data table, these data are incorrectly applied such that OS in the health-state occupancy calculation reaches zero at week 170. The EAG believes this is an unequivocal error because the first row of the data in the health-state occupancy calculation selects from the appropriate dataset in which the KM data is spaced out to provide a time appropriate estimate for each model cycle. This error is corrected in the EAG base case analysis.

(ii) *Zero health state occupancy in first model cycle*

In the first row of the health-state occupancy calculation for both the intervention and comparator arms of the model (Sheets 'Calc-int' and 'Calc-comp'), the health state occupancy is set to zero. This effectively excludes QALYs and costs related to health state occupancy from being accrued in the first week of the model. The costs for PFS health state are also hard coded as being zero at the first cycle of the model. The EAG considers that all patients should be in the progression-free health state during this first model cycle (before half-cycle correction would be applied) and costs and QALYs from this first week of progression-free survival should not be excluded. The EAG notes that the company's model does not include half-cycle correction and considers this should have been included, however, considering its likely minimal impact on the ICER, this issue has not been corrected by the EAG.

(iii) *Programming errors in HRs for OS and rPFS*

The model contains NMA results for two networks described in the model as the 'basic network' and the network 'with additional abiraterone and enzalutamide studies' with the latter corresponding to the results reported in the CS. However, the EAG identified that the model was referring to cells reporting the 95% CrIs from the former network when estimating the standard error (SE) of the HRs for OS and rPFS. The midpoint estimates used for the deterministic analysis correctly refer to the data that correspond to the HRs reported in the CS. This error therefore only affects the company's PSA results. (NB: The PSA for the EAG's base case analysis is not affected by this error as it uses the CODA samples from the EAG's preferred NMA instead of using the SEs to sample the HRs from a lognormal distribution).

(iv) *Programming errors in incidence of AEs for cabazitaxel*

The company's model applies the incidence data for AEs for SOC to both SOC and cabazitaxel when calculating the utility decrements for AEs. The EAG believes that this is an error, rather than an assumption that the AE rates would be similar between cabazitaxel and SOC, because the estimate of

resource use and costs for the cabazitaxel arm uses data for AE incidence which are specific to cabazitaxel. This error only affects the company's scenario analysis where utility values for health-states are treatment independent and utility decrements for AEs are incorporated.

(v) Incorrect data on breakdown of opioids used as concomitant treatment

The breakdown for concomitant opioids for oxycodone and tramadol are incorrectly linked to cells that relate to usage of enzalutamide (an ARPI) and dexamethasone (a corticosteroid), respectively. This has no impact on the base case analysis comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel, since SOC is not included for either of the treatment groups. For the comparison against SOC, the impact is minor, whereby correction of the error increased the company's base case ICER by £2.

(vi) Duration of cabazitaxel pre-medication

The EAG noticed that the duration of cabazitaxel pre-medication had been hard coded in as 5.06 months. This figure is the duration of cabazitaxel used in the calculation of cabazitaxel costs when rounded to 2 decimal places. This hard coding means that this value does not correspond with the duration of cabazitaxel treatment when this is varied within the PSA.

(vii) Implementation of scenario analyses exploring alternative utility inputs

The EAG was unable to replicate the results for the scenario analyses reported in CS, Table 91 for the comparison against cabazitaxel using the original submitted model. The EAG identified that this was because selecting the option to use treatment-independent health state utility values did not update the post-progression utility value for cabazitaxel. When correcting the model to ensure that the same post-progression utility value was selected for SOC and cabazitaxel in this scenario, the EAG was able to reproduce the results in Table 91 of the CS, using the original submitted model. The EAG confirmed that this same error was also present in the post-clarification model.

The EAG was also unable to replicate the results for the scenario analysis reported in CS, Table 89 by selecting options provided in the original submitted model. Instead, it was necessary to manually set the pre-progression utility value equal to the average value across both arms of VISION ([redacted]), whilst leaving all other inputs at their base case values, to obtain matching results.

(2) Applicability of cost-effectiveness estimates to those who are ineligible to receive taxanes

The EAG notes that the economic analysis is populated predominantly with evidence from the VISION and CARD trials where patients received both ARPIs and taxanes prior to enrolment. Therefore, the

cost-effectiveness estimates obtained may have limited applicability to those patients who are ineligible to receive taxanes (subgroup 3).

(3) Issues relating to company's survival modelling

As noted in Sections 4.2.4.2.1 and 4.2.4.2.2, the EAG broadly agrees with the company's base case model choice for OS and rPFS for ^{177}Lu vipivotide tetraxetan + SOC and SOC alone arm. Nonetheless, the EAG disagrees with the approach used to extrapolate OS for the cabazitaxel arm in the base case (the RWE analysis for the cabazitaxel arm was used while the extrapolation for ^{177}Lu vipivotide tetraxetan and SOC arms were based on the VISION trial data). The median OS for cabazitaxel in the RWE analysis was shorter than the median OS for the SOC arm of VISION ([redacted] months vs. 11.3 months). The company explains that patients in clinical trials may have longer OS compared to what would be anticipated in real-world clinical practice because patients in trials receive enhanced monitoring through more frequent visits, and this effect is likely greater for patients in the control arms of trials. The EAG believes that while this provides a potential explanation regarding why the median OS from the RWE for cabazitaxel was shorter than the median OS for SOC in VISION, it does not justify the company's approach for modelling the cabazitaxel arm independently using the RWE, and ^{177}Lu vipivotide tetraxetan and SOC arms using the VISION trial evidence. The company's approach introduces bias in estimating the relative effect between cabazitaxel and ^{177}Lu vipivotide tetraxetan as: (i) it only uses a naïve unanchored indirect comparison, (ii) it penalises the efficacy of cabazitaxel, but not ^{177}Lu vipivotide tetraxetan and SOC as the RWE was used for cabazitaxel arm and trial evidence was used for ^{177}Lu vipivotide tetraxetan and SOC. The EAG believes a more appropriate approach is to apply the HR for OS from the NMA to the extrapolated^{177}Lu vipivotide tetraxetan arm.

(4) Uncertainty surrounding relative treatment effects

As described in Sections 3.3 and 3.5, the EAG believes that there is considerable uncertainty around the relative efficacy of ^{177}Lu vipivotide tetraxetan against cabazitaxel due in particular to the methods incorporated in the company's NMA including:

- Breaking of randomisation by using the subgroup with ARPI as part of SOC for the SOC arm of the VISION trial but not the ^{177}Lu vipivotide tetraxetan + SOC arm,
- Excluding the TheraP trial which provides a head-to-head comparison of ^{177}Lu vipivotide tetraxetan and cabazitaxel,
- Including of TROPIC and ALYSYMPCA studies in the NMA (the removal of TROPIC also meant that the following studies were no longer relevant; PROfound, COU-AA-301, AFFIRM and Sun *et al*. 2016),
- Assuming that PSA progression-free survival is the same as rPFS when analysing rPFS,

- Using a fixed effect model.

The EAG also considers that there is further uncertainty around the relative efficacy of ^{177}Lu vipivotide tetraxetan compared to SOC due to the impact of imbalanced withdrawals between arms in the VISION trial and the open-label nature of the trial (see Section 3.2.2).

The EAG also notes that whilst all patients in the VISION trial had previously received both an ARPI and at least one taxane treatment, a substantial proportion had received both docetaxel and cabazitaxel previously ([redacted] for ^{177}Lu vipivotide tetraxetan and [redacted] for SOC). Therefore, the VISION trial comprises a mixture of patients who would be eligible to receive ^{177}Lu vipivotide tetraxetan either fourth-line or third-line. Although prior use of cabazitaxel was not a pre-specified subgroup, the company presented analyses suggesting that fourth-line patients could be more treatment resistant (HR for OS= [redacted]) when compared to any patient having had prior docetaxel (HR for OS= [redacted]) (see clarification response,[17] question A10). *Post doc* analyses on VISION trial data for OS between patients who had previously received one rather than two taxanes prior to entry into the VISION trial (Figure 9) also show [redacted].

However, the evidence used to populate the model is not specific to whether patients are being treated third-line or fourth-line. The EAG also re-iterates their comment that the comparison against SOC appears to be relevant to [redacted]. These groups are likely to have differing outcomes, but the company has not provided separate analyses for these subgroups and the model is informed by data from VISION which represents a mix of third-line and fourth-line patients.

(5) Issues relating to HRQoL

The EAG has concerns regarding the company's assumption that the pre-progression utility value for cabazitaxel would be equivalent to that of SOC, and their choice of a post-progression utility value for cabazitaxel that was lower than for both SOC and ^{177}Lu vipivotide tetraxetan, which is not justified by the evidence provided.

In response to clarification question B20, the company cited a utility value of 0.6266 post progression from the UK EAP, citing the analysis by Bahl *et al*. (2015).[17,72] The company subsequently clarified, during the factual accuracy check, that this utility value was based on a later analysis of the UK EAP dataset reported in the committee papers for TA391.[15] The EAG noted that the EQ-5D values presented by Bahl *et al*. (2015)[72] from the EAP were close to 0.7 at baseline and increased subsequently by a

reported 0.065 by cycle 10. Whilst this increase was not statistically significant, Bahl *et al*. (2015) concluded that patients treated with cabazitaxel in the UK EAP showed stable QoL scores with a trend towards improvement after previously progressing on docetaxel.[72] Furthermore, an earlier abstract reporting EQ-5D data from the UK EAP reported a baseline utility of 0.698 (95%CI: 0.654 to 0.741, N=100), and a post-treatment utility of 0.695 (95%CI: 0.633 to 0.756, N=62).[73] These data from the UK EAP appear to contradict the company's position that the toxicity of cabazitaxel would result in utility values that are lower than SOC, as the evidence from the UK EAP suggests that utility values may be relatively stable during and after cabazitaxel treatment. Although the post-progression utility estimate from the UK EAP is lower than the post-treatment estimate, the EAG notes that this estimate is based on only 25 UK EAP participants who were identified as having both disease progression and an EQ-5D summary score recorded 30 days after their last treatment. Therefore, this estimate is associated with a wide confidence interval (0.627, 95%CI: 0.510 to 0.743) and is highly uncertain.[15,73]

The EAG notes that the TheraP trial did report lower incidences of troublesome symptoms such as diarrhoea for ^{177}Lu vipivotide tetraxetan versus cabazitaxel (31.2% vs 55.4%, p=0.001) and statistically significant differences (p<0.05) in some domains of the EORTC QLQ-C30 (diarrhoea, fatigue and insomnia in favour of ^{177}Lu vipivotide tetraxetan and social functioning in favour of cabazitaxel).[29] These data support the potential for improved HRQoL for ^{177}Lu vipivotide tetraxetan compared with cabazitaxel. However, it is unclear whether the modelled differences in utility between ^{177}Lu vipivotide tetraxetan and cabazitaxel are realistic given they are not based on a direct comparison of utility values. Given the lack of data directly comparing utility values in patients having ^{177}Lu vipivotide tetraxetan and cabazitaxel, the EAG prefers the approach used in the company's scenario analysis, whereby treatment-independent utility values are applied to the pre- and post-progression health states, and these are adjusted to account for differences in AEs and SSEs. This allows a consistent approach to be applied across all three treatments being compared. It is also consistent with the company's claim that cabazitaxel would have worse HRQoL due to toxicity which should be reflected in the AE rates.

Furthermore, the EAG notes that baseline EQ-5D values were higher in both arms of VISION for those who patients who dropped out of the study before being able to contribute further EQ-5D data. The proportion of patients dropping out was also higher in the SOC arm than in the ^{177}Lu vipivotide tetraxetan (clarification response to question B15)[17], which suggests that the treatment specific utility values might be biased by informative censoring that differs between the two trial arms. The EAG believes that although it is difficult to predict the impact of conducting an analysis adjusting for informative censoring, the treatment-independent utility values are not subject to bias related to the

differential dropout rates between the two arms and this further supports their preference for using treatment-independent utility values.

The EAG notes that the company has chosen to incorporate utility decrements for SSEs and AEs that were applied in a previous TA. In the case of SSEs, estimates from Fassler *et al*. (2011)[58] have been used in preference to more recent estimates reported in papers identified in the company's systematic review (CS, Appendix H) which the company has not summarised within their submission. Saad *et al*. (2017) provides estimates of the utility decrement associated with skeletal-related events (SREs) from an analysis of the PREVAIL trial which recruited patients with mCRPC who were chemotherapy-naive at baseline.[74] The utility decrement estimated for radiation or surgery to bone (-0.06, 95% CI: -0.10 to -0.02) is similar to the estimate from Fassler *et al*. (2011)[58] of -0.07 for radiation to bone in metastatic prostate cancer patients. The estimate from PREVAIL for pathological bone fracture is greater (-0.20 versus -0.13) and the estimate for spinal cord compression is lower (-0.24 versus -0.55). A second paper identified in the company's HRQoL review (CS, Appendix H) provides validation of the estimates from the PREVAIL trial reported by Saad *et al*. (2017), in an abstract reporting outcomes from the ALSYMPCA trial which compared radium-223 to placebo. The abstract which focused on the impact of SSEs on utility, reported predicted differences in mean utilities of -0.0978 (95% CI: -0.1101 to -0.08553) for patients with an SSE compared to those without an SSE.[75] This difference is similar to the utility decrement of -0.11 (95%CI: -0.15 to -0.06) reported by Saad *et al*. (2017) from the PREVAIL trial. Given the availability of the estimates from Saad *et al*. (2017), it is unclear why the company preferred to use utility decrements for SSE from Fassler *et al*. (2011)[58] which provided limited details of the source studies, did not restrict source studies to patients with prostate cancer and included estimates for the utility decrement from spinal cord compression from a study in patients with metastatic breast cancer.

(6) Issues relating to costs

The EAG identified four concerns around the company's costing approach within the economic model. These relate to: (i) the exclusion of SOC costs from the ^{177}Lu vipivotide tetraxetan and cabazitaxel treatment arms; (ii) pre-medication/concomitant medication costs for cabazitaxel; (iii) administration costs for oral concomitant medications and (iv) the calculation of mean number of doses of ^{177}Lu vipivotide tetraxetan from the mean duration of treatment. These issues are detailed in turn below.

The company's base case analysis does not include the costs of SOC therapies for patients receiving ^{177}Lu vipivotide tetraxetan, which the EAG believes is inappropriate, given that patients in the ^{177}Lu vipivotide tetraxetan arm of the VISION trial received these treatments and the potential impact on their

trial outcomes is uncertain. The company's rationale for excluding other SOC medications for the ^{177}Lu vipivotide tetraxetan arm in the company's base case analysis was that ^{177}Lu vipivotide tetraxetan was modelled as a monotherapy, [redacted]. However, the EAG disagrees with this rationale, as SOC medications were administered within the VISION trial based on clinical judgement and were optimised for all patients regardless of randomisation arm and disease status. Therefore, the usage of SOC medications within VISION is not related to whether these medications [redacted].

The company's rationale for excluding other SOC medications for the cabazitaxel arm in the company's base case analysis was that the model only considered concomitant medications that were mandated for all patients receiving cabazitaxel in the CARD trial protocol or the SmPC. The EAG understands the company's rationale for excluding G-CSF and concomitant corticosteroids from the SOC costs for cabazitaxel (CS, Table 55) as these form part of the concomitant medications associated with cabazitaxel (CS, Table 54) and inclusion of these within SOC may lead to double-counting in the cabazitaxel arm. However, usage of GM-CSF and corticosteroids are already set to zero within the summary of SOC medications for the cabazitaxel arm in CS, Table 54. It is unclear to the EAG why patients receiving cabazitaxel would not also be eligible for other SOC medications (antiemetics, antifungals, bisphosphonates, erythropoietin stimulating agents, opioid analgesics), similar to those received in either the SOC or ^{177}Lu vipivotide tetraxetan arms of the VISION trial.

The CS assumes that all patients receiving cabazitaxel receive pre-medication with an antihistamine (chlorphenamine), H2 antagonist (ranitidine), corticosteroid (dexamethasone) and G-CSF (filgrastim). In the model, the antihistamine, H2 antagonist and corticosteroid pre-medications are assumed to be taken orally daily for the duration of cabazitaxel treatment (5.06 months), with the exception of G-CSF which is assumed to be taken by home injection on 14 days out of each 21-day cycle. The clinical advisors to the EAG indicated that whilst there is likely to be variation between centres in the exact regimen used for pre-medication, the antihistamine, H2 antagonist and corticosteroid pre-medications are given intravenously on the day of cabazitaxel only and not continued daily. In addition, granisetron (1mg orally) is given on the day of treatment and metoclopramide (10mg three times daily) is offered for the 3 days following treatment. The clinical experts of the EAG advised that usage of G-CSF varies between centres but when prescribed it is usually for days 5-7 only of the 21-day cabazitaxel cycle. The EAG also notes that prednisone or prednisolone is required continuously during cabazitaxel treatment according to the SmPC, but this is not included within the company's model.
The EAG also disagreed with the company's decision to apply the Healthcare Resource Group (HRG) cost for delivering an oral chemotherapy (SB11Z: deliver exclusively oral chemotherapy; outpatient

setting; £207.79) for each oral medication received as part of SOC. The EAG considered that it was likely that these medications would be prescribed as part of routine care which is already captured by the outpatient visits included within the health state costs (CS, Table 59).

The EAG noticed that the unit costs for epoetin alpha (erythropoietin stimulating agents) and filgrastim (G-CSF) did not correspond to the cheapest and/or more plausible combination available in BNF. In the case of epoetin alpha, the company includes the unit cost for a medicinal form that would require too many injections given the estimated dosage (1,000 units for a dosage of [redacted] units); the EAG considers more appropriate to use the unit cost from the 40,000 medicinal form instead. For filgrastim, the company includes the unit costs for the correct formulation, but for a pack of one pre-filled syringe when there is a comparatively cheaper option with 5 syringes. The EAG notes that the cost of epoetin alpha only has a small impact on the base case analysis comparison against SOC (increases ICER by [redacted]), whilst the costs of filgrastim only impacts on the base case analysis comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel (increase of [redacted]).

The EAG noticed that the company's approach of basing the number of doses of ^{177}Lu vipivotide tetraxetan on the mean duration of treatment in VISION (4.54 doses) may have marginally over-estimated the mean number of doses administered which the EAG estimated to be 4.46 based on data reported on the distribution of number of doses in the CSR.

(7) Concerns regarding the estimating of SSE incidence

The method used in the base case results in a cumulative incidence of SSE over the 10-year model time horizon which is substantially higher than the incidence observed in the trial period of VISION for both SOC and ^{177}Lu vipivotide tetraxetan. In addition, the log-normal parametric survival distribution results in a flattish survival curve in the long-term which crosses the OS survival curves. To avoid having an incidence of SSE that is greater than the proportion of patients alive in the model, the company has capped the SSE incidence at the level of OS for each model cycle. However, this effectively results in 100% of surviving patients being assumed to have a first incidence of SSE in each model cycle in the long-term extrapolation which lacks face validity. This happens from 9.8 years for ^{177}Lu vipivotide tetraxetan and from 4.9 years for SOC. This appears to be because the company has fitted the survival cures for time-to-first SSE in which the event of interest is an SSE rather than SSE or death. In comparison, CS Figure 7, which is based on SSE-free survival, shows that few patients are at risk of further SSEs at the end of the study follow-up for the VISION trial. Therefore, although further SSEs would be expected between 3 and 10 years, it is likely that the approach used in the company's base case analysis overestimates the number of additional SSEs occurring beyond the trial follow-up period.

In the cabazitaxel arm, the cumulative incidence of SSEs increases from [redacted] to [redacted] when the error in implementing the OS for cabazitaxel from the RWE is corrected as the incidence of SSE is restricted by the proportion of patients surviving falling to zero at 6.25 years.

The company's alternative approach, in which the cumulative SSE incidence of SSEs from the VISION and CARD trials is applied to each arm using time of progression as a proxy for time of SSE lacks clinical face validity because it means that the cumulative incidence for each modelled treatment over the 10-year model time horizon matches the cumulative incidences observed in the VISION and CARD trials which had follow-up of less than 10 years. It therefore probably underestimates the number of patients experiencing SSEs over the 10-year horizon, although this underestimation may be small given that a low proportion remain at risk of SSE according to CS, Figure 7. In addition, the timing of the SSEs is driven by the hazard function for rPFS meaning that the timing of the SSEs modelled does not match the KM data for time-to-first SSE during the period when follow-up data are available. However, the EAG believes this alternative approach is preferable to the approach used in the company's base case, which results in a cumulative incidence of SSE that is much higher than observed in the trials. The company's approach also introduces a difference between SSE rates for ^{177}Lu vipivotide tetraxetan and cabazitaxel which is not supported by the indirect comparisons of time-to-first SEE rates or cumulative incidence of SSEs in the VISION and CARD trials.

4.4 Exploratory analyses undertaken by the EAG

4.4.1 EAG exploratory analysis: methods

EAG preferred analyses

The EAG undertook exploratory analyses (EAs) using the company's updated model submitted at the clarification stage. The EAG's preferred analysis is comprised of twelve sets of amendments; these are detailed below. The EAs were undertaken using the deterministic version of the model; additional probabilistic analyses were also undertaken for the EAG's preferred analyses (EA13, described below). All analyses were implemented by one modeller and checked by a second modeller.

All analyses presented in this section include discounted prices for ^{177}Lu vipivotide tetraxetan and the list prices for cabazitaxel and all other drugs included in the model. The results of the analyses including cPAS discounts for cabazitaxel and all drugs used in the model are presented in a separate confidential appendix to this report.

EA1: Correction of errors

The EAG applied the following corrections to the company's original model:

(a) *Implementation of the RWE OS data for cabazitaxel*

The EAG linked the model trace for OS when incorporating the RWE for cabazitaxel to the KM data table where one row corresponded to one model cycle to ensure that the OS KM data from the RWE were applied to the time-appropriate model cycle.

(b) *Zero health state occupancy in first model cycle*

The EAG set the health state occupancy in both the intervention and comparator arms equal to 1 for the progression-free health state and ensured that health state related costs and QALYs were being accrued in the first model cycle.

(c) *HRs for rPFS and OS*

The EAG corrected the cells calculating the SE of the HRs to use the 95%CrIs that corresponded to the NMA results reported in the CS. The EAG also corrected the apparent transcription error in the lower 95%CrI for the rPFS HR for cabazitaxel vs. ^{177}Lu vipivotide tetraxetan, thus replacing [redacted] with [redacted].

(d) Incidence of AEs for cabazitaxel

The EAG corrected the model to apply the AE incidence for cabazitaxel, as per CS, Table 44 when this is selected as the comparator in the model instead of the incidence of AEs for SOC.

(e) Breakdown of concomitant opioids

The EAG corrected the model to ensure that the breakdown of opioid usage between oxycodone and tramadol was based on the appropriate model inputs rather than being incorrectly linked to data related to other treatments.

(f) Duration of cabazitaxel pre-medication

This was set equal to the duration of cabazitaxel rather than using the same number but rounded to 2 decimal places. This ensure that it varies with cabazitaxel treatment duration within the PSA.

(g) Corrections necessary to generate the scenario analyses for alternative utility inputs

The EAG amended the model to generate the scenario analyses for applying treatment-independent health state utility values for cabazitaxel in a manner that was consistent to the approach used for SOC. The EAG also corrected the model to generate the scenario analysis implementing the overall pre-progressed health utility value from VISION for cabazitaxel. These changes were intended to bring the model implementation in line with the method the EAG believes the company used to generate the results in CS Tables 89 and Table 91.

All subsequent exploratory analyses include these model corrections.

EA2: EAG preferences for unit costs for epoetin alpha and filgrastim

The EAG replaced the unit costs for epoetin alpha and filgrastim in the model with the least expensive and/or more plausible combination available in the BNF. For epoetin alpha, the unit costs for the least expensive option available from the 40,000 units medicinal form was included, whilst for filgrastim the unit costs of the pack with 5 syringes have been included.

EA3: EAG preferences for cabazitaxel pre-medications and concomitant medications

The EAG replaced the company's pre-medications / concomitant medications for cabazitaxel with the following:

- Dexamethasone 8mg iv on day of cabazitaxel infusion
- Chlorphenamine 10mg iv on day of cabazitaxel infusion
- Ranitidine 50mg iv on day of cabazitaxel infusion
- Granisetron 1mg orally on day of cabazitaxel infusion
- Metoclopramide 10mg orally three times per day for 3 days after cabazitaxel infusion
- 5 days of G-CSF (filgrastim; dose as per CS) per 21 days cycle
- Prednisolone 10mg orally daily for duration of cabazitaxel treatment (5.06 months)

The total cost of these medication is £2,960 across the treatment course of cabazitaxel, with most being attributable to the G-CSF (£2,930). This is substantially lower than the cost applied by the company of £8,102, of which £7,913 is attributable to G-CSF.

EA4: Costs for SOC concomitant medications

The EAG preferred to include costs for SOC concomitant medications for ^{177}Lu vipivotide tetraxetan and cabazitaxel, with usage set to zero only for steroids and GM-CSF for cabazitaxel as per CS, Table 54. The EAG also removed the administration costs for oral medications (antifungals, antiemetics, corticosteroids and opioid analgesics) given as part of SOC as they assumed that this would already be covered by routine care included within the health state cost.

EA5: Cost of ^{177}Lu vipivotide tetraxetan

The EAG preferred to base the estimate of costs for ^{177}Lu vipivotide tetraxetan on the distribution of doses received in VISION, as reported in the CSR, rather than from the mean duration of treatment, as per the company's base case.

EA6: Approach for health state utility values

The EAG preferred the approach used in the company's scenario analysis whereby the utility values for the health states were the same across all treatments, based on utility values estimated across both arms of the VISION trial, with additional utility decrements applied for AEs and SSEs that were treatment-specific. In this exploratory analysis the estimates for SSE incidence were based on the log-normal extrapolation of time-to-first SSE and disutility values for SSE from Fassler *et al*. (2011), as used in the company's scenario analysis incorporating treatment-independent utilities.

EA7: Alternative approach for SSE incidence

In this exploratory analysis, the EAG explored the approach used in the company's scenario analysis where the SSE incidence was based on the total incidence of SSEs reported, rather than using the log-normal extrapolation of the KM data. The EAG notes that this change will impact only on costs related to SSE, since this analysis uses the treatment-specific utility values for the health states and does not include utility decrements related to SSE.

EA8: Alternative approach for SSE incidence and disutilities

This exploratory analysis combines the changes applied in EA6 and EA7, and thereby uses treatment-independent utility values for the health states from the VISION study, with additional utility decrements applied for AEs and SSEs by treatment, and SSE incidence based on the total incidence of SSEs reported in VISION and CARD.

EA9: Alternative source for SSE disutilities

The EAG preferred to use the disutilities for SSEs obtained from the PREVAIL study (Saad *et al*. [2017]). This analysis is implemented in conjunction to the changes applied in EA8.

EA10: Alternative rPFS and OS HR estimates for cabazitaxel

In this analysis, the EAG explored the impact of changing the NMA estimates for OS and rPFS to the EAG's preferred HR estimates to estimate the OS and rPFS for cabazitaxel. The analysis applies the HR for rPFS from the EAG's base case NMA, which included the TheraP trial (0.73, 95% CI: 0.43 to 1.25), to the rPFS curve for ^{177}Lu vipivotide tetraxetan, to estimate rPFS for cabazitaxel. When estimating the OS for cabazitaxel, the analysis applies the HR from the EAG's base case NMA (0.84, 95%CrI: 0.37 to 1.87) instead of the HR from the company's original NMA. However, the EAG notes that the change in the HR estimate for OS has no effect in this analysis, since the RWE is still applied to estimate the OS for cabazitaxel. However, it does have an impact when this scenario is combined with EA11 in scenario EA12.

EA11: Use of NMA instead of RWE to estimate OS for cabazitaxel

In this analysis, the EAG preferred to use the HR from the company's NMA [redacted]), applied to the OS curve for ^{177}Lu vipivotide tetraxetan, to estimate the OS for cabazitaxel, rather than the RWE used in the company's base case.

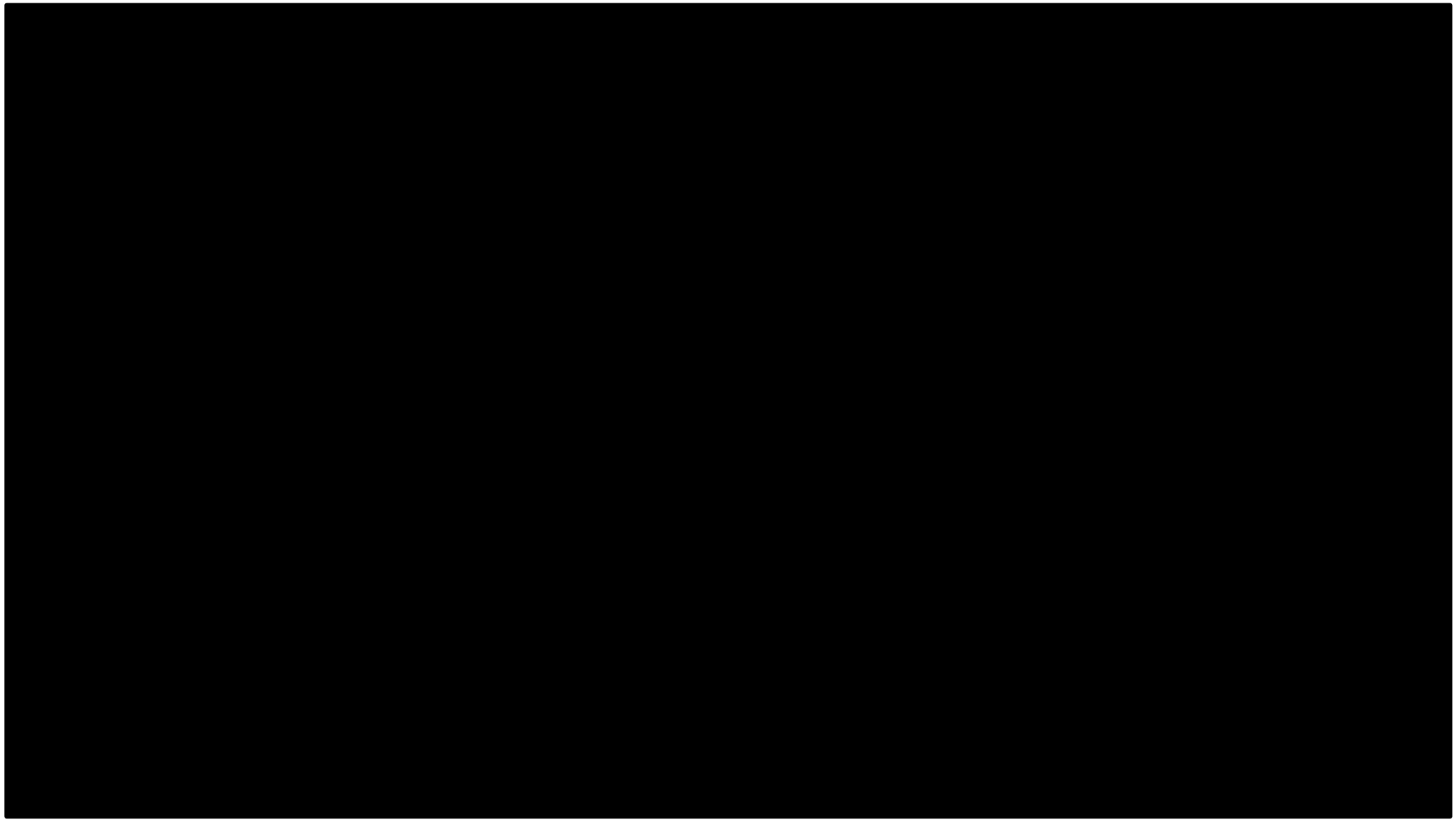
EA12: Alternative rPFS and OS estimates and use of NMA instead of RWE to estimate OS for cabazitaxel

This exploratory analysis combines the changes applied in EA10 and EA11, and as a result applies the HR estimates from the EAG's preferred NMA to the rPFS and OS curves for ^{177}Lu vipivotide tetraxetan, to estimate rPFS and OS for cabazitaxel. This is instead of applying the rPFS HR from the company's original NMA to estimate the rPFS for cabazitaxel and instead of using the RWE data directly to estimate the OS for cabazitaxel. Extrapolations for OS when combining the EAG's preferred HRs for the EAG's preferred parametric survival function for OS (stratified flexible Weibull with 2 knots, which is the same as the company's base case) can be found in Figure 22. Extrapolations for rPFS when combining the EAG's preferred HR with the EAG's preferred parametric survival function for rPFS (stratified flexible Weibull with 2 knots, which is the same as the company's base case) can be found in Figure 23.

EA13: EAG's preferred analyses

The EAG's preferred analyses incorporate EA1 to EA12 inclusive. When running the PSA for this scenario, the EAG used the CODA samples from the EAG's NMA.

Figure 22: Plot showing EAG's OS extrapolations for the EAG's base case (stratified flexible Weibull with 2 knots) and scenario analyses



Abbreviations: ^{177}Lu, Lutetium-177; OS, overall survival; EAG, External Assessment Group.

Figure 23: Plot showing EAG's rPFS extrapolations for the EAG's base case (stratified flexible Weibull with 2 knots) and scenario analyses

Abbreviations: ^{177}Lu, Lutetium-177; rPFS, radiographic progression-free survival; EAG, External Assessment Group.

Additional sensitivity analyses

The EAG undertook additional sensitivity analyses (ASAs) which include changing the chosen parametric model for OS and rerunning the model using adjustments for informative censoring separately for rPFS and OS. For each of these analyses, results are presented using the EAG's preferred analysis.

ASA1: Use of stratified flexible Weibull (2 knots) survival model for OS with IPCW adjustment for informative censoring

Within this additional analysis, the model was re-run using the IPCW adjustment for informative censoring with the original parametric survival model chosen for OS (stratified flexible Weibull [2 knots]).

ASA2: Use of stratified flexible Weibull (2 knots) survival model for rPFS with interval imputation adjustment for interval censoring

Within this additional analysis, the model was re-run using the interval imputation adjustment for interval censoring with the original parametric survival model chosen for rPFS (stratified flexible Weibull [2 knots]).

ASA3: Alternative parametric survival curves for OS – stratified gamma

This sensitivity analysis is the same as the EAG's preferred analysis, except that within this sensitivity analysis, the model was re-run using the stratified gamma to estimate OS for ^{177}Lu vipivotide tetraxetan and SOC, as an alternative to the stratified flexible Weibull (2 knots) preferred by the company. The resulting OS extrapolation for this scenario can be found in Figure 22.

ASA4: Alternative parametric survival curves for OS – stratified flexible Weibull (3 knots)

This sensitivity analysis is the same as the EAG's preferred analysis, except that within this sensitivity analysis, the model was re-run using the stratified flexible Weibull (3 knots) to estimate OS for ^{177}Lu and SOC, as an alternative to the stratified flexible Weibull (2 knots) preferred by the company. The resulting OS extrapolation for this scenario can be found in Figure 22.

ASA5: Alternative parametric survival curves for rPFS – stratified flexible Weibull (1 knot)

This sensitivity analysis is the same as the EAG's preferred analysis, except that within this sensitivity analysis, the model was re-run using the stratified flexible Weibull (1 knot) to estimate rPFS for ^{177}Lu and SOC, as an alternative to the stratified flexible Weibull (2 knots) preferred by the company. The resulting rPFS extrapolation for this scenario can be found in Figure 23.

4.4.2 EAG exploratory analysis: results

EAG preferred analysis results – ^{177}Lu vipivotide tetraxetan versus cabazitaxel

Table 48 presents the results of the EAG's preferred analyses for the comparison of ^{177}Lu vipivotide tetraxetan versus cabazitaxel. Individual changes are applied relative to the company's base case in EAs 1 to 12; all individual changes are combined in EA13. The results indicate that using the company's base case and fixing the remaining errors the ICER for ^{177}Lu vipivotide tetraxetan versus cabazitaxel is estimated to be [redacted] per QALY gained. The PSA results for this EAG corrected version of the company's base case are consistent with the deterministic results (i.e. with £1000 per QALY, see Appendix 3). Changing preferences around unit costs of drugs and the duration of treatment for ^{177}Lu vipivotide tetraxetan, using the alternative estimates for SSE incidence (without including SSE disutilities) and using the EAG's NMA estimates for modelling rPFS for cabazitaxel do not have a substantial impact on the ICER (EA2, EA4, EA5, EA7 and EA10). However, using alternative preferences for cabazitaxel premedication costs, using treatment-independent utilities for health states (including AE and SSE disutilities) and using the EAG's NMA estimates for modelling OS for cabazitaxel are key drivers of the ICER (EA3, EA6, EA8, EA11). Under the EAG's preferred scenario, the ICER for ^{177}Lu vipivotide tetraxetan versus cabazitaxel is estimated to be [redacted] (deterministic) and [redacted] (probabilistic) per QALY gained. The probabilistic ICER is higher as it incorporates the wide credible intervals around the HRs for OS and rPFS (see Figure 29, in Appendix 4).

Table 48: EAG preferred analysis of ^{177}Lu vipivotide tetraxetan versus cabazitaxel, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's base case							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA1 – Correction of errors							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA2 – EAG preferences for unit costs for epoetin alpha and filgrastim							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA3 – EAG preferences for cabazitaxel pre-medications and concomitant medications							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA4 – Costs for SOC concomitant medications							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA5 – Cost of ^{177}Lu vipivotide tetraxetan							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA6 – Approach for health-state utility values							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA7 – Alternative approach for SSE incidence							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA8 – Alternative approach for SSE incidence and disutilities (EA6+EA7)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA9 – EA8 + Alternative source for SSE disutilities							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA10 – Alternative rPFS and OS HR estimates for cabazitaxel							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA11 – Use of NMA instead of RWE to estimate OS for cabazitaxel							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA12 – Alternative rPFS and OS estimates and approach to estimate OS for cabazitaxel (EA10+EA11)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA13 – EAG's preferred analysis (deterministic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA13 – EAG's preferred analysis (probabilistic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Undiscounted

Abbreviations: ^{177}Lu, Lutetium-177; LYG, life year gained; QALY, quality-adjusted life year; Inc., incremental; ICER, incremental cost-effectiveness ratio; EA, exploratory analysis; EAG, External Assessment Group.

Table 49 presents the results of the EAG's additional sensitivity analysis for ^{177}Lu vipivotide tetraxetan versus cabazitaxel. As shown in the table, using IPCW adjustment for informative censoring for modelling OS decreases the deterministic ICER to [redacted] per QALY gained, whilst using interval imputation adjustment for informative censoring for rPFS increased the ICER to [redacted] per QALY gained. The alternative parametric models explored for OS and rPFS produced ICERs ranging from [redacted] to [redacted] per QALY gained.

Table 49: EAG additional sensitivity analyses of ^{177}Lu vipivotide tetraxetan versus cabazitaxel, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EAG's preferred analysis (deterministic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASA1 – Use of stratified flexible Weibull (2 knots) survival model for OS with IPCW adjustment for informative censoring							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASA2 - Use of stratified flexible Weibull (2 knots) survival model for rPFS with interval imputation adjustment for informative censoring							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASA3 - Alternative parametric survival curves for OS – stratified gamma							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASA4 - Alternative parametric survival curves for OS – stratified flexible Weibull (3 knots)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASA5 - Alternative parametric survival curves for rPFS – stratified flexible Weibull (1 knot)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Undiscounted

Abbreviations: LYG, life year gained; QALY, quality-adjusted life year; Inc., incremental; ICER, incremental cost-effectiveness ratio; EA, exploratory analysis; EAG, External Assessment Group.

EAG's preferred analysis results – ^{177}Lu vipivotide tetraxetan versus SOC

Table 50 presents the results of the EAG's preferred analyses for the comparison of ^{177}Lu vipivotide tetraxetan versus SOC. Some of the exploratory analyses presented against cabazitaxel are not applicable to the comparison against SOC (EA3, EA10, EA11 and EA12), so they are not presented in the table.

The results indicate that using the company's base case and fixing the remaining errors the ICER for ^{177}Lu vipivotide tetraxetan versus cabazitaxel is estimated to be [redacted] per QALY gained. The PSA results for this EAG corrected version of the company's base case are consistent with the deterministic results (i.e. with £1000 per QALY, see Appendix 3). Using treatment-independent utility values for health states (including AE and SSE disutilities) and combining it with the alternative approach for SSE incidence has the most impact to the ICER, which increases to [redacted] per QALY gained (EA8). Using alternative preferences for SOC costs is also a key driver of the ICER (EA4). Under the EAG's preferred scenario, the ICER for ^{177}Lu vipivotide tetraxetan versus SOC is estimated to be [redacted] (deterministic) and [redacted] (probabilistic) per QALY gained.

Table 50: EAG preferred analysis of ^{177}Lu vipivotide tetraxetan versus SOC, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's base case							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA1 – Correction of errors							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA2 – EAG preferences for unit costs for epoetin alpha and filgrastim							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA4 – Costs for SOC concomitant medications							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA5 – Cost of ^{177}Lu vipivotide tetraxetan							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA6 – Approach for health-state utility values							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA7 – Alternative approach for SSE incidence							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA8 – Alternative approach for SSE incidence and disutilities (EA6+EA7)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA9 – EA8 + Alternative source for SSE disutilities							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA13 – EAG's preferred analysis (deterministic) [NB: EA3 and EA10 to EA12 do not apply here]							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA13 – EAG's preferred analysis (probabilistic)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Please note that the exploratory analyses EA3, EA10, EA11 and EA12 do not impact on the results of 177-Lu vipivotide tetraxetan versus SOC, and therefore they are not presented in the table.
*Undiscounted
Abbreviations: ^{177}Lu, ^{177}Lu, Lutetium-177; LYG, life year gained; QALY, quality-adjusted life year; Inc., incremental; ICER, incremental cost-effectiveness ratio; EA, exploratory analysis; SOC, standard of care; EAG, External Assessment Group.

Table 51 presents the results of the EAG's additional sensitivity analysis for ^{177}Lu vipivotide tetraxetan versus SOC. Whilst using IPCW adjustment for informative censoring for modelling OS leads to a moderate increase in the ICER, using interval imputation adjustment for informative censoring for rPFS modelling had a smaller upwards impact on the ICER. The alternative parametric models examined for rPFS and OS produces ICERS ranging from [redacted] to [redacted] per QALY.

Table 51: EAG additional sensitivity analyses of ^{177}Lu vipivotide tetraxetan versus SOC, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EAG's preferred analysis (deterministic)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASA1 – Use of stratified flexible Weibull (2 knots) survival model for OS with IPCW adjustment for informative censoring							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASA2 - Use of stratified flexible Weibull (2 knots) survival model for rPFS with interval imputation adjustment for informative censoring							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASA3 - Alternative parametric survival curves for OS – stratified gamma							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASA4 - Alternative parametric survival curves for OS – stratified flexible Weibull (3 knots)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASA5 - Alternative parametric survival curves for rPFS – stratified flexible Weibull (1 knot)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Undiscounted
Abbreviations: LYG, life year gained; QALY, quality-adjusted life year; Inc., incremental; ICER, incremental cost-effectiveness ratio; EA, exploratory analysis; EAG, External Assessment Group.

4.5 Discussion

The model submitted by the company was implemented to a reasonable standard although it was associated with some errors, which were identified and corrected by the EAG in their exploratory analyses. The EAG, in addition, preferred alternative assumptions to those used by the company which markedly increased the ICER.

The factors having the greatest impact on the cost-effectiveness of ^{177}Lu vipivotide tetraxetan relative to cabazitaxel are the uncertainty regarding the relative effectiveness of these treatments including the relevance of the TheraP trial for the outcome of rPFS and the relevance of the RWE for cabazitaxel for OS. The appropriate pre- and post-progression utility values for patients receiving cabazitaxel and costs associated with G-CSF during cabazitaxel treatment are also areas of significant uncertainty.

The factors having the greatest impact on the cost-effectiveness of ^{177}Lu vipivotide tetraxetan relative to SOC are the inclusion of costs for concomitant medications received alongside ^{177}Lu vipivotide tetraxetan in the VISION trial, the implementation of treatment-independent pre- and post-progression utility values in combination with including SSE disutilities and using the total incidence as the approach for estimating SSEs.

5 END OF LIFE

The CS claims that ^{177}Lu vipivotide tetraxetan should be considered as an end-of-life treatment for adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes and summarises the evidence supporting this position in CS, Table 31.[1] The EAG agrees that the treatment is indicated for a population with a life expectancy normally less than 24 months, and that ^{177}Lu vipivotide tetraxetan extended OS by an additional 3 months in the VISION trial compared to SOC. The EAG notes that in the company's base case analysis, the extension in OS modelled is greater than 3 months for both the comparison against cabazitaxel and the comparison against SOC. In the EAG's preferred analysis, the extension to OS for ^{177}Lu vipivotide tetraxetan compared to SOC is unchanged. However, the extension to OS compared to cabazitaxel within the EAG's preferred analysis is only [redacted] months. Therefore, the EAG considers that the end-of-life criteria are met for patients unable to receive cabazitaxel, whose only remaining treatment option would be SOC, but the end-of-life criteria are not met for those eligible to receive cabazitaxel.

6 OVERALL CONCLUSIONS

The company has broadened the population in this submission to also include those patients who are not medically suitable for taxanes. This subgroup is estimated to be around 42% of the total population eligible for ^{177}Lu vipivotide tetraxetan by the company. However, there is no evidence presented in the CS that estimates the effectiveness or cost-effectiveness of ^{177}Lu vipivotide tetraxetan in patients who are not medically suitable for taxanes.

The company excludes radium-223 as a comparator in the submission. The EAG believes that radium-223 should be a relevant comparator in the subset of patients who have bone metastases without visceral metastases. However, the evidence available limits the potential for an unbiased indirect comparison between ^{177}Lu vipivotide tetraxetan and radium-223.

The pivotal trial (VISION) was a Phase III trial of ^{177}Lu vipivotide tetraxetan + SOC compared to SOC alone in adult patients with PSMA-positive mCRPC. The EAG assessed the VISION trial as being at high risk of bias according to the Cochrane ROB criteria, due to concerns relating to the failure to control for some known prognostic factors (e.g., tumour volume/burden); imbalances between arms due to withdrawals; and the risk of bias potentially affecting one or more outcomes due to the open-label nature of the trial. The VISION trial reported significantly improved OS for ^{177}Lu vipivotide tetraxetan + SOC compared with SOC alone in the FAS population (HR 0.62, 95% CI: 0.52 to 0.74, p<0.001; n=831) and significantly improved rPFS for ^{177}Lu vipivotide tetraxetan + SOC compared with SOC alone in the PFS-FAS population (HR 0.40, 95% CI: 0.29 to 0.57, p<0.001, n=581). ^{177}Lu vipivotide tetraxetan + SOC produces high frequencies of AEs, Grade 3 AEs, drug-related AEs, and SAEs than SOC alone, especially anaemia, thrombocytopenia, fatigue, myelosuppression, dry mouth, nausea and vomiting, hypersensitivity and leukopenia. Clinical advice received by the EAG suggested that the safety profile was consistent with expectations.

In the absence of Phase III trial data directly comparing ^{177}Lu vipivotide tetraxetan with the relevant comparator cabazitaxel, the CS presented the following evidence for consideration: an NMA comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel and other potentially relevant comparator therapies (seven Phase III RCTs plus VISION), and supporting evidence including a Phase II trial comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel (the TheraP trial) and a RWE analysis on cabazitaxel. The company's NMA showed a significant benefit for OS ([redacted]) and rPFS ([redacted]) for ^{177}Lu vipivotide tetraxetan compared to cabazitaxel.

The EAG has several concerns regarding the company's NMA and conducted an alternative NMA analysis. The EAG's base case NMA shows a benefit for OS (HR 0.84, 95% CrI: 0.37, 1.87) and rPFS (HR 0.74, 95% CrI: 0.47, 1.16) for ^{177}Lu vipivotide tetraxetan compared to cabazitaxel, but the magnitude of the benefit was less than that suggested by the company's NMA and the results were not statistically significant.

The EAG considers that the company's economic analysing comparing ^{177}Lu vipivotide tetraxetan to cabazitaxel is relevant to people with [redacted]. The deterministic version of the company's base case model suggests that ^{177}Lu vipivotide tetraxetan is expected to generate an additional [redacted] QALYs when compared to cabazitaxel, at an additional cost of [redacted] per patient and corresponding ICER of [redacted] per QALY gained.

The key differences between the company's base case and the EAG's preferred analysis were the following: including SOC costs for all treatment groups; a shorter duration of G-CSF use during each cabazitaxel cycle; using the EAG's NMA for cabazitaxel; using the NMA instead of the RWE to estimate OS for cabazitaxel; using the cumulative incidence of SSEs rather than a log-normal extrapolation of the time-to-first SSE data; and using treatment-independent utilities adjusted for differences in AEs and SSEs.

Overall, the EAG's additional analyses indicate that the ICER for comparing ^{177}Lu vipivotide tetraxetan versus cabazitaxel is likely to be substantially higher than estimated by the company and particularly sensitive to uncertainty around the difference in OS between ^{177}Lu vipivotide tetraxetan and cabazitaxel. This comparison is also particularly sensitive to the method used to estimate pre- and post-progression utilities and the duration of G-CSF use during each cabazitaxel cycle. The ICER for the EAG's preferred scenario is [redacted] per QALY for ^{177}Lu vipivotide tetraxetan versus cabazitaxel when using the outputs of the PSA. This is higher than the deterministic ICER for the EAG's preferred scenario of [redacted] per QALY, because the probabilistic ICER incorporates the wide credible intervals around the HRs for OS and rPFS.

The EAG considers that the company's economic analysis comparing ^{177}Lu vipivotide tetraxetan to SOC is relevant to patients with [redacted]. Whilst the company claims this comparison is also applicable to patients who are not medically suitable for taxanes, the EAG notes that none of the evidence incorporated in the economic analysis has been sourced from patients who are previously untreated with taxanes.

In the comparison against SOC, the company's deterministic version of the model suggests that ^{177}Lu vipivotide tetraxetan generates an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is [redacted] per QALY gained. However, the EAG additional analyses suggest that the company has potentially underestimated the ICER. Under the EAG's preferred scenario, the ICER for ^{177}Lu vipivotide tetraxetan versus SOC is estimated to be [redacted] (deterministic) and [redacted] (probabilistic) per QALY gained. The key factors which increase the ICER in the EAG's preferred analysis are the inclusion of costs for interventions received as part of SOC in the ^{177}Lu vipivotide tetraxetan arm of the VISION trial, the EAG's preference for using treatment-independent utilities adjusted for AEs and SSEs and the approach used to estimate the cumulative incidence of SSEs.

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8 APPENDICES

Appendix 1: Data used in the EAG's NMA

Table 52: Data used in the EAG's OS NMA

Study	Treatment 2	Treatment 1	HR	95% CI
CARD	Cabazitaxel + Prednisone	ARPI	0.64	(0.46, 0.89)
VISION (SOC-ARPI subgroup)	^{177}Lu + SOC	ARPI	0.54	(0.41, 0.70)

Abbreviations: ^{177}Lu, Lutetium-177; HR, hazard ratio; CI, confidence interval; ARPI; SOC, standard of care; OS, overall survival; NMA, network meta-analysis.

Table 53: Data used in the EAG's rPFS NMA

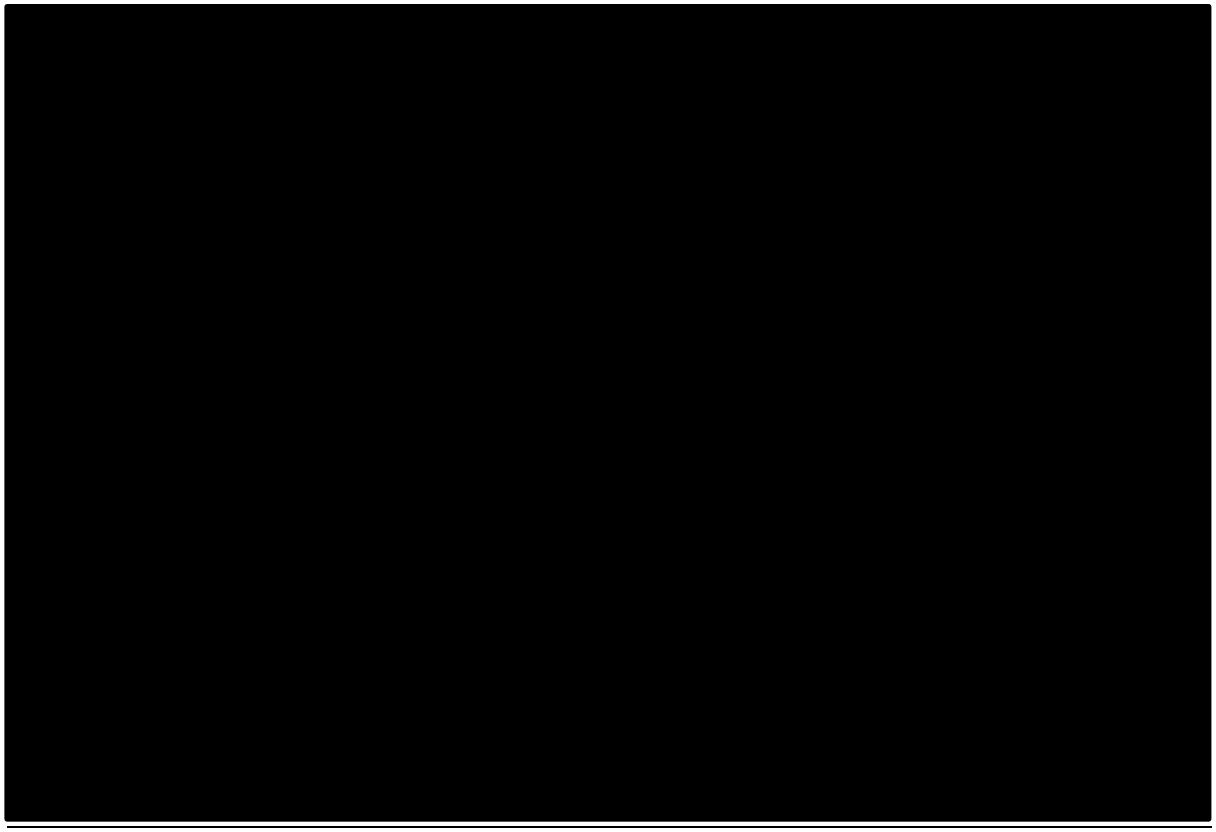
Study	Treatment 2	Treatment 1	HR	95% CI
CARD	Cabazitaxel + Prednisone	ARPI	0.54	(0.40, 0.73)
VISION (SOC-ARPI subgroup)	^{177}Lu + SOC	ARPI	0.53	(0.37, 0.76)
TheraP	^{177}Lu + SOC	Cabazitaxel + Prednisone	0.64	(0.46, 0.88)

Abbreviations: ^{177}Lu, Lutetium-177; HR, hazard ratio; CI, confidence interval; ARPI; SOC, standard of care; rPFS, radiographic progression-free survival; NMA, network meta-analysis.

Appendix 2: Markov trace for base case OS

Figure 24 shows the Markov trace for based on the actual implementation within the company model.

Figure 24: Company's base case OS survival curves for ^{177}Lu vipivotide tetraxetan and comparators (model traces)



Abbreviations: SOC, standard of care; OS, overall survival.

Appendix 3: Results from EA1: EAG correction to company's base case analysis (probabilistic)

Table 54: EAG exploratory analysis 1 (EA1 – correction of errors) of ^{177}Lu vipivotide tetraxetan versus cabazitaxel, deterministic and probabilistic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EA1 – Correction of errors (deterministic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA1 – Correction of errors (probabilistic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 25: EAG's EA1 analysis cost-effectiveness plane, ^{177}Lu vipivotide tetraxetan versus cabazitaxel

[redacted]

Abbreviations: QALY, quality-adjusted life year.

Figure 26: EAG's EA1 analysis cost-effectiveness acceptability curve, ^{177}Lu vipivotide tetraxetan versus cabazitaxel

Abbreviations: SOC, standard of care.

Table 55: EAG exploratory analysis 1 (EA1 – correction of errors) of ^{177}Lu vipivotide tetraxetan versus SOC, deterministic and probabilistic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EA1 – Correction of errors (deterministic)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA1 – Correction of errors (probabilistic)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 27: EAG's EA1 analysis cost-effectiveness plane, ^{177}Lu vipivotide tetraxetan versus SOC

Abbreviations: QALY, quality-adjusted life year.

Figure 28: EAG's EA1 analysis cost-effectiveness acceptability curve, ^{177}Lu vipivotide tetraxetan versus SOC

Abbreviations: SOC, standard of care.

Appendix 4: Results from the EAG's preferred analysis (probabilistic)

Figure 29: EAG's preferred analysis cost-effectiveness plane, ^{177}Lu vipivotide tetraxetan versus cabazitaxel

Abbreviations: QALY, quality-adjusted life year.

Figure 30: EAG's preferred analysis cost-effectiveness acceptability curve, ^{177}Lu vipivotide tetraxetan versus cabazitaxel

Abbreviations: SOC, standard of care.

Figure 31: EAG's preferred analysis cost-effectiveness plane, ^{177}Lu vipivotide tetraxetan versus SOC

Abbreviations: QALY, quality-adjusted life year.

Figure 32: EAG's preferred analysis cost-effectiveness acceptability curve, ^{177}Lu vipivotide tetraxetan versus SOC

Abbreviations: SOC, standard of care.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 27 June 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Section 1: Factual Inaccuracies

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 11 (Table 1, Issue 1) states, “Broadening of population to include patients who are not medically suitable for (or do not tolerate) taxanes”	“Broadening of population to include patients who are not medically suitable for taxanes”.	The additional terminology used by the EAG [redacted] is not used in the CS and implies patients who receive treatment with a taxane but discontinue, likely due to adverse event(s). Discontinuation of a taxane due to tolerance is not included in the description of reasons for patients not being medically suitable for taxanes, presented on page 27 of the CS. This additional terminology should be removed throughout the EAG report, to ensure clarity between subpopulations considered in the CS	The EAG agrees. The text has been amended as suggested by the company. To clarify the issue, the EAG added the following text in Issue 1 box: “The EAG notes that patients who have not received taxane-based chemotherapy are outside of the final scope and there is no evidence presented…”.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13 states, “Subgroup 1: Patients who have received at least two prior lines of treatment in the metastatic setting with an ARPI and at least one taxane-based chemotherapy; and who are eligible to receive further	Please consider amending these subgroups throughout the EAG report to remove the specification that treatment must be received in the metastatic setting. Additionally, with regards to Subgroup 2, please consider amending to “Patients who have received at least two prior lines of	The first amendment clarifies that patients in all subgroups may receive treatment with an ARPI in the high-risk non-metastatic setting. This amendment should be applied throughout the EAG report for	The EAG agrees. Both amendments have been made as suggested by the company.

taxane treatment with cabazitaxel (third-line positioning of 177Lu vipivotide tetraxetan)" Pages 14, 26 and 92 states, "Subgroup 2: Patients who have received at least two prior lines of treatment in the metastatic setting with an ARPI and are ineligible to receive further taxanes…" Page 14 states, "Subgroup 3: Patients who have received one prior line of treatment in the metastatic setting, but are unsuitable for treatment with taxanes (second-line positioning of 177Lu vipivotide tetraxetan)."	treatment with an ARPI and at least one taxane-based chemotherapy and are ineligible to receive further taxanes"	clarity where subgroups are described. The second amendment clarifies that patients in this subgroup will have received treatment with both an ARPI and a taxane-based chemotherapy. This amendment should be applied throughout the EAG report for clarity where this subgroup described.	

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19 states, "The EAG prefers to estimate the relative treatment effect from the NMA as this eliminates the impact of any differences in the standard of care provided within the trial and real-world clinical settings."	Please consider amending to: "The EAG prefers to estimate the relative treatment effect from the NMA as this eliminates the impact of any differences in the standard of care provided within the trial and real-world clinical settings. **However, it is noted that the NMA does not account for differences in trial-related standard of care, that may influence individual treatment effect estimates.**"	The company acknowledge that the NMA eliminates the impact of any differences in the standard of care provided within VISION and real-world clinical settings. However, given the noted inter-trial heterogeneity in the NMA, it should be acknowledged that differences between trial-related standard of care is a drawback of positioning the NMA as the preferred estimate for relative treatment effects.	This is not a factual inaccuracy. The EAG notes that the pooling only occurs at the relative effect level. The inter-trial heterogeneity has been accounted for using a random effect model. No amendment has been made.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 24-25 states, "The company notes that the ^{68}Ga gozetotide is expected to receive an approval from the Medicines and Healthcare products Regulatory Agency (MHRA) in [redacted] and a technetium-99m[99mTc]-labelled PSMA radiotracer is currently in development by the University of California"	Please consider amending throughout to: "The company notes that the ^{68}Ga gozetotide is expected to receive an approval from the Medicines and Healthcare products Regulatory Agency (MHRA) in [redacted] and a technetium-99m[99mTc]-labelled PSMA radiotracer is currently in development by the University of California"	The company acknowledge that the EAG report reflects the CS. However, the date of anticipated MHRA approval for ^{68}Ga gozetotide was in error and has since been updated. The proposed amendment reflects the accurate anticipated approval date.	The text has been amended as suggested by the company.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 43 states, The EAG assessed the VISION trial to be only moderate quality according to the York CRD criteria (Table 6) and as having a high risk of bias according to the Cochrane RoB criteria (Table 7) given the following issues: the failure to control for some known prognostic factors (e.g., tumour volume/burden)…" Page 74 states, "The VISION trial was at a high risk of bias due to its failure to control for some known	The company suggests that this is removed from the EAG report as tumour volume/burden was controlled for in VISION through one of the stratification factors for randomisation, lactate dehydrogenase (LDH; (≤ 260 IU/L vs. > 260 IU/L). The company please request that the quality assessment of the VISION trial is re-considered in light of this amendment and that this amendment is reflected throughout the EAG report (e.g., Table 6, Table 7).	LDH is widely recognised as a representative marker for tumour burden, as it reflects the underlying oncologic cellular turnover, being raised in greater tumour burden. LDH was included as a stratification factor in VISION for this purpose. This amendment will thus be reflective of the VISION trial design and lead to a more accurate quality assessment of VISION.	The lead author of the published trial acknowledged that this was not considered in the trial, in response to a query on this issue (letter cited in report): Olivier Sartor response: 'Kashihara and Kashihara raise the important issues of tumor volume and … in the outcomes reported in our trial. We concur that these are critical factors needing more exploration. ... A variety of

prognostic factors (e.g., tumour volume/burden)…" Page 160 states," The EAG assessed the VISION trial as being at high risk of bias according to the Cochrane ROB criteria, due to concerns relating to the failure to control for some known prognostic factors (e.g., tumour volume/burden)…"			clinical, radiographic, and laboratory variables need additional analysis with regard to patient outcomes in our trial. Some of these factors — such as volume of disease, location of disease, PSMA expression, dosimetry, age, various pretreatments, pain, and serum biomarkers (e.g., alkaline phosphatase) — need assessment as baseline prognostic markers. In addition, changes in various markers or clinical variables after therapy will be important to ascertain relationships with clinically relevant outcomes.' Clinical advice to the EAG on this issue also confirmed that LDH was not viewed as a valid and/or robust prognostic marker and was not routinely collected in prostate cancer in the UK. We therefore question whether this concern regarding tumour volume represents a factual inaccuracy. The EAG has added the discussion of this

			issue in the report on page 43.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 46 (Table 7, Overall risk of bias column) states, 'High risk of bias' and 'Multiple 'Some concerns' assessments indicates high risk of bias'.	Please amend this overall assessment to 'Some concerns' or detail the rationale for the EAG's confidence in the VISION trial results.	The reference provided by the EAG, Sterne et al. 2019, states:[1] 'The study is judged to be at high risk of bias in at least one domain for this result, or the study is judged to have some concerns for multiple domains in a way that *substantially lowers confidence in the result*'. Multiple 'Some concerns' assessments alone does not justify labelling a trial as 'High risk of bias'.	'Some concerns' were identified and detailed across three of the five risk of bias domains (EAG report Table 7). These assessments – and the overall assessment - represent the interpretation of the EAG in accordance with the Cochrane algorithm and is not a factual inaccuracy. No amendment has been made.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 51 states, "Patients in the SOC only arm were arguably more heavily pre-treated (a potential prognostic factor): the SOC only arm had a higher proportion of patients than the	Please consider amending to: "Patients in the SOC only arm were arguably more heavily pre-treated (a potential prognostic factor): the SOC only arm had a higher proportion of patients than the ^{177}Lu vipivotide tetraxetan + SOC arm who had	The values presented here in the EAG report refer to the proportion of patients who received 2 regimens of ARPIs (not ≥2). Additionally, this proportion in the PFS-FAS in 39.0% (not 39.9%).	The EAG agrees. The text has been amended as suggested by the company.

177Lu vipivotide tetraxetan + SOC arm who had received >2 regimens of ARPIs (PFS-FAS: 43.9 vs 39.9%; FAS: 45.7% vs 38.7%) and two taxanes (PFS-FAS: 46.9% vs 44.9%; FAS: 43.6% vs 39.9%)."	received 2 regimens of ARPIs (PFS-FAS: 43.9 vs 39.0%; FAS: 45.7% vs 38.7%) and two taxanes (PFS-FAS: 46.9% vs 44.9%; FAS: 43.6% vs 39.9%)."		

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 69 states that TheraP was excluded "on the basis of study design (as a Phase II study)"	Please consider amending to: "on the basis of study design (as a Phase II study). Additional factors limiting TheraP's role in decision-making include: the TheraP version of ^{177}Lu vipivotide tetraxetan was hospital-compounded, VISION and TheraP differed in their stratification factors for randomisation, the dosing of ^{177}Lu vipivotide tetraxetan in TheraP diverged from recommended dosing, TheraP excluded patients with FDG-positive disease sites with minimal PSMA expression, and that TheraP was primarily designed to evaluate PSA response and was not powered sufficiently to evaluate secondary endpoints, OS and rPFS relevant to economic modelling."	A full justification for the unsuitability of TheraP to inform efficacy estimates in the CEM, and thus rationale for exclusion from the NMA should be provided for context.	This is not a factual inaccuracy. The paragraph on page 69 refers to the reason why TheraP was excluded from both the review and the NMA. As the review inclusion criteria was Phase III trials only, the reason for excluding TheraP from both the review and the NMA was due to study design, which was also confirmed in the company's response to clarification question A9. No amendment has been made.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 71 states, “The CS reported that TheraP did not contribute to the efficacy evidence in the economic model due to differences between TheraP and VISION in the diagnostic process, the intervention production and dose, and the stratification of patients	Please consider amending to: “The CS reported that TheraP did not contribute to the efficacy evidence in the economic model due to differences between TheraP and VISION in the diagnostic process, the intervention production and dose, and the stratification of patients. TheraP was also primarily designed to evaluate PSA response (defined as a reduction of PSA ≥50% from baseline) and was not powered sufficiently to evaluate secondary endpoints, OS and rPFS relevant to economic modelling”.	A full justification for the unsuitability of TheraP to inform efficacy estimates in the CEM, and thus rationale for exclusion from the NMA should be provided for context.	The EAG agrees. The text has been amended to read “The CS reported that TheraP did not contribute to the efficacy evidence in the economic model due to differences between TheraP and VISION in the diagnostic process, the intervention production and dose, and the stratification of patients (CS, Section B.2.8.1), and TheraP was also not powered to robustly investigate OS and has not yet published any results for this endpoint.” to reflect the rational provided in the CS.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 73 states, “Due to challenges in definition and validity of data (CS, Section B.2.8.1), only the results for OS were calculated and compared”.	Please consider amending to: “Disease progression, rPFS or PFS, is challenging to capture in database analyses, and often relies on the commencement of a new treatment to act as a proxy for progression. However, in mCRPC that has already progressed despite multiple prior	Full context regarding the difficulties in measuring disease progression via database analysis in advanced mCRPC should be provided, to justify why the company RWE was not able to capture rPFS data.	This is not a factual inaccuracy. The EAG summarised the challenges and referenced the CS for more details. However, the text has been amended to

	therapies, this proxy becomes inconsistent, especially when patients do not go on to receive another therapy leading to high levels of censored data. Thus, this RWE analysis was not able to capture data on rPFS, only OS"		reflect the full context provided in the CS: "The RWE analysis only analysed OS data, but not rPFS given "*Disease progression, rPFS or PFS, is challenging to capture in database analyses, and often relies on the commencement of a new treatment to act as a proxy for progression. However, in mCRPC that has already progressed despite multiple prior therapies, this proxy becomes inconsistent, especially when patients do not go on to receive another therapy leading to high levels of censored data*" (CS, Section B.2.8.1)."

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 78 presents Table 24 with the caption, "Table 24: Patient baseline characteristics across studies included in the NMA (reproduced from CS, Appendix D.1.3, Table 8)"	Please consider amending to: "Table 24: Patient baseline characteristics across studies included in the NMA (adapted from CS, Appendix D.1.3, Table 8)"	Table 8 in Appendix D.1.3 of the CS does not present the final three columns of this table and therefore 'adapted' is more accurate than 'reproduced'.	The EAG agrees. The text has been amended as suggested by the company.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 92 states, "Clinical advice received by the company considers that there is *"no reason to believe that the efficacy of ^{177}Lu vipivotide tetraxetan should differ in patients suitable or unsuitable for taxanes"*."	Please consider amending to: "Clinical advice received by the company considers that there is *"no reason to believe that the efficacy of ^{177}Lu vipivotide tetraxetan should differ in patients suitable or unsuitable for taxanes",* **given eligibility for taxanes is not based on ability to respond to treatment, but rather on risk of severe side effects limiting treatment tolerability or outweighing any potential benefits of treatment. There is currently no clinical argument that 0, 1, or >1 rounds of taxane chemotherapy would affect response to radioligand therapy**."	The Company provide a rationale for the statement quoted by the EAG in the response to clarification question B4, but has been omitted here. This context should be included to ensure the committee are presented with the full justification for the use of the VISION trial data to inform efficacy for patients ineligible for taxanes.	The EAG agrees. The text has been amended to also quote the rationale provided in response to clarification question B4: "Clinical advice received by the company considers that there is *"no reason to believe that the efficacy of ^{177}Lu vipivotide tetraxetan should differ in patients suitable or unsuitable for taxanes*" given "*eligibility for taxanes is not based on ability to respond to treatment, but rather on risk of severe side effects limiting treatment tolerability or outweighing any potential benefits of treatment*"."

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93 states "The EAG notes that the company has not provided any evidence that corroborates that data from VISION is generalisable to patients ineligible for taxanes but who are eligible for ^{177}Lu	Please consider amending to: "The EAG notes that **no clinical data were available** that corroborates that data from VISION is generalisable to patients ineligible for taxanes but who are eligible for ^{177}Lu	Whilst the company acknowledge that no clinical data are available for patients ineligible for taxanes. However, this statement could imply that data were available which the company chose not to provide. In the absence of clinical	The EAG agrees. The text has been amended as suggested by the company.

vipivotide tetraxetan (third subgroup in Figure 1)"	vipivotide tetraxetan (third subgroup in Figure 1)"	data, the company did present evidence for the generalisability of the VISION trial results to patient ineligible for taxanes in the form of clinical expert advice.	

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93 states, "In the company's model, patients are assumed to receive 25 mg/m2 of cabazitaxel administered via IV every 3 weeks (Q3W) for a total of 10 doses"	Please consider amending to: "In the company's model, patients are assumed to receive 25 mg/m^2 of cabazitaxel administered via IV every 3 weeks (Q3W) **for a maximum of 10 doses (modelled doses = 7.33, determined from the mean treatment exposure of 5.1 months for cabazitaxel in the CARD trial)**"	This amendment will accurately reflect the company's model.	This sentence has been amended to say "for a maximum of 10 doses" rather than "for a total of 10 doses". A later sentence in the same paragraph explains that treatment duration is based on median exposure from the CARD trial and details on the mean duration and mean number of doses modelled are provided on pages 113 and 131.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 95 states, "The model does not include any additional	Please consider amending both instances to:	The amendment ensures accurate representation of the response to	This is not a factual inaccuracy. However, the EAG

constraints to ensure that the mortality risks for patients with mCRPC must be at least as high as those for the age- and sex-matched general population of the UK". The same statement is made on page 97.	"The model does not include any additional constraints to ensure that the mortality risks for patients with mCRPC must be at least as high as those for the age- and sex-matched general population of the UK. **Modelled mortality rates never fell below those for the age- and sex-matched general population of the UK**"	B29 in the EAG clarification questions.	has added the following for context on page 95. "However, modelled mortality rates never fell below age- and sex-matched estimates for the general population of the UK." In addition the same statement on page 97 has been removed.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 96 states, "The company's model does not include half-cycle correction."	Please consider amending to: "**As the one-week cycle length is relatively short compared to the model's 10-year time horizon,** the company's model does not include half-cycle correction."	This amendment will reflect the rationale for excluding a half-cycle correction in the model.	This is not a factual inaccuracy. It is also not a significant omission as we already comment on page 137 that including a half-cycle correction would have minimal impact on the ICER. No amendment has been made.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 98, Table 28 (Row: SSE management costs), states "Distribution of individual SSEs from the VISION trial; unit costs from NHS Reference Costs	Please consider amending to: "Distribution of individual SSEs from the VISION trial and unit costs from NHS Reference Costs 2019/20"	Clinical expert opinion was only used to inform the duration of SSEs, which is used for calculating	Table 28 has been amended as suggested by the company.

2019/20 and clinical expert opinion"		utility decrements and not associated management costs	

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 101, Table 29 (Row: Scenario), appears to present the incorrect value for the mean OS for ^{177}Lu vipivotide tetraxetan + SOC: [redacted].	Please consider amending this value [redacted], as presented in the CS Table 39.	The amendment ensures accurate representation of the CS.	The EAG agrees. The value has been amended as suggested by the company.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 102 states: "The company states that this approach provides the most relevant evidence relating to UK patients currently treated with cabazitaxel, who would be considered eligible for ^{177}Lu vipivotide tetraxetan."	Please consider amending to: "The company states that this approach provides the most relevant evidence relating to UK patients currently treated with cabazitaxel, who would be considered eligible for ^{177}Lu vipivotide tetraxetan, **and that this approach was supported by clinicians and HE experts consulted within an advisory board setting.**"	The selection of the RWE to inform the base case inputs for OS in the cabazitaxel arm was supported by clinicians and health economics experts consulted by the company during submission development. This context should be reported to ensure the full justification for this assumption is provided to the committee.	The EAG has gone back to the company's report of the UK HTA advisory board meeting (report dated 25th Feb 2022) to assess whether to amend this text to include the company's' assertion that this approach was supported by clinicians and HE experts. The advisory board meeting report states that *"Advisors concluded that ideally the additional outcomes from RWE would be supplementary to the model inputs, to provide a supportive validation of the cost-effectiveness model, if*

			available." Therefore, the EAG disagrees with the company's assertion that the company's approach, which used RWE as a model input rather than as a form of external validation, was supported by clinical and HE experts. No amendment has been made.

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 108 states: "The company replied that these assumptions were validated by clinical expert opinion, which advised that the likely lower pre-progression utility value for cabazitaxel in relation to ^{177}Lu vipivotide tetraxetan was related to patients experiencing a negative psychological response to being offered cabazitaxel, if they previously had a poor experience with docetaxel, with many opting not to receive cabazitaxel despite its potential to extend life."	Please consider amending to: "The company replied that these assumptions were validated by clinical expert opinion, which advised that the likely lower pre-progression utility value for cabazitaxel in relation to ^{177}Lu vipivotide tetraxetan was related to patients experiencing a negative psychological response to being offered cabazitaxel, if they previously had a poor experience with docetaxel, with many opting not to receive cabazitaxel despite its potential to extend life, **and given toxicity associated with cabazitaxel (cabazitaxel-induced-diarrhoea particularly impacts patients' quality of life)**."	The justification for the assumption that the pre-progression utility value for cabazitaxel is lower than that for ^{177}Lu vipivotide tetraxetan was based on both the potential negative psychological response to being offered cabazitaxel and the substantial toxicity associated with cabazitaxel treatment, as per the company response to clarification question B19. The full justification for this assumption should be reported.	This is not a factual inaccuracy. The very next sentence describes the substantial toxicity as being an issue. Therefore, the EAG also does not believe that this is a significant omission. No amendment has been made.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 118 states, "Drug acquisition and administration costs were taken from eMIT, BNF, MIMS and NHS Reference Costs 2019/20"	Please consider amending to: "Drug acquisition and administration costs were taken from eMIT, BNF, and NHS Reference Costs 2019/20"	No costs were sourced from MIMS for the company model.	EAG agrees. MIMS has been removed from the list of unit cost sources as suggested by the company.

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 124 states, "Some of these analyses involve varying parameters according to their 95% CIs where available, or using +/- 25% of the expected value where 95% CIs were not available."	Please consider amending to: "Some of these analyses involve varying parameters according to their 95% CIs where available, or using **+/- 10%** of the expected value where 95% CIs were not available."	The amendment ensures accurate representation of the company model.	EAG agrees. Text on page 124 has been amended to say +/- 10% rather than +/- 25%. The EAG notes that the data in Table 44 accurately reported the relevant parameters as being varied by +/- 10%.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 138 states, "This hard coding means that this value does not correspond with the duration of cabazitaxel treatment when this is varied within the PSA."	No text amendment is proposed.	The company agrees with the EAG's identified issue. However, each of the cabazitaxel premedication durations and cabazitaxel durations are sampled independently in the PSA. The EAG's correction does not address	The EAG has updated the model so that the duration of cabazitaxel premedication is linked to the duration of cabazitaxel treatment for both the deterministic and PSA analyses by updating cells

		this because it links to the mean cabazitaxel duration (H46) and not the sampled value (Z46). Please consider amending the EAG's model accordingly.	X89:X92 of the Default Data sheet to use the value in cell X46 when this EAG correction is applied. The report has been amended to include the updated results within Tables 2, 48, and 54 and Figures 25, 26, 29, and 30 and relevant text on pages 22,153 and 161. (only comparisons against cabazitaxel using the PSA are affected). The EAG notes that the results are extremely close to those provided previously.

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 140 states: "The EAG was unable to verify this estimate from the cited reference and noted that the EQ-5D values presented by Bahl et al. (2015) from the EAP were close to 0.7 at baseline and increased subsequently by a reported 0.065 by cycle 10."	No text amendment is proposed.	This utility value was derived from NICE TA391 (ERG report table 29), as cited in the economic model. In this TA's ERG report, it states that this data are more up to date than reported in the Bahl et al. (2015) publication. Please reconsider this section of the EAG's report based on the information reported in this source.	Thank you for providing this additional information. We now understand that the value of 0.627, which is cited as being taken from TA391, is in fact estimated from the UK EAP and is therefore the same estimate as the value of 0.6266 quoted in the response to clarification question B20 with an incorrect citation of Bahl 2015. We have made amendments on page 108 and 141 to reflect our updated

			understanding of this data source.

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 141 states: "These data from the UK EAP appear to contradict the company's position that the toxicity of cabazitaxel would result in utility values that are lower than SOC, as the evidence from the UK EAP suggests that utility values may be relatively stable during and after cabazitaxel treatment and would be expected to be higher than the value of 0.627 applied in the company's base case."	Please consider amending to: "These data from the UK EAP appear to contradict the company's position that the toxicity of cabazitaxel would result in utility values that are lower than SOC, as the evidence from the UK EAP suggests that utility values may be relatively stable during and after cabazitaxel treatment and would be expected to be higher than the value of 0.627 applied in the company's base case. **However, it should be noted that patients in the UK EAP cohort were less heavily pre-treated than patients in VISION**."	The ERG report fails to acknowledge that the patients in the UK EAP cohort were less heavily pre-treated than patients in VISION, which may contribute to the utility values reported being higher than would be expected in the target population for this submission. This important context should be reported.	In light of the additional information provided by the company under Issue 24, we have updated the text on page 141 to provide additional details regarding the uncertainty around the estimate of 0.627. The EAG has not included the additional comment suggested by the company about patients being less heavily pre-treated on page 141 as this context is already provided on page 108.

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 143 states: "The company's rationale for excluding other SOC medications for both the cabazitaxel and the 177Lu vipivotide tetraxetan arms in the	Please consider amending to: "The company's rationale for excluding other SOC medications for the ^{177}Lu vipivotide tetraxetan arm in the company's base case analysis was that ^{177}Lu vipivotide tetraxetan	The justification for the exclusion of SOC medications was reported in Table 63 of the company submission.	The EAG has amended the text on page 143 to provide the company's rationale for excluding SOC medications.

company's base case analysis is unclear."	was modelled as a monotherapy, [redacted]. The company's rationale for excluding other SOC medications for the cabazitaxel arm in the company's base case analysis was that the model only considered concomitant medications that were mandated for all patients receiving cabazitaxel in the CARD trial protocol or the SmPC."		For balance, the EAG has also added a comment on why they disagree with this rationale.

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 167 (Table 52) presents data used in the EAG's OS NMA. In the 'VISION (SOC-ARPI subgroup)' row, the HR is reported as 0.54 and the 95% CI is reported as (0.57, 0.87). This HR appears to be sourced from the ^{177}Lu vipivotide tetraxetan + SOC arm of VISION (with ARPI). This 95% CI appears to be sourced from the ^{177}Lu vipivotide tetraxetan + SOC arm of VISION (without ARPI)	Please consider amending the HR to that presented for the ^{177}Lu vipivotide tetraxetan + SOC arm of VISION (with ARPI): (0.41, 0.70). Please clarify the 95% CI applied in the NMA and if this also requires amendment, and any associated results.	The 95% CI appears to be misreported in the EAG report. If these values were applied in the EAG's OS NMA, the results will not be accurate.	The EAG agrees that the 95% CI was misreported in Table 52. The values have been amended as suggested by the company. The EAG notes that the correct 95% CI was used in the EAG's NMA.

References

1. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K,

White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898. doi: 10.1136/bmj.l4898. PMID: 31462531.

Section 2: Confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 73	Missing AIC highlighting.	"A cohort of [redacted] patients was identified, of which [redacted] patients had no recorded follow-up and hence were censored from further survival analysis (CS, Section B.2.8.1 and Appendix N)" Please also update this highlighting in Table 21 of the EAG report. The company acknowledges that the overall cohort of patients identified in the RWE was not marked AIC in the CS. This will be amended in the CS accordingly.	AIC highlighting has been added as suggested by the company.
Page 93	Missing CIC highlighting.	"SOC is considered by the company to be a relevant comparator in the group of patients who are ineligible for treatment with cabazitaxel or unsuitable for treatment with taxanes (subgroups 2 and 3).	CIC highlighting has been added as suggested by the company.
Page 130	Missing AIC highlighting.	"For example, at [redacted] months the cumulative OS for cabazitaxel is [redacted] despite it not showing as reaching its minimum point until [redacted] months in CS, Figure 10. Due to these slight differences between	AIC highlighting has been added as suggested by the company.

		the original KM and the extracted KM used in the model, the restricted mean OS calculated by the company in the model is slightly lower than reported in CS, Table 17 (13.30 months versus [redacted] months)."	
Page 150–151 present OS and rPFS extrapolations for the EAG's base case.	Missing AIC highlighting.	Application of AIC highlighting to Figures 23-34.	AIC highlighting has been added to the plots showing OS and rPFS extrapolations. (Figures 22 to 24)
Appendices 3 and 4 (pages 169-173) present figures showing the cost-effectiveness planes [Figures 25, 27, 29, and 31] and cost-effectiveness acceptability curves [Figures 26, 28, 30, and 32] resulting from cost-effectiveness modelling of 177Lu vipivotide tetraxetan.	Missing CIC highlighting.	Application of CIC highlighting to Figures 25-32.	CIC highlighting has been added to all figures showing cost-effectiveness results (Figures 25 to 32)

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Technical engagement response form

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **8 August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Technical engagement response form

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

NICE National Institute for Health and Care Excellence

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Advanced Accelerator Applications (AAA) (UK & Ireland) Ltd.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Key issues for engagement

Table 1: Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Broadening of population to include people who are not medically suitable for taxanes	No	An urgent unmet medical need exists in the subpopulation of patients who are not medically suitable for taxanes following ARPI treatment, as these patients currently have very few treatment options. Therefore, in the portion of these patients who are deemed medically suitable for treatment with ^{177}Lu vipivotide tetraxetan, patients should not be prevented from accessing appropriate treatment with ^{177}Lu vipivotide tetraxetan. The company acknowledge the EAGs concerns regarding the lack of clinical evidence for patients who are considered not medically suitable for taxanes. However, as stated in the company submission (CS), excluding these patients from treatment with ^{177}Lu vipivotide tetraxetan would create inequity biased against those patients who are not medically suitable for treatment with taxanes, but who would be considered medically suitable for treatment with ^{177}Lu vipivotide tetraxetan. Reasons for medical unsuitability to taxanes may include but are not limited to: hypersensitivity to active substance or excipients, neutropenia <1,500 cells/mm^3, severe hepatic impairment, poor performance status (ECOG ≥3, ECOG ≥2 with substantial comorbidities, and lack of social support or impaired cognitive understanding sufficient to impact upon treatment compliance or toxicity monitoring.[1] Mechanistically, there is no reason that the efficacy and safety of ^{177}Lu vipivotide tetraxetan would be significantly different in patients who are ineligible for taxanes, unless patients present with significantly more comorbidities;

		patients who are not medically suitable to receive taxanes for PSMA-positive mCRPC are still likely to derive clinical benefit from ^{177}Lu vipivotide tetraxetan. This has been confirmed in further consultation with clinical experts, who advised that despite the lack of clinical evidence, they would not expect patients deemed medically unsuitable for taxanes to respond significantly differently to ^{177}Lu vipivotide tetraxetan, compared with the VISION population. It should also be noted that in addition to the criteria for medical unsuitability for taxane treatment described above, clinical experts were in unanimous agreement that patient choice following appropriate education from a physician would also form part of the criteria for medical suitability for taxane treatment. As such where patients have been deemed medically unsuitable for treatment with taxanes on the basis of patient refusal, there is no rationale for preventing access to ^{177}Lu vipivotide tetraxetan. Patient choice has previously been accepted as a criterion for medical unsuitability for treatment in other oncology indications.[2] Given the uncertainty surrounding the subpopulation who are not medically suitable for taxanes, the company would also welcome exploration of potential managed access routes for this subpopulation. As highlighted by the EAG, the PSMAfore study (NCT04689828) could provide additional clinical data for patients receiving ^{177}Lu vipivotide tetraxetan who have not received prior treatment with taxanes, however, it should be noted that whilst patients in PSMAfore have not received prior treatment with taxanes, they are not necessarily ineligible for taxane treatment, and so these patient populations do not completely align. Furthermore, NICE have previously accepted that defining the criteria for taxane eligibility is particularly challenging, and therefore, exploration of this subpopulation via a managed access route may permit collection of data from patients enrolled in clinical practice which could support establishment of more robust criteria for taxane ineligibility.[3]

Issue 2: Exclusion of radium-223 as a comparator for people with bone metastases	No	The company accept that the EAG's position that radium-223 may be a relevant comparator in a small minority of patients with mCRPC, namely those with symptomatic bone metastases and no visceral metastases. However, the lack of suitable evidence for radium-223 precludes robust indirect comparison of this agent to ^{177}Lu vipivotide tetraxetan, and as such the company has been unable to include radium-233 in as a comparator in this appraisal. It is also important to highlight the differences between radium-223 and ^{177}Lu vipivotide tetraxetan. ^{177}Lu vipivotide tetraxetan offers targeted delivery of radiotherapy to the primary tumour and PSMA-positive metastases, whereas radium-223 mimics calcium and delivers radiotherapy preferentially at sites of bone metastases.[4] As reflected in NICE's recommendation for treating symptomatic prostate cancer bone metastases, radium-223's primary action is to palliate bone pain.[1] As the ALSYMPCA trial did not require patients to have been treated with prior-ARPIs, the patient population is likely to be less heavily pre-treated than patients eligible for ^{177}Lu vipivotide tetraxetan, which precludes robust indirect comparison of this trial to VISION.[5] Further clinical expert opinion sought by the company at the technical engagement stage has confirmed that clinical experts view the life-extending ability of radium-223 in this heavily pre-treated population to be limited, particularly given the context of the NICE restrictions placed on radium-223, which mean that the majority of patients receiving radium-223 do so at an advanced stage of disease where the efficacy of radium-223 is unproven.[6]
Issue 3: Concerns regarding company's network meta-analysis	Yes (New analyses; Appendix 1)	The company acknowledge the EAGs concerns regarding the breaking of randomisation in the original company NMA, and as such have provided an updated base case NMA in which the EAGs preferred approach of utilising the VISION data for the subpopulation of patients who received ARPI as part of SOC in both VISION

		treatment arms within the NMA, in order to maintain randomisation, has been accepted. The company also acknowledge that patients in several trials included in the NMA appear to be less heavily pre-treated than patients in VISION, introducing heterogeneity. However, the company do not agree with the exclusion of the TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials (which form a closed loop) on this basis, with the resulting comparison for ^{177}Lu vipivotide tetraxetan versus cabazitaxel for OS relying solely on the VISION and CARD trials.[7-10] Clinical experts consulted as part of this response noted that the CARD population was generally healthier and represented a less heavily pre-treated population than patients in VISION; patients in CARD were only required to have previously received docetaxel, whereas 41% in VISION had received >2 lines of taxane therapy. It is therefore inconsistent to exclude these additional trials from the network on the basis of differences in prior treatments, whilst maintaining inclusion of CARD. In addition, patients in the CARD trial were required to have previously experienced disease progression during 12 months of treatment with an ARPI, and as such the CARD patient population may be more likely be resistant to ARPI treatment.[11] No such eligibility criteria was applied to enrolment in the VISION trial, which is likely to bias the relative treatment effect in favour of cabazitaxel in the NMA. Given these limitations, it is more appropriate to include TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 in the NMA, such that the comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel is based on the largest possible evidence base.[7-10] Given ALYSYMPCA and PROfound do not form closed loops in the NMA, the company agree to their exclusion. The company also disagree with the inclusion of TheraP in the NMA, as the study compound utilised in TheraP was a “home-brew” compound, for which bioequivalence with ^{177}Lu vipivotide tetraxetan (Pluvicto™) has not been established. It is therefore

		inappropriate to compare ^{177}Lu vipivotide tetraxetan to the study drug used in the TheraP trial.[12] Furthermore, in TheraP the dose of study drug was reduced from an initial dose of 8.5 GBq by 0.5 GBq each cycle (maximum six cycles; Q6W) to a minimum dose of 6.0 GBq.[12] This is not aligned to VISION, in which patients received a consistent dose of 7.4 GBq (+/- 10%) of ^{177}Lu vipivotide tetraxetan (maximum six cycles; Q6W).[13] It should also be noted that in TheraP, patients who experienced an exceptional response to the study drug (defined as a marked reduction in uptake at all sites of disease with minimally-avid or non PSMA-avid, as assessed by 24 hour post treatment SPECT/CT) were eligible for treatment suspension.[12] The option to suspend further treatment in those patients who respond most promisingly to treatment with the study drug may bias the results of TheraP towards the cabazitaxel treatment arm. As a result of these limitations, the company have not included TheraP in the updated base case NMA. Finally, the company has significant concerns regarding the use of a random effects model with an informative prior; given the sparsity of the network, it is unlikely that this approach could accurately address the heterogeneity within the NMA network. For completeness, results from both fixed effects models and random effects models with and without informative priors have been explored. The hazard ratio (HR) for the comparison of ^{177}Lu vipivotide tetraxetan versus cabazitaxel for OS based on the fixed effect model was [redacted] (95% credible intervals [CrI]: [redacted]). The HR for OS based on the random effects model with a non-informative prior was [redacted]; the use of informative priors had a limited impact on the point estimate of the HR, but reduced the width of the CrIs. The hazard ratio (HR) for the comparison of ^{177}Lu vipivotide tetraxetan versus cabazitaxel for rPFS based on the fixed effect model was [redacted]. The HR for rPFS based on the random effects model with a non-informative prior was [redacted]; similar to OS, the use of informative priors had a limited impact on the point estimate of the HR, but reduced the

		width of the CrIs. Scenario analyses were also explored where individual trials (COU-AA-301, AFFIRM and Sun *et al.* 2016) were excluded to explore the sensitivity of the NMA results to their inclusion/exclusion. In the company's revised base case economic analysis, rPFS for cabazitaxel was informed by the NMA analysis using a fixed effects model, in line with the approach taken in the original company submission. Full details of the assumptions, methodology, and results for the updated company base case NMA are presented in Appendix 1. However, as stated in the CS, the company's view is that there remain several important limitations to the NMA which mean that this is not the most appropriate source of relative efficacy for overall survival (OS) for ^{177}Lu vipivotide tetraxetan versus cabazitaxel. The key limitation of this NMA is inter-trial heterogeneity between ^{177}Lu vipivotide tetraxetan and comparator populations. Of specific importance to the comparison of interest, substantial heterogeneity was identified between CARD and VISION in terms of trial inclusion/exclusion criteria, and patient baseline demographic and clinical characteristics. For example, the key differences across the included disease severity, prior treatment status, prostate-specific membrane antigen (PSMA) positivity, and median PSA levels. Patients included in VISION had more severe disease as indicated by a higher prior treatment count and at least 40% of patients in VISION previously receiving treatment with cabazitaxel. In addition, patients in the CARD trial were required to have previously experienced disease progression during 12 months of treatment with an ARPI, and as such the CARD patient population may be more likely be resistant to ARPI treatment. Due to limited available data, these differences would not have been corrected in any population-adjusted indirect treatment comparison and would have potentially had a confounding effect on the results, and contravened conventional effect modifier assumptions. Additionally, the small sample size and data immaturity of comparator trials limits the interpretation of the NMA results, and the

		limited number of trials identified for inclusion in the network necessitates the use of fixed effects models which are subject to considerable uncertainty. Given the previously described limitations of TheraP and the NMA, the company consider the OS data from the RWE analysis as the most reflective of the efficacy of cabazitaxel in the population of relevance to this submission (post-ARPI, post-taxane), as they were reported directly from patients receiving cabazitaxel in UK clinical practice, where its positioning is in line with the intended positioning of ^{177}Lu vipivotide tetraxetan. Furthermore, the sample size for this RWE analysis is considerably larger than the patient numbers in CARD.[11] The use of the RWE to inform OS was supported by health economics expert [redacted], who has supported closely on technical aspects of the dossier and is familiar with the methodology, results and clinical relevance of the NMA and RWE.[14] However, the company acknowledge the EAG's concern regarding the naïve comparison of VISION data with RWE for cabazitaxel. As such, a propensity score weighting analysis has been conducted in an attempt to control for population differences between these studies, and provide a more robust comparison (see response to Issue 4 for further details). It should be noted that following weighting, the effective sample size for cabazitaxel remains higher than the number of patients receiving cabazitaxel in CARD.[11]
Issue 4: Concerns regarding OS estimates for cabazitaxel in the model	Yes (New analyses; Appendix 2)	The company position is that any increased OS relating to additional patient monitoring received in the RCT setting would be greater for patients in the control arms of these trials, who are expected to receive less regular oncological follow-up and imaging in real-world practice than patients receiving active oncological therapy. Therefore, it is expected that patients in real-world practice receiving SOC would experience shorter OS than that observed in VISION. Therefore, whilst the company acknowledge the EAG's concern regarding the median survival in the original RWE analysis for cabazitaxel being lower than median survival

		in the SOC arm of VISION ([redacted] months vs. 11.3 months). It should be noted that patients the VISION SOC arm are likely to have received enhanced monitoring through more frequent visits to physicians and imaging, and these patients are expected to have longer OS compared to what would be anticipated in real-world practice. Further clinical expert opinion sought during technical engagement has confirmed that experts would expect this effect to be greater for patients in the SOC arm for VISION compared with the ^{177}Lu vipivotide tetraxetan. The rationale for this is that much of the additional monitoring and follow up conducted in the ^{177}Lu vipivotide tetraxetan arm would be mandated in clinical practice as per the SmPC, and therefore the care provided in VISION is more reflective of clinical practice for the ^{177}Lu vipivotide tetraxetan arm than the SOC arm. In order to address uncertainty in the naïve comparison of VISION data to the RWE, a propensity score weighting analysis was explored in an attempt to control for population differences between these two studies. This analysis included all patients treated with cabazitaxel in the RWE cohort who had also received a prior taxane and ARPI (in line with the eligibility criteria for VISION) [n=[redacted]]. In the analysis, patients in the RWE cohort were assigned propensity score weights such that baseline characteristics matched those of the overall population in VISION. The characteristics that were matched across each treatment arm included: median age, proportion of patients with an ECOG score of 0 or 1, median time since diagnosis, Gleason score, and whether patients had undergone previous prostatectomy. After weighting the standardised mean differences between studies for most characteristics were small and non-significant, indicating that the treatment arms were broadly well-balanced between the RWE cohort and VISION (see Table 10). Furthermore, the effective sample size for the cabazitaxel cohort remained high (n=[redacted]) and there was a reasonable overlap in propensity score distributions between the two studies.

		After propensity score weighting, the median OS for patients treated with cabazitaxel remained consistent ([redacted] months [95% CI: [redacted] months]). Further clinical expert opinion has confirmed that this value is consistent with the expected median OS for patients initiating cabazitaxel in UK clinical practice. Full details of the methodology and results for the PSW analysis are presented in Appendix 2. The impact of using weighted OS data from the RWE cabazitaxel cohort on cost-effectiveness results in isolation is presented in Table 3. Weighted OS data from the RWE cabazitaxel cohort were incorporated into the Company's revised base case, the full results of which are presented in Appendix 4.
Issue 5: Use of pre-progression utility values for cabazitaxel that are equivalent to standard of care and use of post-progression utility values for cabazitaxel that are lower than for both standard of care and ^{177}Lu vipivotide tetraxetan	Yes (New analyses; Appendix 3)	Utilising treatment-independent utility values in the cost-effectiveness analyses may fail to capture the substantial phycological burden placed on patients who are receiving cabazitaxel in the post-docetaxel setting. Given the poor tolerability profile and considerable side effects that are associated with taxane treatment, it is likely that a sizeable proportion of patients have had a poor experience with docetaxel, and as such are likely to experience phycological impact if placed on a subsequent treatment with the same mechanism of action (cabazitaxel). This assumption has been validated further with clinical experts who have stated that patients are typically reluctant to receive further chemotherapy after suffering side effects of initial chemotherapy treatment, with some patients refusing to receive further chemotherapy treatment, even if comparatively young and healthy. It should also be noted that in the scenario based on treatment-independent utility values which is favoured by the EAG, differences in HRQoL between treatment arms are driven by AE/SSE frequency (via application of an associated disutility). However, patients in CARD were considered to be less heavily pre-treated and frail compared to those in VISION, meaning that these patients may be reasonably expected to experience fewer AEs/SSEs than the target population of this appraisal.[11] Further

		validation received from clinical experts has confirmed that clinicians would expect patients in the CARD population to experience fewer AE/SSEs than the VISION population, due to these patients being less heavily pre-treated. As well as resulting in a potential underestimation of costs associated with cabazitaxel AE/SSE management, differences in HRQoL between ^{177}Lu vipivotide tetraxetan and cabazitaxel arms are likely to be underestimated in the scenario based on treatment-independent utility values. The company have conducted a re-evaluation of the VISION EQ-5D data, in order to further explore the observed differences in HSUVs between the treatment arms, and address the highly similar pre- and post-progression HSUVs for patients in the SOC treatment arm. In VISION, EQ-5D-5L data were collected from patients during screening (i.e. baseline), and then on Day 1 of each treatment cycle (i.e. Weeks 7, 14, 21 etc.), whereas radiographic imaging to determine rPFS status was performed at baseline and then every eight weeks during the first 24 weeks of treatment, and every 12 weeks thereafter.[15] Patients in VISION are assumed to be progression-free until radiographic progression is demonstrated, and so in the original analysis all EQ-5D-5L assessments were considered to contribute to the pre-progression HSUV until confirmed radiographic progression. However, the difference in the assessment timepoints for EQ-5D-5L and rPFS may result in inaccurate categorisation of individual assessments. Patients may progress at any point during the ~8 weeks between rPFS assessments, but EQ-5D-5L assessments are assumed to reflect the pre-progression health state until an rPFS assessment where radiographic progression is confirmed. This is likely to have a more substantial impact on the treatment arm with a faster rate of progression (SOC). This is demonstrated by the precipitous drop in rPFS for the SOC arm which occurs at Week 8; at this time patients will have been administered

two post-baseline EQ-5D-5L assessments, the results of which would contribute to the pre-progression HSUV, as the first rPFS assessment did not occur until Week 9.

To address this issue, the following measurements were censored, as it is not possible to ascertain whether the patient had progressed disease at the time of EQ-5D-5L assessment or not:

1. EQ-5D measurements recorded after last progression assessment in which the patients remained progression-free
2. EQ-5D measurements recorded directly before a rPFS assessment in which the patient demonstrated radiographic progression
3. Patients with no HRQoL assessment with progression data, or only 1 visit

The original and updated HSUVs are presented in Table 2. As expected, the difference between the pre-progression and post-progression utility values for SOC widened in the revised analysis. It should also be noted that the updated HSUV for the SOC treatment arm in the post-progression health state is very similar to the published value used for the cabazitaxel treatment arm in the cost effectiveness analysis (0.627).[16]

Table 2: Treatment specific HSUVs derived from VISION (original and revised analysis)

Health state	Overall	^{177}Lu vipivotide tetraxetan	SOC
Original analysis			
Pre-progression	[redacted]	[redacted]	[redacted]

		Post-progression [redacted] [redacted] [redacted] ***Revised analysis*** Pre-progression [redacted] [redacted] [redacted] Post-progression [redacted] [redacted] [redacted] **Abbreviations:** HSUV: health state utility value Full methodology informing revised utility assumptions are presented in Appendix 3, and their impact on cost-effectiveness results in isolation are presented in Table 3. It should also be noted that the preferred utility assumptions were incorporated into the Company's revised base case, the full results of which are presented in Appendix 4.
Issue 6: Exclusion of standard of care costs from the ^{177}Lu vipivotide tetraxetan treatment and cabazitaxel treatment arms	No	As part of technical engagement, the company consulted clinical experts who generally agreed that SOC would be received by all patients receiving ^{177}Lu vipivotide tetraxetan or cabazitaxel. Clinical experts also confirmed that with the exception of ARPIs, the components of SOC received by patients in the VISION trial was consistent with UK clinical practice. As such, the company accept the EAGs preferred assumptions for concomitant SOC and as such have included estimates of concomitant therapies for all treatment strategies in the updated analysis. As per the scenario analysis explored in the original CS, the components of concomitant SOC are based on data from VISION for ^{177}Lu vipivotide tetraxetan treatment arm, and data averaged across both treatment arms of the VISION trial for cabazitaxel. The impact of revised concomitant SOC assumptions on cost-effectiveness results in isolation is presented in Table 3. These revised concomitant SOC assumptions were incorporated into the Company's revised base case, the full results of which are presented in Appendix 4.

Issue 7: Costing of pre-medication and concomitant medications for cabazitaxel	No	After further consultation with clinical experts, the company acknowledge that the 14-days of G-CSF per 21-day cabazitaxel treatment cycle which is specified in the SmPC represents and overestimation of the duration of G-CSF received on average by patients in clinical practice.[17] However, clinical experts also reported that the 5-day duration suggested by the EAG represented an underestimation of clinical practice, particularly in the post-COVID-19 setting. Clinical experts advised that with 5-days treatment there would be a considerable risk of patients experiencing severe AEs (i.e. neutropenic sepsis), and that in order to lessen the risk of AEs, 7–9 days of G-CSF treatment was typical in clinical practice. As such the company have adopted a nine day G-CSF duration (per 21-day cabazitaxel treatment cycle) in the updated base case analysis. The impact of the revised approach to pre-medication on cost-effectiveness results in isolation is presented in Table 3. This approach to modelling pre-medications has been incorporated into the Company's revised base case, the full results of which are presented in Appendix 4.
Issue 8: Estimation of symptomatic skeletal event (SSE) incidence	No	The company acknowledge the EAGs concerns with the original approach, which resulted in a cumulative incidence of SSEs that is much higher than observed in the trials despite the Kaplan-Meier plot of time-to-first SSE or death being relatively complete by the end of the VISION trial follow-up. As such, the company have accepted the preferred EAG assumptions in which the cumulative incidence of SSEs is based on rates observed in the VISION trial for ^{177}Lu vipivotide tetraxetan and SOC, and rates observed in the CARD trial for cabazitaxel.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 3: Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Company base case before technical engagement (including corrections in response to EAG clarification questions)	**Incremental QALYs** • Cabazitaxel: [redacted] • SOC: [redacted]	**Incremental costs** • Cabazitaxel: £[redacted] • SOC: £[redacted]	**ICER (£/QALYS)** • Cabazitaxel: £49,714 • SOC: £122,003
Issue 3: Concerns regarding company's network meta-analysis	To include VISION in the NMA, a distinct subpopulation of patients was analysed post-hoc. This subpopulation included all patients in the ^{177}Lu vipivotide tetraxetan arm and those patients in the SOC arm who received an ARPI as a component of SOC at the time of initial randomisation. Including VISION, the NMA consisted of a total of eight RCTs that were connected through a common comparator arm of ARPI and mitoxantrone/placebo plus	The company acknowledge the EAGs concerns regarding the breaking of randomisation in the original company NMA, and the subpopulation of patients who received ARPI as part of SOC in both VISION treatment arms was used within the NMA, in order to maintain randomisation. Despite investigating patient populations who were less heavily pre-treated than those in VISION, given the limitations of the CARD study (e.g. differences in trial inclusion/exclusion criteria, patient baseline demographic and clinical characteristics), TROPIC, COU-AA-301, AFFIRM and Sun *et*	**Cabazitaxel** • ICER (£/QALYs) = £46,052 • Change from original base case ICER = -£3,662 **SOC** • ICER (£/QALYs) = £122,003 • Change from original base case ICER = £0

	prednisone. TheraP was excluded from the NMA. Given the sparsity of the networks, a fixed effects model was used in the base case.	*al.* 2016 were included in the NMA, such that the comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel is based on the largest possible evidence base.[7-10] Given ALYSYMPCA and PROfound do not form closed loops in the NMA, the company agree to their exclusion. The Company maintain that TheraP should be excluded from the NMA. A fixed effects model was used given the sparsity of the network in line with the approach taken in the original company submission.	
Issue 4: Concerns regarding OS estimates for cabazitaxel in the model	OS for cabazitaxel was informed directly by RWE for patients who received cabazitaxel in UK clinical practice	There remain several important limitations to the NMA which mean that this is not the most appropriate source of relative efficacy for OS for ^{177}Lu vipivotide tetraxetan versus cabazitaxel. The key limitation of this NMA is inter-trial heterogeneity between ^{177}Lu vipivotide tetraxetan and comparator populations, as outlined in the response to Issue 4. In order to address uncertainty in the naïve comparison of VISION data to the RWE, a propensity score weighting analysis was explored in an attempt to control for population differences between these two studies. This analysis included all patients treated with cabazitaxel in the RWE cohort who had also received a prior taxane and ARPI (in line with the eligibility criteria for VISION) [n=[redacted]]. The weighted OS data for from the RWE	**Cabazitaxel** • ICER (£/QALYs) = £46,329 • Change from original base case ICER = £3,384 **SOC** • ICER (£/QALYs) = £122,003 • Change from original base case ICER = £0

		cabazitaxel cohort were incorporated into the revised base case.	
Issue 5: Use of pre-progression utility values for cabazitaxel that are equivalent to standard of care and use of post-progression utility values for cabazitaxel that are lower than for both standard of care and **^{177}Lu** vipivotide tetraxetan	Treatment-specific utility values for the 'pre-progression' and 'progressed' health states were derived from EQ-5D data from VISION for ^{177}Lu vipivotide tetraxetan and SOC. Based on feedback from clinical experts, the 'pre-progression' utility value for cabazitaxel was assumed to be equivalent to SOC, given its greater toxicity than ^{177}Lu vipivotide tetraxetan, and the utility value for the 'progressed' health state was sourced from NICE TA391.	Treatment-specific utility values were maintained in the revised company base case. Additional clinical expert feedback confirms that using treatment-independent utility values, differences in HRQoL between treatment arms are driven by AE/SSE frequency (via application of an associated disutility), may fail to capture the substantial phycological burden placed on patients who are receiving cabazitaxel in the post-docetaxel setting. In addition, AE/SSE rates from CARD and applied to cabazitaxel in the model, may represent an underestimate of the AE/SSE rates expected for the target population, due to these patients being less heavily pre-treated than patients in VISION. Treatment-specific utility values for ^{177}Lu vipivotide tetraxetan and SOC were derived from a revised analysis, where EQ-5D measurements recorded directly before the rPFS assessments in which the patient demonstrated radiographic progression were censored. As per the original base case, the 'pre-progression' utility value for cabazitaxel was assumed to be equivalent to SOC, and the utility value for the 'progressed' health state was sourced from NICE TA391.	**Cabazitaxel** • ICER (£/QALYs) = £49,119 • Change from original base case ICER = -£594 **SOC** • ICER (£/QALYs) = £117,604 • Change from original base case ICER = -£4,399
Issue 6: Exclusion of standard of care costs from the ^{177}Lu vipivotide	^{177}Lu vipivotide tetraxetan was modelled as monotherapy; cabazitaxel is given alongside	The company accept the EAGs preferred assumptions for concomitant SOC and as such have included estimates of concomitant	**Cabazitaxel** • ICER (£/QALYs) = £49,604 • Change from original base case

tetraxetan treatment and cabazitaxel treatment arms	recommended premedications; SOC concomitant treatment use was based on VISION, adjusted for the UK setting.	therapies for all treatment strategies in the updated analysis. Components of concomitant SOC are based on data from VISION for ^{177}Lu vipivotide tetraxetan treatment arm, and data averaged across both treatment arms of the VISION trial for cabazitaxel.	ICER = -£109 **SOC** • ICER (£/QALYs) = £137,420 • Change from original base case ICER = £15,417
Issue 7: Costing of pre-medication and concomitant medications for cabazitaxel	Patients in the cabazitaxel arm were assumed to receive 14 days of G-CSF per 21-day cabazitaxel treatment cycle, as specified in the SmPC.[17]	Clinical experts advised that 7–9 days of G-CSF treatment was typical in clinical practice. As such the company have adopted an nine day G-CSF duration (per 21-day cabazitaxel treatment cycle) in the updated base case analysis.	**Cabazitaxel** • ICER (£/QALYs) = £55,628 • Change from original base case ICER = £5,914 **SOC** • ICER (£/QALYs) = £122,003 • Change from original base case ICER = £0
Issue 8: Estimation of symptomatic skeletal event (SSE) incidence	Time-to-first SSE	Incidence from trials	**Cabazitaxel** • ICER (£/QALYs) = £48,886 • Change from original base case ICER = -£827 **SOC** • ICER (£/QALYs) = £123,154 • Change from original base case ICER = £1,151
Company's revised base case following technical engagement	**Incremental QALYs** • Cabazitaxel: [redacted] • SOC: [redacted]	**Incremental costs** • Cabazitaxel: [redacted] • SOC: [redacted]	**Cabazitaxel** • Cabazitaxel • ICER (£/QALYs) = £50,158 • Change from original base case

			ICER = £445 **SOC** • ICER (£/QALYs) = £133,574 • Change from original base case ICER = £11,571

Abbreviations: AE: adverse event; ARPI: androgen-receptor pathway inhibitor; EAG: external assessment group; G-CSF: granulocyte colony-stimulating factor; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; NMA: network meta-analysis; QALYs: quality-adjusted life years; rPFS: radiographic progression-free survival; RWE: real-world evidence; SOC: standard of care; SSE: symptomatic skeletal event.

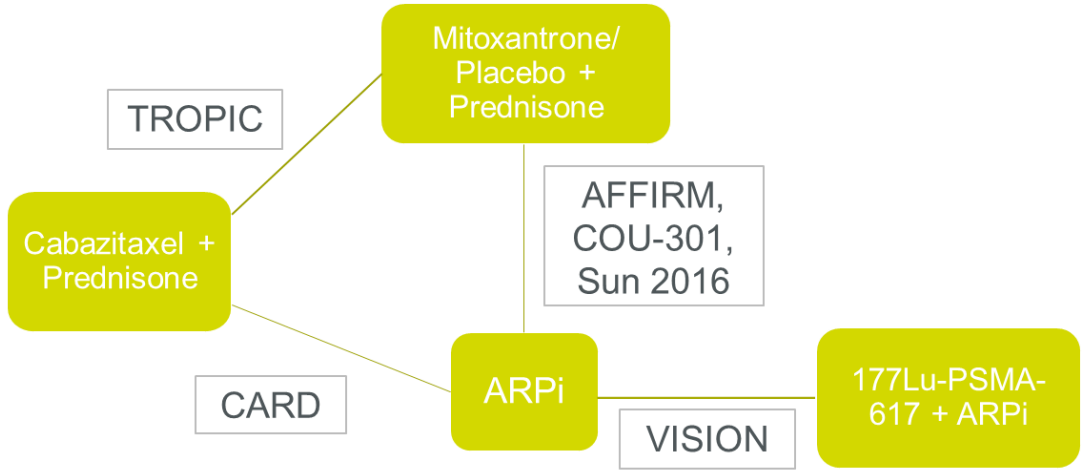
Sensitivity analyses around revised base case

All scenario analyses explored in the original Company submission have been rerun using revised base case inputs (Appendix 4).

Appendix 1: NMA methodology

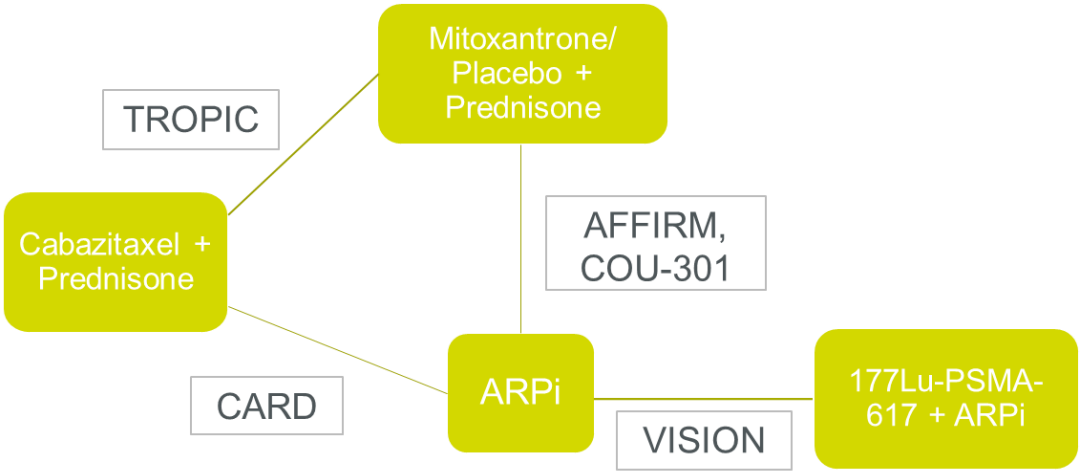
Of the eight RCTs included in the original Company NMA (see Table 18 of the Company submission, six were included in the revised NMA, connected through a common comparator arm of ARPI and mitoxantrone/placebo plus prednisone (Figure 1 and Figure 2). In line with the EAG's preferences, the subpopulation of patients who received ARPI as part of SOC in both VISION treatment arms was used within the NMA, in order to maintain randomisation. TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 were included in the NMA, such that the comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel was based on the largest possible evidence base.[7-10] ALYSYMPCA and PROfound were not included as they did not form closed loops.

Figure 1: OS network



Abbreviations: ARPI: androgen receptor pathway inhibitor.

Figure 2: rPFS network



Abbreviations: ARPI: androgen receptor pathway inhibitor.

Technical engagement response form

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

NMA methods

The NMA was conducted using the summary results reported in study publications and included the synthesis of the HR of time to event endpoints of OS and rPFS. In this analysis, a linear model with normal likelihood distribution was used for the time to event outcomes (log HR and standard error [SE]). The NMA was performed using the MCMC software. This method includes the synthesis of all included data (direct and indirect comparisons), resulting in a single set of effective sizes. The NMA model inputs included natural log of HR (logHR) and SE of logHR. The results of the NMA were based on enough iterations (e.g., 100,000 iterations) on at least three chains, with a burn-in of 20,000 iterations. Convergence was assessed by visual inspection of trace plots.

For each outcome, fixed and random effects models were explored and model fit statistics evaluated. However, for small networks where only a small number of studies are included (as in this network), there is limited information to estimate the heterogeneity standard deviation and the prior distribution may be too heavy tailed. The heterogeneity parameter is therefore difficult to estimate, necessitating the use of the fixed effects model. However, random effect models were also evaluated to compare the HR and credible interval.

In total four scenarios were evaluated for OS, and three scenarios were evaluated for rPFS by excluding the studies which compared the efficacy of ARPi vs placebo + prednisone, to explore the sensitivity of the NMA to the inclusion of these additional studies. The scenarios explored are presented in Table 4 and Table 5 for OS and rPFS, respectively.

Table 4: Scenarios evaluated for OS

Scenario	Description
1	Including all the available studies for ARPi vs Placebo + prednisone comparison
2	Including only AFFIRM and COU-301 trials for ARPi vs Placebo + prednisone comparison
3	Including only COU-301 trial for ARPi vs Placebo + prednisone comparison
4	Including only AFFIRM trial for ARPi vs Placebo + prednisone comparison

Abbreviations: ARPi: angrogen receptor pathway inhibitor; OS: overall survival.

Table 5: Scenarios evaluated for rPFS

Scenario	Description
1	Including all the available studies for ARPi vs Placebo + prednisone comparison
2	Including only COU-301 trial for ARPi vs Placebo + prednisone comparison
3	Including only AFFIRM trial for ARPi vs Placebo + prednisone comparison

Abbreviations: ARPi: angrogen receptor pathway inhibitor.; rPFS: radiographic progression-free survival.

As suggested by EAG, the above scenarios were evaluated with informative priors with truncation at 10-times and 5-times. The mean effect as well as the credible interval did not change much due to the paucity of the information.[18]

Technical engagement response form

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

Table 6: DIC and residual deviance values for OS using fixed effects and random effects models for Scenario 1

Value	Fixed Effects Model	Random Effects Model
DIC	[redacted]	[redacted]
Dbar	[redacted]	[redacted]
pD	[redacted]	[redacted]
gelman.diag	[redacted]	[redacted]

Abbreviations: DIC: Deviance information criteria; Dbar: Posterior mean of the deviance; pD: Effective number of parameters.

Table 7: DIC and residual deviance values for rPFS using fixed effects and random effects models for Scenario 1

Value	Fixed Effects Model	Random Effects Model
DIC	[redacted]	[redacted]
Dbar	[redacted]	[redacted]
pD	[redacted]	[redacted]
gelman.diag	[redacted]	[redacted]

Abbreviations: DIC: Deviance information criteria; Dbar: Posterior mean of the deviance; pD: Effective number of parameters.

NMA results

The results of NMA are presented in terms of 'point estimates' (median of posterior) for the comparative treatment effects, along with the 95% credible intervals (95% CrI). Table 8 and Table 9 show the results of various scenarios. Figure 3 to Figure 8 show the forest plots for scenario 1 for OS and rPFS.

Table 8: NMA results – OS

Scenario	Model	HR – ^{177}Lu vipivotide tetraxetan vs		
		Cabazitaxel	ARPi	Mitoxantrone/ placebo
1	FE	[redacted]	[redacted]	[redacted]
	RE with non-informative priors	[redacted]	[redacted]	[redacted]
	RE with 10x truncation	[redacted]	[redacted]	[redacted]
	RE with 5x truncation	[redacted]	[redacted]	[redacted]
2	FE	[redacted]	[redacted]	[redacted]

	RE with non-informative priors	[redacted]	[redacted]	[redacted]
	RE with 10x truncation	[redacted]	[redacted]	[redacted]
	RE with 5x truncation	[redacted]	[redacted]	[redacted]
3	FE	[redacted]	[redacted]	[redacted]
	RE with non-informative priors	[redacted]	[redacted]	[redacted]
	RE with 10x truncation	[redacted]	[redacted]	[redacted]
	RE with 5x truncation	[redacted]	[redacted]	[redacted]
4	FE	[redacted]	[redacted]	[redacted]
	RE with non-informative priors	[redacted]	[redacted]	[redacted]
	RE with 10x truncation	[redacted]	[redacted]	[redacted]
	RE with 5x truncation	[redacted]	[redacted]	[redacted]

Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; FE: fixed effects; HR: hazard ratio; OS: overall survival; RE: random effects.

Table 9: NMA results – rPFS

Scenario	Model	HR (95% CrI) – ^{177}Lu vipivotide tetraxetan vs		
		Cabazitaxel	ARPi	Mitoxantrone/ placebo
1	FE	[redacted]	[redacted]	[redacted]
	RE with non-informative priors	[redacted]	[redacted]	[redacted]
	RE with 10x truncation	[redacted]	[redacted]	[redacted]
	RE with 5x truncation	[redacted]	[redacted]	[redacted]
2	FE	[redacted]	[redacted]	[redacted]
	RE with non-informative priors	[redacted]	[redacted]	[redacted]

	RE with 10x truncation	[redacted]	[redacted]	[redacted]
	RE with 5x truncation	[redacted]	[redacted]	[redacted]
3	FE	[redacted]	[redacted]	[redacted]
	RE with non-informative priors	[redacted]	[redacted]	[redacted]
	RE with 10x truncation	[redacted]	[redacted]	[redacted]
	RE with 5x truncation	[redacted]	[redacted]	[redacted]

Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; FE: fixed effects; HR: hazard ratio; RE: random effects; rPFS: radiographic progression-free survival.

Figure 3: NMA results – OS (fixed-effects model) – Scenario 1

Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival.

Figure 4: NMA results – OS (random-effects model – 5x truncation) –Scenario 1

Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival.

Figure 5: NMA results – OS (random-effects model – non-informative prior) –Scenario 1

Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival.

Figure 6: NMA results – rPFS (fixed-effects model) – Scenario 1

Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; HR: hazard ratio; NMA: network meta-analysis; rPFS: radiographic progression-free survival.

Figure 7: NMA results – rPFS (random-effects model – 5x truncation) – Scenario 1

Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; HR: hazard ratio; NMA: network meta-analysis; rPFS: radiographic progression-free survival.

Figure 8: NMA results – rPFS (random-effects model – non-informative prior) –Scenario 1

Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; HR: hazard ratio; NMA: network meta-analysis; rPFS: radiographic progression-free survival.

Appendix 2: RWE propensity score weighting analysis

In order to address uncertainty in the naïve comparison of VISION data for ^{177}Lu vipivotide tetraxetan to the real-world evidence (RWE) data for patients undergoing cabazitaxel treatment, a propensity score weighting (PSW) analysis was explored in an attempt to control for population differences between these two studies. Propensity score weighting aims to reduce bias by adjusting for the observed differences between the two cohorts by increasing or decreasing the relative contributions of individual patients such that, after weighting, the two cohorts have similar average baseline characteristics. This analysis included all patients treated with cabazitaxel in the RWE dataset who had also received a prior taxane and ARPI, in line with the eligibility criteria for VISION) (n=[redacted]).

Methods

Patients in the RWE and VISION cohorts were weighted following the methods of Rosenbaum and Rubin, in which propensity scores were estimated as the conditional probability of patients in the RWE cabazitaxel cohort being assigned to the VISION cohort, given a set of variables.[19] Variables available in both datasets included:

- Median age
- ECOG score 0 or 1
- Median time since diagnosis
- Gleason score (8–10, unknown)
- Previous prostatectomy
- Previous ARPI (such as abiraterone acetate and enzalutamide)
- One previous regimen of taxanes (e.g., paclitaxel and docetaxel)
- Two previous regimens of taxanes (e.g., paclitaxel and docetaxel)
- Previous cabazitaxel

Selection of variables for the propensity score analysis was performed via univariable linear regression of each variable, as being associated with cohort assignment. Variables selected for the propensity score model included: median age, ECOG score, median time since diagnosis, Gleason score, and receipt of previous prostatectomy. Propensity scores were estimated via a logistic regression comprising the selected variables. Inverse odds of sampling weights were applied for weight estimation, according to the following formula:[20]

$$Weight(VISION = 0) = \frac{PS(RWE = 1)}{1 - PS(RWE = 1)} \times \frac{P(RWE\ cohort)}{P(VISION\ cohort)}$$

Results

Baseline characteristics

Patient baseline characteristics before and after weighting in the propensity score analysis of VISION ^{177}Lu vipivotide tetraxetan versus the RWE cabazitaxel cohort are presented in Table 10. Before weighting, baseline characteristics were generally well-balanced across the treatment arms. After weighting, differences across the majority of characteristics (dichotomous variables ECOG stage, Gleason score and previous prostatectomy) were small and non-significant, indicating that the treatment arms were broadly well-balanced.

Table 10: Baseline characteristics before and after weighting – ^{177}Lu vipivotide tetraxetan versus RWE cabazitaxel

Characteristic	VISION (FAS) (N=831)	*Before PSW*			*After PSW*		
		RWE cabazitaxel cohort (N=[redacted])	Difference*	*P*	RWE cabazitaxel cohort (N_{eff}=[redacted])	Difference*	*P*
Median age (range), years	74 (67, 80)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG = 1, n (%)	769 (93%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median time from diagnosis (range), days	873 (94, 2,460)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gleason score 8-10, n (%)	494 (59%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous prostatectomy, n (%)	288 (35%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

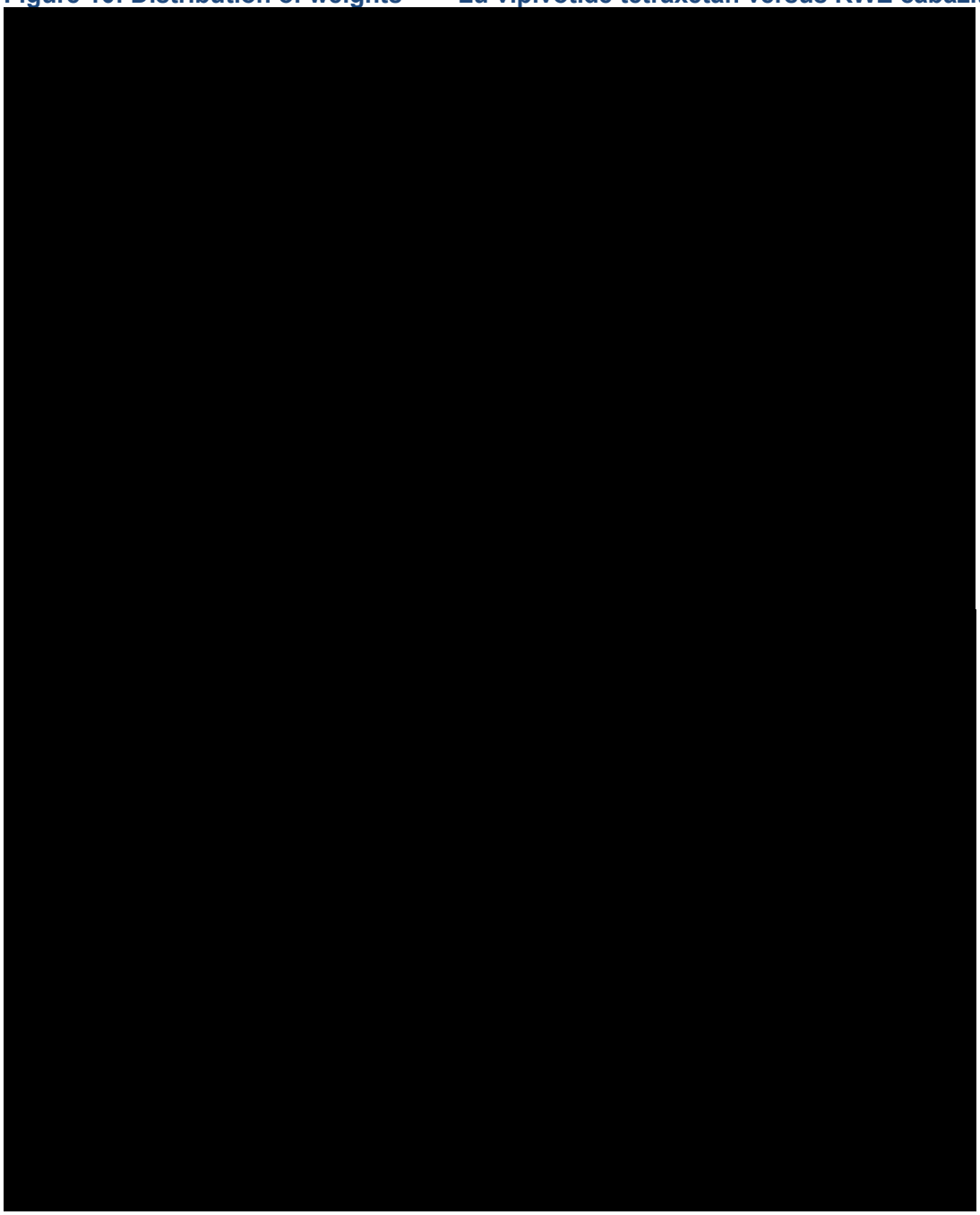
ECOG status as reported at the point of cabazitaxel initiation.
* p-value of the differences between VISION and corresponding pre and post PSW RWE variables were estimated with an F-test with Satterthwaite approximation for continuous variables, and a Pearson's chi-square with Rao & Scott adjustment for categorical ones.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; PSW: propensity score weighting; RWE: real-world evidence.
Source: Sartor et al. 2021[13]

The propensity score density histogram for ^{177}Lu vipivotide tetraxetan from VISION (VISION = 1) versus the RWE cabazitaxel cohort (VISION = 0) is presented in Figure 9, showing significant overlap between the treatment arms. Similarly, distribution of weights presented in Figure 10 demonstrate a lack of extreme weights. No patients in the RWE cabazitaxel cohort were assigned zero weight.

Figure 9: Propensity score density plot – ^{177}Lu vipivotide tetraxetan versus RWE cabazitaxel

Abbreviations: RWE: real-world evidence.

Figure 10: Distribution of weights – ^{177}Lu vipivotide tetraxetan versus RWE cabazitaxel



Abbreviations: RWE: real-world evidence.

Overall survival

Median OS for the RWE cabazitaxel cohort was similar before and after weighting. Kaplan–Meier curves for OS before and after weighting are presented in Figure 11, 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 11: OS for patients in the RWE cabazitaxel cohort, before and after PSW

	n	Events	Median	95% CI
Before PSW	[redacted]	[redacted]	[redacted]	[redacted]
After PSW	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS: overall survival; RWE: real-world evidence; PSW: propensity score weighting.

Figure 11: OS for patients in the RWE cabazitaxel cohort, before and after PSW

a) Before weighting

b) After weighting

Abbreviations: OS: overall survival; RWE: real-world evidence; PSW: propensity score weighting.

Appendix 3: Revised Company base case methodology

VISION EQ-5D analysis: updated progression definition

The progression variable has been updated to exclude uncertainty in progression with respect to the timing of EQ-5D values and progression visits. Only those EQ-5D observations where there is certainty as to whether the patient had progressed (or not) at that visit are included. The ADTTE data has been used in preference to information in the ADRS dataset for alignment with previous analysis.

The two categories used for the analysis were:

1. Progressed = no, HRQoL = Before or at time of progression assessment
2. Progressed = yes, HRQoL = After or at time of progression diagnosed

Observations within the following categories have been excluded from the analysis:

3. Progressed = no, HRQoL = After last progression assessment, patient may have progressed

4. Progressed = yes, HRQoL = In-between patient being diagnosed as not progressed and progressed, patient may not have progressed

5. Patients with no HRQoL assessment with progression data, or only 1 visit

Analysis of EQ-5D data in the VISION trial using UK value set

EQ-5D-5L utility scores in the VISION trial have been generated using the United Kingdom (UK) value set. Current guidance recommends the crosswalk from the EQ-5D-5L to the EQ-5D-3L.[21]

Descriptive statistics for EQ-5D utility values have been provided by planned treatment arm, visit, and for the pre- and post-progression (based on rPFS). Utility scores were lower for the post-progression period compared to the pre-progression period for both the ^{177}Lu vipivotide tetraxetan + SOC and SOC treatment arms. Further, values were higher for ^{177}Lu vipivotide tetraxetan + SOC compared with SOC in both pre-progression (post-baseline) and post-progression periods based on the descriptive statistics. Baseline utility values were lower for ^{177}Lu vipivotide tetraxetan + SOC compared to SOC.

Table 12: Descriptive statistics for EQ-5D Utility based on UK value set

State	EQ-5D Utility Value, Mean (SD) n		
	All treatments	SOC	^{177}Lu vipivotide tetraxetan + SOC
Pre-progression (excluding baseline)	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]
Cycle			
Baseline	[redacted]	[redacted]	[redacted]
Cycle 1	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]

Cycle 15	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]
End to treatment	[redacted]	[redacted]	[redacted]

Note: descriptive statistics have been created according to a pre-specified analysis plan. Baseline data relates to screening or cycle 1 day 1 data where screening data was not available. Patients may contribute more than one value to the pre and post progression periods. Cycle 1 data relates to data that is post baseline, i.e. where baseline was at screening, and the next EQ-5D data was at cycle 1.
Abbreviations: SD: standard deviation; SOC Standard of care.

Descriptive statistics stratified by ARPI at baseline indicated similar conclusions to those for the overall population, with pre-progression utilities higher than post-progression utilities, and those for patients in the ^{177}Lu vipivotide tetraxetan + SOC treatment arm being higher than the SOC treatment arm.

Table 13: Descriptive statistics for EQ-5D Utility based on UK value set for patients not receiving concomitant ARPI at baseline

State	EQ-5D Utility Value, Mean (SD) n		
	All treatments	SOC	^{177}Lu vipivotide tetraxetan + SOC
Pre-progression (excluding baseline)	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]
Cycle			
Baseline	[redacted]	[redacted]	[redacted]
Cycle 1	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]
End to treatment	[redacted]	[redacted]	[redacted]

Note: descriptive statistics have been created according to a pre-specified analysis plan. Baseline data relates to screening or cycle 1 day 1 data where screening data was not available. Patients may contribute more than one value to the pre and post progression periods. Cycle 1 data relates to data that is post baseline, i.e. where baseline was at screening, and the next EQ-5D data was at cycle 1.
Abbreviations: SD: standard deviation; SOC Standard of care.

Table 14: Descriptive statistics for EQ-5D Utility based on UK value set for patients receiving concomitant ARPI at baseline

State	EQ-5D Utility Value, Mean (SD) n		
	All treatments	SOC	^{177}Lu vipivotide tetraxetan + SOC
Pre-progression (excluding baseline)	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]
Cycle			
Baseline	[redacted]	[redacted]	[redacted]
Cycle 1	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]
End to treatment	[redacted]	[redacted]	[redacted]

Note: descriptive statistics have been created according to a pre-specified analysis plan. Baseline data relates to screening or cycle 1 day 1 data where screening data was not available. Patients may contribute more than one value to the pre and post progression periods. Cycle 1 data relates to data that is post baseline, i.e. where baseline was at screening, and the next EQ-5D data was at cycle 1.
Abbreviations: SD: standard deviation; SOC Standard of care.

The results of the mixed model analysis, which considers the repeated measures for patients within the VISION trial, also indicated that utility scores were lower for the post-progression period compared to the pre-progression (post-baseline) period for both treatment arms. There

was statistically significant evidence that the difference between the ^{177}Lu vipivotide tetraxetan + SOC and SOC treatment arms differed by health state, after adjusting for age, baseline utility and ECOG status.

Table 15: Summary of Utility Values from Mixed Model Analysis of VISION Data (Marginal Means by Health State and Planned Treatment at Baseline) based on the UK value set

State	Utility Value	
	Mean (SE)	95% CI
Pre-progression		
^{177}Lu vipivotide tetraxetan + SOC	[redacted]	[redacted]
SOC	[redacted]	[redacted]
Post-progression		
^{177}Lu vipivotide tetraxetan + SOC	[redacted]	[redacted]
SOC	[redacted]	[redacted]

A generalized linear mixed model has been fitted to the data using xtmixed in Stata was performed according to a pre specified analysis plan, with utility index postbaseline as the dependent variable. The following fixed effects were initially considered: planned treatment, time of visit (since randomization), age, baseline utility, baseline Eastern Cooperative Oncology Group (ECOG) status, androgen receptor pathway inhibitor (ARPI) and an interaction term between planned treatment and health state. Results based on marginal means from a mixed model reduced using stepwise regression included fixed effects for planned treatment and time of visit (since randomization). Covariates included in the model included baseline utility scores, ECOG status and an interaction term between planned treatment and health state.

Abbreviations: CI: confidence interval; SD: standard deviation; SOC Standard of care.

A further simplified model was run which did not consider planned treatment, the results are shown in Table 16.

Table 16: Summary of Utility Values from Mixed Model Analysis of VISION Data (Marginal Means by health state) using UK value set

State	Utility Value	
	Mean (SE)	95% CI
Pre-progression	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]

A generalized linear mixed model has been fitted to the data using xtmixed in Stata was performed according to a pre specified analysis plan, with utility index postbaseline as the dependent variable. Results based on marginal means from a mixed model reduced using stepwise regression, which excluded planned treatment as a variable in the model. As such the model included a fixed effect for time of visit (since randomization). Covariates included in the model included baseline utility scores, ECOG status and health state.

Abbreviations: CI: confidence interval; SD: standard deviation; SOC Standard of care.

As there was statistically significant evidence of an interaction between treatment and health state in the mixed model, the results based on the model which included health state and treatment interaction shown in Table 15 is considered a more appropriate than the results based on a model which did not include treatment or the interaction between treatment and health state (shown in Table 16).

Technical engagement response form

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

Appendix 4: Revised Company base case results

The assumptions included in the revised company base case are described in full in Table 3.

Revised base case deterministic results

Table 17: Base-case results at ^{177}Lu vipivotide tetraxetan PAS price (deterministic)

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYGa	Inc. QALYs	ICER inc. (£/QALY)
177Lu vipivotide tetraxetan	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,158
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	133,574

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

Probabilistic sensitivity analyses

The PSA methodology is described in Section B.3.8.1 of the company submission. Revised probabilistic base case results are presented in Table 18 and are very similar to deterministic results.

Table 18: Base-case results at ^{177}Lu vipivotide tetraxetan PAS price (probabilistic)

Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER inc. (£/QALY)
^{177}Lu vipivotide tetraxetan vs. cabazitaxel					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	50,284
^{177}Lu vipivotide tetraxetan vs. SOC					
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]			
SOC	[redacted]	[redacted]	[redacted]	[redacted]	132,809

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

Figure 12 and Figure 13 present the cost-effectiveness planes for ^{177}Lu vipivotide tetraxetan (with a PAS discount applied) compared with cabazitaxel and SOC, respectively, which show that 100% of the 5,000 iterations were in the North-East quadrant. This means that ^{177}Lu vipivotide tetraxetan resulted in more QALYs and higher costs compared with cabazitaxel and SOC.

Figure 12: Scatter plot of probabilistic results on the cost-effectiveness plane for ^{177}Lu vipivotide tetraxetan at PAS price (^{177}Lu vipivotide tetraxetan vs. cabazitaxel)

Abbreviations: ^{177}Lu: Lutetium-177; PAS: patient access scheme; QALYs: quality-adjusted life years; PSA: probabilistic sensitivity analysis; SOC: standard of care.

Figure 13: Scatter plot of probabilistic results on the cost-effectiveness plane for ^{177}Lu vipivotide tetraxetan at PAS price (^{177}Lu vipivotide tetraxetan vs. SOC)

Abbreviations: 177Lu: Lutetium-177; PAS: patient access scheme; QALYs: quality-adjusted life years; PSA: probabilistic sensitivity analysis; SOC: standard of care.

Figure 14 and Figure 15 present the cost-effectiveness acceptability curves for ^{177}Lu vipivotide tetraxetan (with a PAS discount applied) compared with cabazitaxel and SOC, respectively. The cost-effectiveness acceptability curve shows that ^{177}Lu vipivotide tetraxetan has a [redacted]% and [redacted]% probability of being cost-effective compared with cabazitaxel and SOC at a willingness-to-pay threshold of £50,000 per QALY.

Figure 14: Cost-effectiveness acceptability curves for ^{177}Lu vipivotide tetraxetan at PAS price (^{177}Lu vipivotide tetraxetan vs. cabazitaxel)

Abbreviations: ^{177}Lu: Lutetium-177; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years SOC: standard of care.

Figure 15: Cost-effectiveness acceptability curves for ^{177}Lu vipivotide tetraxetan at PAS price(^{177}Lu vipivotide tetraxetan vs. SOC)

Abbreviations: 177Lu: Lutetium-177; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years SOC: standard of care.

Deterministic sensitivity analysis

The DSA methodology is described in Section B.3.8.2 of the company submission. Figure 16 and Figure 17 presents univariate sensitivity analysis results for ^{177}Lu vipivotide tetraxetan (with a PAS discount applied) versus cabazitaxel and SOC, respectively. The figures present the 10 parameters that had the largest impact on the ICER when they were increased or decreased (upper or lower bounds, respectively). To provide a summary of the most influential parameters.

Figure 16: Tornado plot (ICER) of deterministic sensitivity analysis for ^{177}Lu vipivotide tetraxetan at PAS price (^{177}Lu vipivotide tetraxetan vs. cabazitaxel)

Abbreviations: ^{177}Lu: Lutetium-177; PAS: patient access scheme; PSMA: prostate-specific membrane antigen; QALYs: quality-adjusted life years SOC: standard of care.

Figure 17: Tornado plot (ICER) of deterministic sensitivity analysis for ^{177}Lu vipivotide tetraxetan at PAS price (^{177}Lu vipivotide tetraxetan vs. SOC)

Abbreviations: ^{177}Lu: Lutetium-177; PAS: patient access scheme; PSMA: prostate-specific membrane antigen; QALYs: quality-adjusted life years SOC: standard of care.

Scenario analyses

All scenario analyses explored in the original Company submission have been rerun using revised base case inputs, as well as the additional exploratory scenarios exploring alternative OS assumptions.

Table 19: Results from scenario analyses for ^{177}Lu vipivotide tetraxetan versus comparators

#	Description	Cabazitaxel			SOC		
		Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. costs	Inc. QALYs	ICER (£/QALY)
Scenario analyses explored in original Company submission							
1	Exploring the use of the Stratified flexible Weibull (1 knot) model for extrapolation of rPFS	[redacted]	[redacted]	50,255	[redacted]	[redacted]	134,176
2	Impact of utilising interval imputation of missing data with flexible 2-knot Weibull model for the rPFS analysis in VISION	[redacted]	[redacted]	51,335	[redacted]	[redacted]	137,355
3	Impact of utilising the Gamma model for OS extrapolation	[redacted]	[redacted]	53,041	[redacted]	[redacted]	149,377
4	Impact of utilising the application of NMA HR to the ^{177}Lu vipivotide tetraxetan + SOC arm of VISION to inform OS	[redacted]	[redacted]	59,594	[redacted]	[redacted]	133,574
5	Impact of utilising IPCW adjustment with stratified flexible Weibull (2 knots) model to inform OS	[redacted]	[redacted]	46,016	[redacted]	[redacted]	142,719
6	Impact of applying SOC SSE rate to cabazitaxel treatment arm	[redacted]	[redacted]	50,158	NA	NA	NA
7	Impact of applying SOC therapeutic intervention use to the cabazitaxel treatment arm	[redacted]	[redacted]	50,158	NA	NA	NA
8	Impact of applying the overall pre-progressed health state utility value from VISION to the cabazitaxel treatment arm	[redacted]	[redacted]	53,050	NA	NA	NA
9	Impact of applying treatment-independent health state utility values	[redacted]	[redacted]	55,905	[redacted]	[redacted]	162,691
Exploratory scenarios conducted at technical engagement							
10	Fixed effects rPFS HRs excluding COU-301 trial	[redacted]	[redacted]	49,981	NA	NA	NA
11	Fixed effects rPFS HRs excluding AFFIRM trial	[redacted]	[redacted]	50,527	NA	NA	NA
12	Random effects rPFS full network HRs with 5x informative prior	[redacted]	[redacted]	50,681	NA	NA	NA
13	Random effects rPFS HRs with 5x informative prior excluding COU-301 trial	[redacted]	[redacted]	50,628	NA	NA	NA
14	Random effects rPFS HRs with 5x informative prior excluding AFFIRM trial	[redacted]	[redacted]	51,018	NA	NA	NA
15	Cabazitaxel OS based on the NMA and fixed effects full network HRs	[redacted]	[redacted]	59,594	NA	NA	NA

16	Cabazitaxel OS based on the NMA and fixed effects HRs excluding Sun2016	[redacted]	[redacted]	59,790	NA	NA	NA
17	Cabazitaxel OS based on the NMA and fixed effects HRs excluding Sun2016 and COU-301 trial	[redacted]	[redacted]	58,031	NA	NA	NA
18	Cabazitaxel OS based on the NMA and fixed effects HRs excluding Sun2016 and AFFIRM trial	[redacted]	[redacted]	64,475	NA	NA	NA
19	Cabazitaxel OS based on the NMA and random effects full network HRs with non-informative prior	[redacted]	[redacted]	65,593	NA	NA	NA
20	Cabazitaxel OS based on the NMA and random effects HRs with non-informative prior excluding Sun2016	[redacted]	[redacted]	67,340	NA	NA	NA
21	Cabazitaxel OS based on the NMA and random effects HRs with non-informative prior excluding Sun2016 and COU-301 trial	[redacted]	[redacted]	68,142	NA	NA	NA
22	Cabazitaxel OS based on the NMA and random effects HRs with non-informative prior excluding Sun2016 and AFFIRM trial	[redacted]	[redacted]	74,522	NA	NA	NA

Abbreviations: HR: hazard ratio; NMA: network meta-analysis; OS: overall survival; rPFS: radiographic progression-free survival; SOC: standard of care; SSE: symptomatic skeletal event.

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

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

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report in section 1.1. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

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

NICE National Institute for Health and Care Excellence

Deadline for comments by **5pm** on **11 August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

NICE National Institute for Health and Care Excellence

Part 1: Treating prostate-specific membrane antigen (PSMA)-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Amit Bahl
2. Name of organisation	University Hospitals Bristol & Weston Hospitals NHS Foundation Trust
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies? ☒ A specialist in the clinical evidence base for PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. What is the main aim of treatment for PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment is to maintain/improve quality of life and increase overall survival in the MCRPC stage.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Maintaining/improving quality of life and improving survival
10. In your view, is there an unmet need for patients and healthcare professionals in PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies?	Yes, this a significant unmet need both for patients and healthcare professionals caring for these patients as the only NICE approved option after 2 or more therapies in this setting would be to offer chemotherapy and there is a high proportion of patients in this setting who are either ineligible for chemotherapy or do not want to have chemotherapy as seen by the relative low numbers of Cabazitaxel chemotherapy use compared to the estimated numbers in this setting.
11. How is PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Current NHS treatment pathway based on NICE approved options in this setting would be to either offer Cabazitaxel chemotherapy or best supportive care. In a few cases if there is symptomatic bone only metastatic disease then Radium 223 is an option. This pathway of care is based on the NICE approved options and is generally followed by the professionals in England and based on availability and suitability there is the option of offering clinical trials. The proportion of patients receiving Cabazitaxel chemotherapy in this setting varies across the NHS and is reflective of the experience and perception of the relative benefits and risks of Cabazitaxel chemotherapy.

• What impact would the technology have on the current pathway of care?	The availability of Lu-PSMA treatment option would be a significant advance in the options available and as stated in answer to Q10, this is an unmet need for patients and healthcare professionals.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology of Radioligand therapy is in use in the NHS in several centres for treatment of neuroendocrine cancers. In prostate cancer treatment, this technology is not in current routine use apart from in some centres which have started the EAMS programme. Once approved by NICE this would be implemented in secondary care specialist oncology/nuclear medicine units to increase availability and accessibility for patients to avail this treatment if appropriate. Facilities for PSMA PET scan and nuclear medicine facility for treatment would be required.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I expect the technology to provide clinically meaningful benefits compared with current care both in terms of increased length of life and also and perhaps more importantly in improvements in health-related quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It is feasible that in future this technology would move earlier in the treatment paradigm of metastatic prostate cancer where it is potentially going to be even more effective. The PSMA positive metastatic disease should have similar benefits. PSMA negative metastatic disease would not be appropriate for this treatment. In my opinion the likelihood of benefit for patients who are unsuitable for taxanes and have PSMA positive disease should be on par with the benefits seen with

	LuPSMA in VISION and it is feasible that as these patients have not had multiple lines of therapy, they may have a better response.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Centres using this technology for treatment for neuro-endocrine treatments should be able to implement this by scaling up. Other centres will require development of Radioligand therapy service with nuclear medicine/molecular therapy assistance. Centres who have set-up EAMS for LuPSMA treatment will be able to upscale and also help in training and facilitating other centres to make this technology available and accessible across the NHS.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This will be based on NICE guidance to assess eligibility based on the criteria. Treatment would be given and continued based on efficacy and tolerability and for the set number of cycles of treatment approved.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	This treatment is given every 6 weeks in comparison with Cabazitaxel chemotherapy which is delivered every 3 weeks. Given the constraints across the chemotherapy departments in the NHS, this treatment will potentially reduce the demand for chemotherapy chair and facility time as this treatment will be delivered in either the nuclear medicine units or molecular therapy units.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	Radioligand therapy has a significant potential in changing outlook in MCRPC and hopefully in MHSPC in future. This innovative technology has increased optimism for patients in MCRPC setting who have limited options.

impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Feedback from patients who have had this treatment and also the data from the trials of this treatment show that treatment is well tolerated and overall has a beneficial effect on the patient's quality of life.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Overall the results from VISION trial can be extrapolated to the UK setting. In VISION trial the patients could have had two ARTA's but NICE approval is for only 1 ARTA, so it is likely that benefits of LuPSMA treatment in the setting of NHS could be potentially more than in the VISION trial.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA391 (Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel); TA412 (Radium-223 dichloride for	Cabazitaxel was approved by NICE based on the TROPIC trial. At the time of the TROPIC trial, there was no ARTA use pre-chemotherapy. Subsequently the use of ARTA has been approved pre-chemotherapy and are now almost routinely used pre-chemotherapy, therefore the Real World Evidence of Cabazitaxel use is more relevant as a comparator for LuPSMA treatment.

treating hormone-relapsed prostate cancer with bone metastases)?	In my opinion Radium 223 is not an appropriate comparator for LuPSMA treatment as Rad223 is only NICE approved for SYMPTOMATIC BONE ONLY METASTATIC disease. The proportion of patients with visceral/lymph nodal metastatic disease increases as the patients progress through various lines of MCRPC treatment and therefore the appropriate comparator for LuPSMA would be Cabazitaxel chemotherapy and not Radium-223.
23. How do data on real-world experience compare with the trial data?	RWE data from the EAMS scheme are not yet available.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	No

• lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Broadening of population to include people who are not medically suitable for taxanes	It is well known that trial inclusion criteria are very restrictive to enable the registration and licensing requirements. In clinical practice, the options for patients who are medically unsuitable for taxanes is very limited and therefore the option of LuPSMA would be important for this group of patients with limited options.
Issue 2: Exclusion of radium-223 as a comparator for people with bone metastases	In my opinion Radium 223 is not an appropriate comparator for LuPSMA treatment as Rad223 is NICE approved for SYMPTOMATIC BONE ONLY METASTATIC disease. The proportion of patients with visceral/lymph nodal metastatic disease increases as the patients progress through various lines of MCRPC treatment and therefore the appropriate comparator for LuPSMA would be Cabazitaxel chemotherapy and not Radium-223.

Clinical expert statement

Issue 3: Concerns regarding company's network meta-analysis **Should the real-world evidence be used for the OS estimate of cabzitaxel (company approach) or should the network meta-analysis (NMA) estimate be used?**	In my opinion, the Real World Evidence for Cabazitaxel should be used as it is akin to the current place and use of Cabazitaxel. In the TROPIC trial patients had not had ARTA's as they were not available at that time. Subsequently the use of ARTA has been approved pre-chemotherapy and are now almost routinely used pre-chemotherapy, therefore the Real World Evidence of Cabazitaxel use is more relevant as a comparator for LuPSMA treatment.
Issue 4: Concerns regarding OS estimates for cabazitaxel in the model • **Should the relative survival of ^{177}Lu vipivotide tetraxetan, cabazitaxel and SOC be based on the NMA or data from the VISION trial** • **Is the median survival in the real-world**	The overall survival for LuPSMA treatment should be from the VISION trial. The overall survival for Cabazitaxel should be from the Real world Evidence as per the explanation given in Issue 3. The ERG network meta-analysis is predominantly based on the CARD trial and there are several aspects of CARD trial which make this not a suitable basis for NMA. The main aspect being the inclusion criteria was for patients progressing within one year of the first ARTA. As we know and compliment NICE on the decision not to offer sequential ARTA's in MCRPC, the CARD trial was to show and prove to the rest of the world the futility of sequential ARTA's in this setting. However, this is not a relevant population for assessing the survival benefit for Cabazitaxel which as we know is more reflected in the Real World Evidence.

Clinical expert statement

evidence analysis of cabazitazel as expected?	
Issue 5: Use of pre-progression utility values for cabazitaxel that are equivalent to standard of care and use of post-progression utility values for cabazitaxel that are lower than for both standard of care and ^{177}Lu vipivotide tetraxetan • **Should utility be dependence on health states or treatment dependant?**	This is acceptable as the progression post-Cabazitaxel not only has a detriment to utility values due to progression but also due to the side-effects of Cabazitaxel and some of these side-effects can be long lasting.
Issue 6: Exclusion of standard of care costs from the ^{177}Lu vipivotide tetraxetan treatment and cabazitaxel treatment arms	It is feasible that SOC costs would be significantly less for LuPSMA in comparison to Cabazitaxel as LuPSMA has lesser side-effects and better efficacy than Cabazitaxel.

Issue 7: Costing of pre-medication and concomitant medications for cabazitaxel • **Are G-CSF medications expected to be used for 5 to 7 days only or for 14 days of every 21-day cabazitaxel cycle?**	When Cabazitaxel was implemented the use of GCSF support was with pegylated GCSF which essentially provides cover for 3 weeks (21 days). My personal experience has been predominantly with use of pegylated GCSF with Cabazitaxel. The appropriate conversion to daily GCSF would be to use it for 14 days based on the ASCO guidelines of GCSF support. Ideally daily GCSF should be used for 14 days and lower usage is likely to increase the potential risk of neutropaenia and neutropaenic sepsis. More importantly, the reduced use of daily GCSF will increase the disproportionality of reduced use of Cabazitaxel compared to the eligible numbers for Cabazitaxel as the potential risks will be higher.
Issue 8: Estimation of symptomatic skeletal event (SSE) incidence	CARD trial was limited to patients who had progressed within 1 year of first ARTA therapy, so was potentially biased in favour of Cabazitaxel in comparison to the second ARTA. The VISION trial included patients without restriction on time to progression on ARPI, therefore likely that results would show better outcomes for Lutetium PSMA than Cabazitaxel. CARD trial was second line therapy in MCRPC whilst the VISION trial was after at least 2 lines of therapy and some patients had 3 or more lines of therapy. The potential to have increased SSE's is there after progression on multiple lines of therapy.
Is the life expectancy and extension to overall survival criteria of end-of-life met in people for whom standard care is the only	Yes it is met.

comparator (including those who are ineligible for or are not medically suitable for taxanes)?	
Are there any important issues that have been missed in ERG report?	No.

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

LuPSMA is a targeted treatment with a novel mechanism of action with a favourable safet-benefit profile.
LuPSMA treatment addresses an area of unmet need for MCRPC patients and Healthcare professionals.
Cabazitaxel is the appropriate comparator for LuPSMA
Radium-223 is not an appropriate comparator for LuPSMA as Radium-223 is only for patients with symptomatic bone metastases.
Overall survival data for LuPSMA from VISION trial and the Overall Survival data from Real World Evidence of Cabazitaxel would be the right comparators for assessment of relative survival benefit

Thank you for your time.

Your privacy

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

☒ **Please tick this box** if you would like to receive information about other NICE topics.

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

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

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

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Clinical expert statement

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

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Part 1: Treating prostate-specific membrane antigen (PSMA)-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr. Amarnath Challapalli
2. Name of organisation	University Hospitals Bristol & Weston Hospitals NHS Foundation Trust
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies? ☒ A specialist in the clinical evidence base for PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or	N/A

Clinical expert statement

indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment is to achieve control of the disease, delay progression and thus increase survival and improve quality of life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Optimising quality of life and improving survival
10. In your view, is there an unmet need for patients and healthcare professionals in PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies?	Patients with hormone relapsed metastatic prostate cancer after 2 therapies would have either exhausted all the standard options of treatment or have the option of 2nd line chemotherapy. Not all patients will be eligible for chemotherapy and hence there is an unmet need for these patients.
11. How is PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Patients with hormone relapsed metastatic prostate cancer after 2 therapies would have either exhausted all the standard options of treatment or have the option of 2nd line chemotherapy. There are no standard guidelines for defining chemotherapy ineligibility. The availability of Lu-PSMA will provide another option of treatment for these patients with unmet need.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This is a new modality of treatment using the concept of radioligand therapy (RLT). RLT is already being used in neuro-endocrine cancers, but is new to prostate cancer.

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The VISION trial has shown this to be a tolerable treatment with the side-effect profile being similar to the placebo arm. The treatment should be used in the secondary care setting with availability of qualified personnel and specialist equipment. Availability of companion diagnostics, training of personnel and special equipment is important.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I believe that this treatment will be a game changer as it is a targeted treatment with a very favourable tolerability profile. In view of this, it will increase survival and quality of life as evidenced by the VISION trial.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The therapy may be less effective in patients whose disease is not PSMA positive.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology will need training and infrastructure. It will be easier for centres which are already using this treatment for neuro-endocrine treatments.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients who are about to be commenced on this will need to have PSMA positive disease. As with any treatment for mCRPC, the rules as per Prostate cancer working group criteria will be used to determine the stop rules.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The technology is a targeted therapy and will be a game changer. It is a new mechanism of action utilising the principle of theranostics. If available it will give an additional option of treatment for patients with PSMA positive mCRPC in a stage of disease where there is an unmet need.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In the VISION trial, there was no substantial difference in the rates of AEs between the active arm and the placebo arm, suggesting that this treatment is well tolerated. This will have a positive impact on patient's quality of life.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	The VISION trial population reflects the UK population.

Clinical expert statement

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA391 (Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel); TA412 (Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases)?	Cabazitaxel was approved by NICE based on the TROPIC trial. At the time this trial was approved, the ARTA's were only available for use post-chemotherapy. Since then the therapeutic landscape has changed with ARTA's predominantly being used in the proe-chemotherapy setting. Therefore, the real world evidence (RWE) data of Cabazitaxel (subsequently published) should be considered. The RWE population will be a true reflection of the current UK population.
23. How do data on real-world experience compare with the trial data?	In the UK the technology is currently available for clinical use as per the Early access scheme. Patients are about to go into this scheme. I have initiated the managed access programme in Bristol and 6 patients have been commenced on this. Our initial experience has been similar to the trial results.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	No.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Broadening of population to include people who are not medically suitable for taxanes	There are no guidelines to define taxane ineligibility. Any treatment which has shown benefit in the 2nd or 3rd line setting, if moved upfront into the treatment pathway, is expected to show a greater magnitude of benefit. This is reflected on the increased benefit of ARTAs (Enzalutamide) and chemotherapy (Docetaxel) which have shown increased benefit when used in the mHSPC setting compared with their use in the mCRPC setting.
Issue 2: Exclusion of radium-223 as a comparator for people with bone metastases	Radium 223 has been approved for mCRPC patients with skeletal metastases. The mechanism of action of Lutetium PSMA is different from that of Radium. Unlike Radium-223 which localises itself in the bone (calcimimetic), Lutetium-PSMA can target metastatic disease in the bone, nodes and other viscera. As patients progress through 3 lines of therapy, the proportion of patients with visceral disease increases (about 40-50%). These patients are not eligible for Radium-223. Therefore, I do not feel that Radium-223 should be a comparator for Lutetium-PSMA. As a part of the

	ERG, I have expressed this similar view.
Issue 3: Concerns regarding company's network meta-analysis **Should the real-world evidence be used for the OS estimate of cabzitaxel (company approach) or should the network meta-analysis (NMA) estimate be used?**	I feel that the estimates for the OS should be used from the real world evidence. Cabazitaxel was approved by NICE based on the TROPIC trial. At the time this trial was approved, the ARTA's were only available for use post-chemotherapy. Since then, the therapeutic landscape has changed with ARTA's predominantly used in the pre-chemotherapy setting. Therefore, the real world evidence (RWE) data of Cabazitaxel (subsequently published) should be considered. The RWE population will be a true reflection of the current UK population.
Issue 4: Concerns regarding OS estimates for cabazitaxel in the model • **Should the relative survival of ^{177}Lu vipivotide tetraxetan, cabazitaxel and SOC be based on the NMA or data from the VISION trial** • **Is the median**	As mentioned above – the OS estimates from the RWE for Cabazitaxel and the VISION trial data of Lu177 should be used.

survival in the real-world evidence analysis of cabazitazel as expected?	
Issue 5: Use of pre-progression utility values for cabazitaxel that are equivalent to standard of care and use of post-progression utility values for cabazitaxel that are lower than for both standard of care and ^{177}Lu vipivotide tetraxetan • **Should utility be dependence on health states or treatment dependant?**	Not my area of expertise.
Issue 6: Exclusion of standard of care costs from the ^{177}Lu vipivotide tetraxetan treatment and cabazitaxel	The standard of care costs should be in favour of Lu177 as it has lesser side-effects and better efficacy

treatment arms	
Issue 7: Costing of pre-medication and concomitant medications for cabazitaxel • **Are G-CSF medications expected to be used for 5 to 7 days only or for 14 days of every 21-day cabazitaxel cycle?**	There is wide variation in the use of G-CSF across the UK. The SPC of the G-CSF and the international ASCO guidelines mandates the use of G-CSF for 14 days. If the G-CSF is used for less than 7 days – there is potential for increased risk of neutropenic sepsis leading to admissions which will increase the cost of patient care having a huge impact on the ICER. Therefore, the G-CSF should be used for 14 days.
Issue 8: Estimation of symptomatic skeletal event (SSE) incidence	CARD trial was limited to patients progressing within 1 year of first ARPI so was likely to show a better outcome with Cabazitaxel in comparison to second ARPI. The VISION trial included patients without restriction on time to progression on ARPI, therefore likely that results would show better outcomes for Lutetium PSMA than Cabazitaxel. Moreover, CARD was second line therapy in MCRPC. VISION included more advanced patients with multiple lines of prior therapy; therefore VISION trial patients are likely to have more SSE's.
Is the life expectancy and extension to overall survival criteria of end-of-life met in people for whom standard care is the only	Yes it is met.

Clinical expert statement

comparator (including those who are ineligible for or are not medically suitable for taxanes)?	
Are there any important issues that have been missed in ERG report?	No.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Lutetium PSMA is a targeted treatment with a novel mechanism of action with a very favourable side-effect profile.
Lutetium PSMA could be an attractive option of treatment in group of mCRPC patients with an unmet need.
Radium-223 is not a valid comparator for Lutetium PSMA as Ra-223 is only for patients with bone metastases.
Survival estimates from the Real World Evidence of Cabazitaxel are appropriate bench mark for ICER calculations
Click or tap here to enter text.

Thank you for your time.

Your privacy

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

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

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies or caring for a patient with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report in section 1.1 and 1.3 to 1.5.

A patient perspective could help either:

Patient expert statement

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Patient expert statement

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **11 August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Patient expert statement

Part 1: Living with this condition or caring for a patient with prostate-specific membrane antigen (PSMA)-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies

Table 1 About you, PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☐ A patient with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission

Patient expert statement

	☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies? **If you are a carer (for someone with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies	

(for example, how ^{177}Lu vipivotide tetraxetan is given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of ^{177}Lu vipivotide tetraxetan over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ^{177}Lu vipivotide tetraxetan help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of ^{177}Lu vipivotide tetraxetan over current treatments on the NHS please describe these. For example, are there any risks with ^{177}Lu vipivotide tetraxetan? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from ^{177}Lu vipivotide tetraxetan or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	

dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies and ^{177}Lu vipivotide tetraxetan? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Issue 1: Broadening of population to include people who are not medically suitable for taxanes	The evidence that has been presented is specifically related to patients who have already been treated with taxanes. It has been well established at other NICE appraisals that there are many patients who are medically unsuitable for taxanes and currently these people would be excluded from a potentially very valuable treatment with Lutetium^{177} were this to gain approval by the Committee. As a patient organisation we have always been very positive in that we believe at treatments should be made available to <u>all</u> appropriate patients - This could even be seen as a potential problem with equality issues. Lutetium^{177}therapy could be of great benefit in all patients who have already been heavily pre-treated with other therapies. Whilst no evidence has been presented to support the use of Lutetium^{177} in patients who have not had taxanes previously, equally there is no evidence presented that it would <u>not</u> be of benefit in this group. There is therefore a conundrum here but for the sake of those patients who are unable or unsuitable to have taxanes at this stage of their disease, we sincerely hope that some form of compromise may be possible.

Patient expert statement

	In order to collect data in this taxane unsuitable group, perhaps it would be possible somehow for the treatment to be made available (?via the cancer drugs fund) For a limited period of time to gain both further data in this group of patients and also to allow adequate treatment in this group?
Issue 2: Exclusion of radium-223 as a comparator for people with bone metastases	Since Radium 223 it is only of benefit in patients with metastases exclusively in bone rather than in both bone and soft tissue (as is the case with Lutetium^{177}), It could be argued that this is not a direct comparator. However whilst taxanes may be effective in metastases in both bone and soft tissue, this is a very different technology to the normal mode of therapy using Lutetium^{177} And thus could be also argued is not I'm exact comparator either. Give him the choice of all three therapies one wonders which the patients would choose. Given that treatments could have equal efficacy, they would undoubtedly choose that therapy with the least side effects.
Issue 3: Concerns regarding company's network meta-analysis	
Issue 4: Concerns regarding OS estimates for cabazitaxel in the model	
Issue 5: Use of pre-progression utility values for cabazitaxel that are equivalent to standard of care and use of post-progression utility values for cabazitaxel	

Patient expert statement

that are lower than for both standard of care and ^{177}Lu vipivotide tetraxetan	
Issue 6: Exclusion of standard of care costs from the ^{177}Lu vipivotide tetraxetan treatment and cabazitaxel treatment arms	
Issue 7: Costing of pre-medication and concomitant medications for cabazitaxel	
Issue 8: Estimation of symptomatic skeletal event (SSE) incidence	
Are there any important issues that have been missed in ERG report?	A number of important facts were apparent during the online technical engagement discussion: • it was clearly evident that the side effect profile of Lutetium^{177} was very acceptable to the patient expert who had received the treatment. Indeed it was commented by one medical expert at in the placebo-controlled trial that it was almost impossible to tell from reports of subjective side effects which patient was on an active treatment and which patient was on placebo. There were, however, differences when blood counts etc were examined. • It was stated by one medical expert that visceral metastases tend to produce worse outcomes for patients than those who had solely bone metastases. This could be a strong argument for the use of a therapy from the outset natural is effective in both bone and visceral metastases rather than Radium^{223} which is effective

Patient expert statement

	in bone metastasis only. A significant number of patients with bone metastases also later develop visceral metastases in addition. • Quality of life issues - both physiological and psychological - are of paramount importance to patients. Those that have already had taxane chemotherapy may well question why further treatment with a similar drug is likely to be of benefit, particularly if they have experienced significant side effects with previous treatments. I would suggest that they would opt for a treatment using a different technology and one which potentially has a low side effect profiled

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies or caring for a patient with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report in section 1.1 and 1.3 to 1.5.

A patient perspective could help either:

Patient expert statement

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

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Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Patient expert statement

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **11 August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Patient expert statement

Part 1: Living with this condition or caring for a patient with prostate-specific membrane antigen (PSMA)-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies

Table 1 About you, PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies, current treatments and equality

1. Your name	Peter Isard
2. Are you (please tick all that apply)	X A patient with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Tackle Prostate Cancer
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) X Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission

Patient expert statement

	☐ I agree with it and **do not wish to** complete this statement X I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	X I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies? **If you are a carer (for someone with PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies) please share your experience of caring for them**	I was diagnosed with metastatic prostate cancer in January 2017; my PSA was over 200 and my gleason score was 9. Since that time, I have been treated with docetaxel and Olaparib, on top of hormone therapy. The efficacy of docetaxel was shortlived; my PSA bottomed at 0.08 in September, but was back at 9 by the end of January 2018. I was given 18 months to live. I began a course of treatment with Olaparib in June 2018 and that went on for just over three years until August 2021 when it became obvious, through tumour growth and a rising PSA, that the drug was no longer effective. In November 2021, I began a course of treatment using Lutetium 177. Between November 2021 and May 2022, I had four rounds of treatment; it was decided to cease treatment at the end of May. The impact of docetaxel and hormone therapy is well documented and there is little that I can add. With Olaparib and Lutetium 177, I suffered no side effects with the former and only some fatigue four weeks after each dose with the latter: this coincided with low blood count. In contrast with docetaxel, neither Olaparib nor Lutetium 177 affected my ability to lead an active life, which included sport three times a week as well as a couple of gym sessions.
7a. What do you think of the current treatments and care available for PSMA-positive hormone-relapsed	My understanding is that the NHS offers just docetaxel and abiraterone/enzalutamide, on top of hormone therapy, as the first two lines of

metastatic prostate cancer after 2 or more therapies on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	treatment. While both are effective, neither has the precision of Lutetium, which is particularly efficacious if there is a small volume of disease. Once the benefits of docetaxel and abiraterone/enzalutamide have been exhausted, the only options remain radium 223, which can treat only bone metastases not those in the lymph nodes, and cabazitaxel, which many patients are too ill to tolerate. Lutetium could fill a gap in the arsenal against prostate cancer. For me, Radium 223 has yet to be an option as I have had no bone metastases, except at the outset.
8. If there are disadvantages for patients of current NHS treatments for PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies (for example, how ^{177}Lu vipivotide tetraxetan is given or taken, side effects of treatment, and any others) please describe these	There is no NHS treatment after abiraterone/enzalutamide that targets lesions in the lymphatic system
9a. If there are advantages of ^{177}Lu vipivotide tetraxetan over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ^{177}Lu vipivotide tetraxetan help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Provided the risks above are managed, the day-to-day side effect profile of Lutetium is minimal, in my experience. That means the quality of life while on the treatment is very high; I was able to work and exercise while undergoing treatment without any issue barring some fatigue a month after each dosage. Additionally, the regime is easy to follow: a day for the treatment itself, a blood test (at my local GP surgery) a month after the administration of each infusion and perhaps a scan; no daily routine that needs to be adhered to. The ability to lead a full life is the single biggest advantage of the treatment Yes, because it is able to attack tumours that are in lymph nodes
10. If there are disadvantages of ^{177}Lu vipivotide tetraxetan over current treatments on the NHS please describe these. For example, are there any risks with ^{177}Lu vipivotide	The unseen side effects of Lutetium 177 are damage to the kidneys and damage to bone marrow. There comes a point, as in my case, when it is decided that the risk bone marrow is too great to carry on with the treatment. The initial day to day disadvantage of the treatment is that the patient is radioactive for a period of around

tetraxetan? If you are concerned about any potential side effects you have heard about, please describe them and explain why	5 days and must be careful about his/her contacts in that period.
11. Are there any groups of patients who might benefit more from ^{177}Lu vipivotide tetraxetan or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Assuming the expression of PSMA, younger, fitter patients with low levels of disease would benefit most from Lutetium 177. Too high a volume of disease undermines the benefit of the treatment's ability to target tumours as it would require too powerful doses of radiation. Those with kidney vulnerability might not be suitable for the treatment
12. Are there any potential equality issues that should be taken into account when considering PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies and ^{177}Lu vipivotide tetraxetan? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	

Patient expert statement

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

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Issue 1: Broadening of population to include people who are not medically suitable for taxanes	We consider patient perspectives may particularly help to address this issue My understanding is that the efficacy of Lutetium 177 – assuming PSMA response – is highly dependent on the volume of disease that is being addressed. The higher the volume of disease, the greater the dosage and the lower the precision. Lutetium 177 could, therefore, be effective for those who cannot tolerate taxanes, provided they did not have too high a volume of disease. As an aside, it seems to me that there is a shortage of options in the current treatment regime for those patients with metastatic disease found only in a limited number of areas.
Issue 2: Exclusion of radium-223 as a comparator for people with bone metastases	

Patient expert statement

Issue 3: Concerns regarding company's network meta-analysis	
Issue 4: Concerns regarding OS estimates for cabazitaxel in the model	
Issue 5: Use of pre-progression utility values for cabazitaxel that are equivalent to standard of care and use of post-progression utility values for cabazitaxel that are lower than for both standard of care and ^{177}Lu vipivotide tetraxetan	
Issue 6: Exclusion of standard of care costs from the ^{177}Lu vipivotide tetraxetan treatment and cabazitaxel treatment arms	
Issue 7: Costing of pre-medication and	

Patient expert statement

concomitant medications for cabazitaxel	
Issue 8: Estimation of symptomatic skeletal event (SSE) incidence	
Are there any important issues that have been missed in ERG report?	

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I have been able to lead a full and active life while on Lutetium 177
- The treatment regime is straightforward but flexible for the patient
- The precise nature of the treatment makes it very effective for patients with small amounts of disease
- Lutetium 177 fulfils an unmet need in the treatment of prostate cancer
- Click or tap here to enter text.

Thank you for your time.

Your privacy

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

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

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Technical engagement response form

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

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Bayer plc
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Current Situation** • Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops. • Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.coresta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. • It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. **Past Situation** In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by Nomad Bioscience GmbH from Bayer in 2012.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Broadening of population to include people who are not medically suitable for taxanes	No	The company submission utilises data from the VISION trial to derive the cost-effectiveness in the broader population of patients who are not suitable for taxanes. However, the VISION trial enrolled patients who were previously treated with taxanes, hence the evidence coming from VISION is not suitable to inform the cost-effectiveness of ^{177}Lu vipivotide tetraxetan in a population that would not be medically suitable for taxanes. Although an ongoing study (NCT04689828) may provide information about the clinical effectiveness of ^{177}Lu vipivotide tetraxetan compared with androgen receptor-directed therapy (ARDT) in patients with PMSA-positive mCRPC not previously treated with taxanes (except when treated in the adjuvant or neo-adjuvant setting more than 12 months previously), this represents a population which has not received taxanes previously and may not be representative of a population which is deemed to be medically unsuitable for taxanes.
Issue 2: Exclusion of radium-223 as a comparator for people with bone metastases	No	According to the final scope of this appraisal, radium-223 is a relevant comparator in patients with bone metastases. In UK practice, patients with bone metastases who do not have visceral metastases, would receive radium-223 in the post-ARPI and taxane setting and post-ARPI where docetaxel is contraindicated or unsuitable setting. Therefore, radium-223 should not be excluded as a comparator in this

		subpopulation. Without a comparison against radium-223, it is not possible to ascertain the cost-effectiveness of ^{177}Lu vipivotide tetraxetan in the subpopulation of patients with bone metastases. Any conclusions drawn from the cost-effectiveness comparison of ^{177}Lu vipivotide tetraxetan with other comparators in the full population should not be applied to the subpopulation of patients with bone metastases, and any such recommendations should be restricted to the population of patients without bone metastases in the post-ARPI and taxane setting.
Issue 3: Concerns regarding company's network meta-analysis	No	The EAG's NMA seems reasonable and evidence from TheraP should be included to maximise the set of information. ALSYMPCA should also be included in the NMA to facilitate an indirect comparison between ^{177}Lu vipivotide tetraxetan and radium-223 in addressing Issue 2.
Issue 4: Concerns regarding OS estimates for cabazitaxel in the model	No	In the absence of supporting RWE for ^{177}Lu vipivotide tetraxetan, the NMA should be used to derive the OS estimate for cabazitaxel, which preserves randomisation and eliminates any biases arising from baseline risk differences between the real world population and trial populations.
Issue 5: Use of pre-progression utility values for cabazitaxel that are equivalent to standard of care and use of post-progression utility values for cabazitaxel that are lower than for both standard of care and ^{177}Lu vipivotide tetraxetan	No	Treatment-independent utility values are the most reasonable approach when also accounting for AEs and SSEs disutilities separately. While patients on chemo may have lower utility, this is typically transient and associated with the adverse events of chemo. Modelling an artificially lower utility value for cabazitaxel on top of the disutilities associated with AEs and SSEs would be double-counting and overestimating the potential negative impact of chemo. Alternatively, TheraP provides EORTC QLQ-C30 data for both treatment arms, which could be mapped to EQ-5D to estimate any utility difference between the two treatments.
Issue 6: Exclusion of standard of care costs from the ^{177}Lu vipivotide tetraxetan treatment and cabazitaxel treatment arms	No	Concomitant treatments should reflect data from VISION. Excluding concomitant treatments in the intervention arm but not in the comparator arms would underestimate incremental costs.

Issue 7: Costing of pre-medication and concomitant medications for cabazitaxel	Yes	Clinical guidelines on the use of G-CSF for chemotherapy support recommend its use as a one-off prophylaxis course for 5 to 7 days; chemotherapy patients should not routinely be prescribed prophylactic G-CSF after their first cycle of chemotherapy.[1]
Issue 8: Estimation of symptomatic skeletal event (SSE) incidence		In VISION, time to first SSE was defined as the time (in months) from the date of randomization to first new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death due to any cause, whichever occurred first. In VISION, most of the events that defined an SSE were death events. Out of 256 events (66.5%) in the 177Lu-PSMA-617 arm and 127 events (70%) in the BSC arm, only 60 events (15.6%) and 34 (17.3%), respectively were non-death events. Therefore, the difference in HR for SSE is mainly driven by the difference in OS between the arms rather than other events outlined in the definition of SSE. In this context, the ERG suggested approach seems reasonable.

[1] Northern Cancer Alliance guideline - https://northerncanceralliance.nhs.uk/wp-content/uploads/2018/11/GCSF-Guidelines-Northern-Cancer-Alliance-January-2018-v1.5.pdf

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Cost of companion diagnostics	Section 2.2		The cost of companion diagnostic for identifying patients as PSMA-positive based on a PSMA-PET scan using a gallium-68 tracer (as in VISION) has not been included in the cost-effectiveness analysis. As these scans are costly and not widely available, this could significantly underestimate the ICER against other comparators which do not require patients to be confirmed as PSMA-positive. We consider this issue to be of high importance for this appraisals, however, it does not seem to have been addressed in the company submission or the EAG report.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

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Sensitivity analyses around revised base case
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Technical engagement response form

NICE National Institute for Health and Care Excellence

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	Sabina Dizdarevic
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	British Nuclear Medicine Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Broadening of population to include people who are not medically suitable for taxanes	Yes	Please provide your response to this key issue, including any new evidence, data or analyses People who are not medically suitable for taxane are those patients with unmet need. They have either exhausted all the standard options of treatment or are also often deemed unsuitable for 2nd line chemotherapy too. The availability of 177Lu- vipivotide tetraxetan (PSMA) will provide a suitable option for treatment for these patients with unmet need and reduced inequality in patients care. Unlike chemotherapy this treatment is very well tolerated with a favourable side-effect profile. This would likely help in optimising their quality of life and expected to improve their OS.
Issue 2: Exclusion of radium-223 as a comparator for people with bone metastases	Yes	Radium-223 would not be a valid comparator. Further to pivotal ALSYMPCA trial, Radium-223 has been approved for mCRPC patients with painful skeletal metastases. Populations included in ALSYMPCA and VISION trials are different. The mechanism of action of Lutetium-177 PSMA is different from that of Radium-223. Radium-223 is exclusive bone targeting agent which mimicking calcium, while 177 Lutetium-PSMA targets disease in the bone, nodes prostate and other viscera.

		So, these 2 agents are entirely different in their mechanisms and hence used for different indications too. Patients who progress with visceral disease (40-50%) are not eligible for 223Radium. Patients with nodal disease (> 3cm) are also not eligible for 223Ra. There is evolving evidence that alpha and beta emitters may have synergistic effect and they can be complementary or sequentially used with benefit in OS (VISION and WARMTH study- Ahmadzadehfar H, et al. *Eur J Nucl Med Mol Imaging*. 2021;48(12):4067-4076).
Issue 3: Concerns regarding company's network meta-analysis	Yes	Since TROPIC trial, the therapeutic landscape has changed with ARTA predominantly used in the pre-chemotherapy setting. Therefore, the real-world evidence (RWE) data of Cabazitaxel should be considered.
Issue 4: Concerns regarding OS estimates for cabazitaxel in the model	*Yes*	RWE population may better reflect the current UK population OS for Cabazitaxel.
Issue 5: Use of pre-progression utility values for cabazitaxel that are equivalent to standard of care and use of post-progression utility values for cabazitaxel that are lower than for both standard of care and ^{177}Lu vipivotide tetraxetan	No	Not clear
Issue 6: Exclusion of standard of care costs from the ^{177}Lu vipivotide tetraxetan treatment and cabazitaxel treatment arms	*No*	177Lu PSMA has lesser side-effects and better efficacy and therefore standard of care should be in favour of PSMA.

Issue 7: Costing of pre-medication and concomitant medications for cabazitaxel	Yes	Potential hospital admission costs and costing other concomitant medication (pre and potentially during hospitalisation, number of days in hospital) for patients receiving Cabazitaxel, should also be considered and costed. The use of G-CSF is not standardised in the UK clinical practice. International **ESMO and ASCO** guidelines and the SPC of the G-CSF mandate the use of G-CSF for 10 (ESMO) to 14 (ASCO, SPC) days. If the G-CSF is used for less than 7 days – there is an increased risk of neutropenic sepsis. This is likely to leading to increasing hospital admissions and increases the cost of patient care having a 'hidden' likely significant cost and impact on the ICER. Clinical practice guidelines Annals of Oncology 27 (Supplement 5): v111–v118, 2016 doi:10.1093/annonc/mdw325 Management of febrile neutropaenia: ESMO Clinical Practice Guidelines† J. Klastersky1, J. de Naurois2, K. Rolston3, B. Rapoport4, G. Maschmeyer5, M. Aapro6 & J.Herrstedt7 on behalf of the ESMO Guidelines Committee
Issue 8: Estimation of symptomatic skeletal event (SSE) incidence		This is related to patients' selection. VISION trial included more advanced patients with multiple lines of prior therapy; therefore, these patients may have more SSEs, than those at earlier stages of disease.

Additional issues

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Issues related to equity or equality	Several sections	Yes	Thera(g)nostic (used for both diagnosis and treatment) PSMA is a molecule of decade. Lu-177 PSMA molecular radiotherapy is a breakthrough treatment for patients with prostate cancer. It is unfortunately aimed to a late-stage disease at present. Unlike in the USA and Europe where this treatment is already available, NHS patients in the UK are having no or very limited early compassionate access to this new modality. Expansion of existing services is required to reduce geographical inequality due to the need for some patients to travel long distances to receive treatment and potentially long waiting times. Limited number of centres (5) can produce Gallium-68 in the UK. Expansion of service producing Ga-68 and evaluation of alternative comparable PSMA

			diagnostic tracers (18F PSMA, 99mTcPSMA) to select patients for treatment should be prioritised. The BNMS agrees that there is a need to improve the UK infrastructure to deliver this treatment fairly and equitably, particularly regarding PSMA imaging, scanning for patients' selection and patient dosimetry. At the very least, the radiation doses delivered should be calculated and recorded.
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

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Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Prostate Cancer UK - Senior Policy Officer
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Broadening of population to include people who are not medically suitable for taxanes	Yes	We believe that broadening the population to include people who are not medically suitable for taxanes seems sensible as these groups of patients will have more limited options after ARPIs and will not have any active treatment beyond Radium-223. Publicly available data from Public Health England released in 2019 links age, stage of disease and treatment received across cohorts of prostate cancer patients from 2013-2017. Prostate Cancer UK analysed these data to understand docetaxel chemotherapy uptake in patient cohorts with stage IV disease by age, focusing specifically on the latest available treatments data from 2016. The results

		showed significant disparity in access to chemotherapy by age. 63.6% of men with a new diagnosis of metastatic prostate cancer aged under 70 receive chemotherapy. This starkly decreases to 21.9% for men aged over 70 and drops further to 5.7% for men aged 80 and above. These data reveal a cohort of men who are not receiving chemotherapy, strongly correlated with their increasing age. This effect parallels that of the uptake of radical prostatectomy by older men with localised disease, where Prostate Cancer UK's analysis of other data in the Public Health England dataset shows a drop from 27% to 3% in the same age range. In both cases it is very unlikely that the sharp decrease in uptake by age is explained purely by patient choice, but by clinical decision over the physical burden on the patient from the treatment. We therefore support the decision to broaden the population for this treatment. We recognise that this cohort of patients were not included in the original VISION trial and that further investigation will be needed to evidence how this treatment will benefit this population.
Issue 2: Exclusion of radium-223 as a comparator for people with bone metastases	No	The exclusion of radium-223 as a comparator seems appropriate as it is only a suitable comparator for a subset of the patients who would be eligible for Lu-PSMA-617. The majority of patients in the VISION trial had bone metastases, however 21.4% of patients had visceral metastases, meaning they would be contraindicated for Ra-223.
I**ssue 3:** Concerns regarding company's network meta-analysis	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 4: Concerns regarding OS estimates for cabazitaxel in the model	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 5: Use of pre-progression utility values for cabazitaxel that	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

are equivalent to standard of care and use of post-progression utility values for cabazitaxel that are lower than for both standard of care and ^{177}Lu vipivotide tetraxetan		
Issue 6: Exclusion of standard of care costs from the ^{177}Lu vipivotide tetraxetan treatment and cabazitaxel treatment arms	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 7: Costing of pre-medication and concomitant medications for cabazitaxel	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 8: Estimation of symptomatic skeletal event (SSE) incidence		

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

^{177}Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies: A Single Technology Appraisal

Addendum: EAG comments on company's technical engagement response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	19th August 2022

1. Introduction

In August 2022, the company submitted their response to technical engagement (TE) for the appraisal of ^{177}Lu vipivotide tetraxetan for treating prostate-specific membrane antigen (PSMA)-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies.[1] The company's TE response includes a written response form which presents a brief discussion of each of the key issues identified in the External Assessment Group (EAG) report.[2]

The company's TE response does not include any new primary data sources. However, it does include some additional input obtained from clinical advisors to the company and new analyses which address some of the key issues listed in the EAG report. The TE response also includes updated economic analyses, and a new version of the model.

This addendum provides a brief commentary on the company's TE response,[1] and should be read in conjunction with the EAG report.[2] Section 2 provides a summary of the company's response and the EAG's critique of these points. Section 3 provides a brief description of the changes in the updated model submitted by the company; whist Section 4 presents a fuller description of the EAG's critique of the main key points and new analyses presented by the company. Section 5 presents the results of the company's updated base case and additional exploratory analyses undertaken by the EAG.

All results presented in this document include the Patient Access Scheme (PAS) discount for ^{177}Lu vipivotide tetraxetan (discount=[redacted]). The results of the analyses including the discounted prices for comparators and other drugs used in the model can be found in a separate confidential appendix.

2. Summary of company's TE response and EAG comments

The main points discussed in the company's TE response and the EAG's comments are summarised in Table 1.

Table 1: Summary of company's TE response and EAG comments

Key issue	Headline points in company's TE response[1]	EAG comments
Key issue 1: Broadening of population to include patients who are not medically suitable for taxanes	• The company acknowledges the issue regarding the lack of clinical evidence for patients who are considered not medically suitable for taxanes. • The company argues that in this subpopulation of patients who are not medically suitable for taxanes following androgen receptor pathway inhibitor (ARPI) treatment there is unmet medical need as there are very few treatment options. Therefore, patients in this subgroup who are suitable for treatment with ^{177}Lu vipivotide tetraxetan should not be prevented from accessing treatment with the technology, and limiting the scope of this appraisal excluding this subgroup would potentially create inequality. • There is no reason that the efficacy and safety of ^{177}Lu vipivotide tetraxetan would be significantly different in patients who are unsuitable for taxanes, unless patients present with significantly more comorbidities. This subgroup of patients would still likely derive clinical benefit from ^{177}Lu vipivotide tetraxetan, which have been confirmed by the company's clinical advisors • The company also notes that clinical opinion obtained by the company indicates that patient's choice would also form part	The EAG's concerns regarding the weak generalisability of the evidence from VISION to the subgroup of patients who are considered unsuitable for taxanes is discussed in Sections 2.3.1, 2.3.6 and 4.3.4 (critical appraisal point 2) of the EAG report. The company has not presented any new evidence to support the claim that the efficacy and safety of ^{177}Lu vipivotide tetraxetan in patients unsuitable for taxanes would be similar to patients who have received previous treatment with taxanes. In addition, the EAG notes that the group who are not medically suitable for taxanes could be very heterogeneous with some being ineligible due to comorbidities and some having not received taxanes based on patient choice. The EAG's view of the available clinical evidence and uncertainty around the relative treatment effects of ^{177}Lu vipivotide tetraxetan in this subgroup remains unchanged. The EAG considers that this issue remains unresolved. The EAG also notes that at the time of technical engagement, the final NICE scope described the population as patients "previously treated with an androgen receptor pathway inhibitor and a taxane based chemotherapy" and therefore the group who are not medically

Key issue	Headline points in company's TE response[1]	EAG comments
	of the criteria for medical suitability for taxane treatment, and therefore access to ^{177}Lu vipivotide tetraxetan should not be prevented where patients have been deemed medically unsuitable for treatment with taxanes on the basis of patient refusal. • The company notes that an ongoing study (the PSMAfore study [NCT04689828]) could provide clinical data on patients without prior taxane treatment. However, these patients may not necessarily be ineligible for taxane treatment and therefore may not align exactly with the group on which data is lacking.	suitable for taxanes falls outside of the scope as defined at the time of writing.
Key issue 2: Exclusion of radium-223 as a comparator for people with bone metastases	• The company agrees with the EAG that radium-223 may be a relevant comparator in patients with metastatic castration-resistant prostate cancer (mCRPC) that have symptomatic bone metastases and no visceral metastases. • The lack of suitable evidence for radium-223 precludes robust indirect comparison of between ^{177}Lu vipivotide tetraxetan and radium-233, and for that reason it was not included as a comparator in this appraisal. • The company also highlights a few differences on the mechanisms of action between radium-223 and ^{177}Lu vipivotide tetraxetan, with the latter offering targeted	As discussed in the EAG report (Sections 1.3, 2.2, and 2.3.3), the EAG disagrees with the exclusion of radium-223 as a comparator for the subgroup of patients with bone metastases who do not have visceral metastases in the post-ARPI and taxane setting and post-ARPI where docetaxel is contraindicated or unsuitable setting. Nonetheless, the EAG recognises that there is uncertainty around the relative treatment effects of ^{177}Lu vipivotide tetraxetan versus radium-223 in this small group of patients, given concerns regarding the generalisability of data from the ALSYMPCA trial.

Key issue	Headline points in company's TE response[1]	EAG comments
	delivery of radiotherapy to the primary tumour and PSMA-positive metastases, whilst radium-223 targets preferentially sites of bone metastases with a treatment aim of palliating bone pain. • Further clinical opinion obtained by the company supports the view that the efficacy of radium-223 to extend survival is uncertain and likely to be limited in 'heavily pre-treated' patients.	The EAG's view remains unchanged and is largely consistent with that of the company in terms of no additional evidence being available that would address this uncertainty, and therefore, this issue remains unresolved.
Key issue 3: Concerns regarding company's network meta-analysis	• The company agrees to use the subgroup of patients who received ARPI as part of standard of care (SOC) in both VISION treatment arms in the network meta-analysis (NMA) to maintain randomisation and also agrees to exclude the ALYSYMPCA and the PROfound trials which do not form closed loops in the NMA. The company provides an updated NMA reflecting these two changes using both a fixed effect and a random effects model. The results from the fixed effect model were used in the updated economic analysis. • The company disagrees the exclusion of the TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials (which form a closed loop) on the basis that patients in these trials appear to be less heavily pre-treated than patients in VISION. The justifications are (i) the CARD population was generally	The EAG disagrees with the inclusion of the TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials in the NMA given that the indirect evidence provided by these trials is not consistent with the direct evidence provided by the CARD trial and there is significant inter-trial heterogeneity between the study populations recruited to these studies and those recruited to the CARD and VISION studies. The EAG also disagrees with the use of a fixed effect model because this model assumes that there is no heterogeneity among the trials included in the NMA which contradicts the company's acknowledgment of inter-trial heterogeneity in the network. Goodness of fit checking conducted by the EAG on the company's updated fixed effect NMA shows that the fixed effect model does not fit the data well.

Key issue	Headline points in company's TE response[1]	EAG comments
	healthier and less heavily pre-treated than patients in VISION, (ii) the CARD patient population may be more likely to be resistant to ARPI treatment because the trial only enrolled patients who have progressed during 12 months of treatment with an ARPI, but no such eligibility criteria was applied in VISION, and (iii) given these limitations, it is more appropriate to include the indirect evidence provided by TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials so that the comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel is based on the largest possible evidence base. • The company disagrees with the inclusion of the TheraP trial because of the use of a "home-brew" compound, different dosage, and the option in the protocol for treatment suspension in those with exceptional PSMA response. • The company also disagrees with the use of a random effects model with an informative prior and argues that given the sparsity of the network, it is unlikely that this approach could accurately address the heterogeneity within the NMA.	While the EAG acknowledges the differences between the TheraP and VISION trial raised by the company, the EAG still believes it is important to include the head-to head evidence (TheraP) in the NMA which provides valuable unbiased estimates of the treatment effect of comparing ^{177}Lu vipivotide tetraxetan versus cabazitaxel. An additional exploratory analysis was conducted for the economic analysis using the EAG's original NMA excluding the TheraP trial to explore the impact this would have the cost-effectiveness estimates. The result is presented in Section 5. However, the EAG's preferred analysis remains one that includes the direct evidence from the TheraP trial in the NMA. A more detailed EAG critique is presented in Section 4 of this addendum.
Key issue 4: Concerns regarding OS estimates for	• The company argues that any increased OS relating to additional patient monitoring received in the randomised controlled trial (RCT) setting would be greater for patients in	The EAG has concerns with the PSW analysis conducted because statistical hypothesis testing was used to identify potential prognostic covariates rather than these being based on disease area expertise and

Key issue	Headline points in company's TE response[1]	EAG comments
cabazitaxel in the model	the control arms of these trials, and it is expected that patients in real-world practice receiving SOC would experience shorter OS than that observed in VISION. • The company performed a propensity score weighting (PSW) analysis to address the EAG's concern that the use of the real-word evidence (RWE) in the original submission was a naïve indirect comparison with ^{177}Lu vipivotide tetraxetan arm in VISION.	a review of the literature. Patients enrolled in clinical trials are generally expected to have better prognosis than those treated in clinical practice. However, the company's PSW analysis shows that the population in the RWE is similar to the VISION trial, and the PSW analysis makes no impact on the OS. A more detailed EAG critique is presented in Section 4 of this addendum.
Key issue 5: Use of pre-progression utility values for cabazitaxel that are equivalent to standard of care and use of post-progression utility values for cabazitaxel that are lower than for both standard of care and ^{177}Lu vipivotide tetraxetan	• The company disagrees with the EAG's approach of using treatment-independent utility values given that (i) this approach may fail to capture the substantial psychological burden on patients who are receiving cabazitaxel in the post-docetaxel setting, (ii) using this approach the differences in utility was driven by adverse event/symptomatic skeletal event (AE/SSE) frequency; however the patients in CARD may be expected to experience fewer AEs/SSEs than patients in VISION because patients in CARD were less-heavily pre-treated and less frail. • The company re-analysed VISION EQ-5D data to address the issue that categorisation of individual's progression status at the time of EQ-5D-5L assessment may be inaccurate due	The EAG disagree with the company's approach in re-analysing VISION EQ-5D data because it would introduce informative censoring. The EAG acknowledges that there would be some psychological distress for patients receiving cabazitaxel post-docetaxel. However, it is difficult to quantify the level of this psychological burden because it would be influenced by many other factors. The TheraP trial shows clinical meaningful improvement in the following quality of life and symptoms domains comparing ^{177}Lu vipivotide tetraxetan to cabazitaxel: social functioning, diarrhoea, fatigue and insomnia. The EAG conducted an additional exploratory analysis using the treatment dependent utility approach in the company's original submission for cabazitaxel and ^{177}Lu vipivotide tetraxetan whilst

Key issue	Headline points in company's TE response[1]	EAG comments
	to the assessment timepoints for EQ-5D-5L and rPFS being different within the trial.	assuming that the utility for cabazitaxel is the average between the utility for ^{177}Lu vipivotide tetraxetan and the utility for SOC. The result is presented in Section 5. However, the EAG's preferred approach to estimating utility values remains unchanged from that presented in the original EAG report. A more detailed EAG critique is presented in section 4 of this addendum.
Key issue 6: Exclusion of standard of care costs from the ^{177}Lu vipivotide tetraxetan treatment and cabazitaxel treatment arms	• Clinical opinion obtained by the company indicates that all patients receiving ^{177}Lu vipivotide tetraxetan or cabazitaxel in clinical practice would receive SOC treatment alongside their treatments. The experts also indicated that the components of SOC received by patients in the VISION trial was consistent with UK clinical practice, with the exception of concomitant ARPIs. • The company accepted the EAGs preferred assumptions for concomitant SOC, which included the costs of SOC for all treatment groups in the updated version of the model. • The components of concomitant SOC are based on data from VISION for ^{177}Lu vipivotide tetraxetan and SOC treatment arms, whilst for cabazitaxel it used the average frequencies for both treatment arms of the VISION trial.	The EAG has no further comments on this issue, and considers it resolved.

Key issue	Headline points in company's TE response[1]	EAG comments
	• The company reports these changes in isolation have a minimal impact on the ICER of ^{177}Lu vipivotide tetraxetan versus cabazitaxel (£49,604, a reduction of £109 in comparison to the company's original base-case), and a small impact in comparison to SOC (£137,420, representing an increase of £15,417 compared to the original base case).	
Key issue 7: Costing of pre-medication and concomitant medications for cabazitaxel	• Further clinical opinion obtained by the company suggests that the mean duration of G-CSF treatment received per 21-day as part of the cabazitaxel pre-medication that is specified in the Summary of Product Characteristics (SmPC) (14 days) represents an overestimation of the costs of this therapy for patients in current clinical practice. • The estimate used by the EAG of 5 days, on the other hand, were considered by the company's experts to be an underestimation of usage in clinical practice, particularly in the post-COVID-19 setting, and the considered that shorter durations of G-CSF could place patients at considerable risk of experiencing severe AEs. Typical treatment in clinical practice would correspond to 7–9 days of G-CSF treatment, and in their updated base-case, the company adopted 9 days (per 21-day cycle) for the G-CSF duration treatment for patients receiving cabazitaxel.	As discussed in the EAG report (Section 4.3.4), the company's original approach for cabazitaxel's premedication assumed G-CSF to be taken by home injection on 14 days out of each 21-day cycle, but it didn't correspond to clinical practice. Clinical advice received by the EAG, at the time that the EAG report was written, was that whilst usage of G-CSF varies between centres, usual duration would be 5-7 days for each cabazitaxel 21-day cycle. The EAG also notes that their clinical advisors described wide variation in usage of G-CSF across the NHS with some centres who had previously used 5 days of G-CSF during the COVID pandemic now unable to prescribe it routinely, some centres only using it at the clinician's discretion, and some using it routinely. Therefore G-CSF may only be prescribed in a proportion of patients across the NHS as a whole. Further clinical opinion received by the EAG at the TE stage agreed with the company that there is risk associated with using lesser

Key issue	Headline points in company's TE response[1]	EAG comments
	• Using 4 extra days of G-CSF treatment per 21-day cycle of cabazitaxel leads to an ICER against cabazitaxel of £55,628 per QALY gained (£5,914 increase from original base case) and no change in the results versus SOC.	number of days of G-CSF which could increase admissions related to neutropenic sepsis, which could lead to increased costs. To explore the impact of uncertainty around the average number of days of G-CSF usage within routine care in the NHS, the EAG conducted an additional exploratory analysis using 7 days treatment duration for G-CSF. The result is presented in Section 5. However, the EAG's preferred approach to treatment duration for G-CSF use remains unchanged from that presented in the original EAG report.
Key issue 8: Estimation of symptomatic skeletal event (SSE) incidence	• The company and the EAG agree that the original approach used by the company resulted in a much higher cumulative incidence of SSEs than observed in the pivotal trials, regardless of the data being considered relatively complete by the end of the VISION trial follow-up. • The company has included in their updated base-case analysis the EAG-preferred approach of using the cumulative incidence of SSEs based on rates observed in the VISION trial for ^{177}Lu vipivotide tetraxetan and SOC, and rates observed in the CARD trial for cabazitaxel. • The company reports that, in isolation, the change in the approach for SSE incidence has a minimal impact on the	The EAG has no comments on this issue, and considers it resolved. However, it notes that the method used to estimates SSEs has a greater impact on cost-effectiveness estimates when using the EAG's preferred approach to estimating utility values.

Key issue	Headline points in company's TE response[1]	EAG comments
	ICER for ^{177}Lu vipivotide tetraxetan versus cabazitaxel (reduction of £827, resulting in an ICER of £48,886 per QALY gained), whilst it leads to an increase on the ICER against SOC of £1,151 in comparison to the original company's base-case, to £123,154 per QALY gained.	

3. Summary on the changes of the updated economic analysis presented by the company

In addition to the new analyses presented for the NMAs, RWE and utilities, at the TE stage the company also submitted an updated version of the economic model. This new model (mentioned from this point onwards as company's updated base case) includes a number of amendments related to some of the key issues raised by the EAG (see Table 2 below). The company has accepted some of the EAG's proposed amendments, including part of the correction of errors described in the EAG report[2] Section 4.3.4 (Issue 1). However, during the verification of the new version of the submitted model, the EAG has identified that some of the other errors and remaining issues originally raised in the EAG report and included in the EAG preferred-analysis have not been included by the company. The EAG notes that these additional changes (or the lack of them) are not mentioned by the company in the TE response.

Table 2 summarises the company's original base case model in the company submission (CS), the EAG's preferred analysis in the EAG report, and the company's updated base case model as presented in the TE response.

Table 2: Summary of company's original base case (CS), EAG-preferred analysis (EAG report) and company's updated base case (TE response)

Aspect of model/ issue identified in the EAG report Section 4.3.4	Company's original base case	EAG-preferred analysis	Company's updated base case	Agreement between EAG-preferred and updated company's base case
EA1 (a); Correction of programming error in implementation of the RWE KM OS data for cabazitaxel	No	Yes	Yes	✓
EA1 (b): Correction of zero health state occupancy in first model cycle	No	Yes	No	✗
EA1 (c): Correction of programming errors in HRs for OS and rPFS	No	Yes	Yes	✓
EA1 (d); Correction of programming errors in incidence of AEs for cabazitaxel	No	Yes	Yes	✓
EA1 (e): Correction of incorrect data on breakdown of opioids used as concomitant treatment	No	Yes	No	✗
EA1 (f): Correction of duration of cabazitaxel pre-medication	No	Yes	No	✗
EA1 (g): Corrections necessary to generate the scenario analyses for alternative utility inputs	No	Yes	Yes	✓
EA2: EAG preferences for unit costs for epoetin alpha and filgrastim	No	Yes	No	✗
EA3: EAG preferences for cabazitaxel pre-medications and concomitant medications	No	Yes	Partially	**Partially**
EA4: Inclusion of SOC costs concomitant medications for ^{177}Lu vipivotide tetraxetan and cabazitaxel	No	Yes	Yes	✓
EA5: Cost of ^{177}Lu vipivotide tetraxetan (use of mean treatment duration, instead of median)	No	Yes	No	✗
EA6: Approach for health state utility values	Treatment-specific (no AEs or SSEs) – original utility analysis	Treatment-independent + decrements for AEs and SSEs –	Treatment-specific (no AEs or SSEs) – new utility analysis	✗

Aspect of model/ issue identified in the EAG report Section 4.3.4	Company's original base case	EAG-preferred analysis	Company's updated base case	Agreement between EAG-preferred and updated company's base case
		original utility analysis		
EA7: Approach for SSE incidence	Time-to-first SSE data	total incidence of SSEs reported in VISION and CARD	total incidence of SSEs reported in VISION and CARD	✓
EA9: SSE disutilities (use of prevail data)	No	Yes	No	✗
EA10: Alternative rPFS and OS HR estimates for cabazitaxel	Company's original NMA	EAG's NMA	Company's new NMA	✗
EA11: Source of OS data for cabazitaxel	RWE – original analysis	Based on HR obtained from EAG's NMA	RWE – new analysis	✗

Note: EA8 from the EAG report was a combination of EA6 and EA7 and so is not described separately in this table.
Abbreviations: CE, correction of errors; HR, hazard ratio; NMA, network meta-analysis; KM, Kaplan-Meier; OS, overall survival; rPFS, radiographic progression-free survival; SSE, symptomatic skeletal event; RWE, real world evidence; EA, exploratory analysis.

The company's updated base case disagrees with the EAG's preferred analysis in the sense that they did not fix the model errors (b), (e) and (f); and did not implement EA2, EA5, EA6, EA9, EA10 and EA11. The model also adopted EA3 partially, by including a 9-day treatment duration for G-CSF. However, it does not include any of the EAG's other preferences for cabazitaxel pre-medications and concomitant medications within EA3 and does not describe why these were not adopted in their TE response.

In the updated model, the company included new hazard ratio (HR) estimates for rPFS and OS for cabazitaxel versus ^{177}Lu vipivotide tetraxetan based on the new NMA (see Section 4,[2] key issue 3), and data from a new analysis of RWE as the source of OS data for cabazitaxel based on the new utility analysis (see Section 4,[2] key issue 4).

The updated model also adopts the company's original approach with treatment-specific utilities for progression-free (PF) and progressed disease (PD) states, with values for ^{177}Lu vipivotide tetraxetan and SOC based on a new utility analysis from VISION data generated by the company (see Section 4,[2] key issue 5). For cabazitaxel the utility values are assumed to be equivalent to SOC for PF state and based on value used in NICE TA391 for PD state as per the company's original base case. The EAG notes that PD utility for cabazitaxel is lower than the PD utilities for the other two treatment groups.

4. EAG's critique on key issue 3, 4 and 5

Key issue 3: Concerns regarding company's network meta-analysis

The company updated the NMA for OS and rPFS in the TE response. The EAG has concerns regarding: (i) inclusion of the TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials, (ii) the use of a fixed effect model, (iii) generalisability of the patient population in the CARD trial, (iv) exclusion of the TheraP trial.

(i) Inclusion of the TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials

The company's updated NMA incorporates the EAG's preference for using the subpopulation of patients who received ARPI as part of SOC in both VISION treatment arms but does not incorporate the EAG's preferences for excluding the TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials (which form a closed loop). The EAG disagree with the inclusion of TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials based on the substantial differences between the patient population in these trials and the CARD trial, which resulted inconsistency between the direct and indirect evidence comparing cabazitaxel against ARPI.

The EAG used the node-split method[3] to check consistency in the company's updated NMA for both OS and rPFS.

Figure 1 shows that there is very limited overlap in the posterior densities of the mean log-hazard ratio calculated using direct evidence (black dotted line) and indirect data (red dotted line) for both OS and rPFS. Test for inconsistency shows there is a statistically significantly difference between the direct and indirect evidence for treatment comparison between cabazitaxel and ARPI (p-value = 0.019 for OS and p-value < 0.001 for rPFS).

Figure 1: Inconsistency checking in NMA: posterior density of the mean log-odds ratio for OS and rPFS (cabazitaxel vs. ARPI)

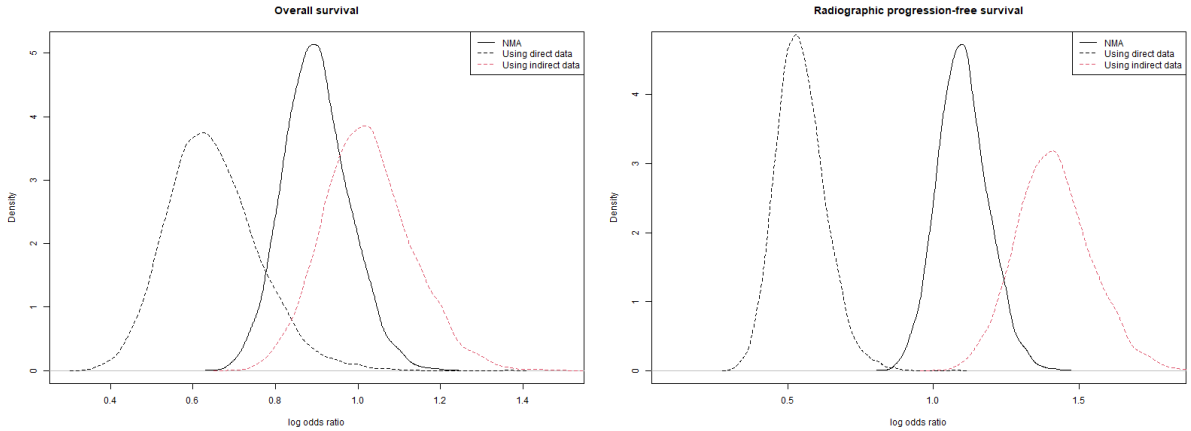

Table 3 shows the summary of the population in the trials included in the NMA. The EAG notes that the TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials contain ARPI-naïve patient population, whereas the population in the CARD trial has progressed with first ARPI and the population in the VISION trial also has progressed with ARPI.

A study of real-world cabazitaxel use and outcomes in mCRPC shows a clear interaction between the duration of first ARPI response and cabazitaxel effectiveness (cabazitaxel was associated with longer OS among patients who progressed within 12 months on first ARPI, but the benefit was not observed among patients who progressed after 12 months on first ARPI).[4] The EAG notes that ARPI-sensitivity could be a confounding factor which contributed to the inconsistency between the direct and indirect evidence in the company's updated NMA. Because of the inconsistency in the company's updated NMA, the EAG believes that it's appropriate to exclude the indirect evidence (the TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials) in the NMA.

Table 3: Summary of studies included in the NMA

Trial Identifier	Study Population	Previous lines of androgen receptor pathway Inhibitors (ARPI)	Intervention (per arm)	Study N (per arm)	Study N (overall)
TROPIC	Patients with mCRPC that are refractory to hormone therapy and previously treated with a docetaxel-containing regimen.	None	Mitoxantrone + Prednisone	377	755
			Cabazitaxel + Prednisone	378	
COU-AA-301	Patients with mCRPC who had previous treatment with docetaxel	None	Abiraterone + Prednisone/prednisolone	797	1195
			Placebo + Prednisone/prednisolone	398	
AFFIRM	Patients with mCRPC who had previous treatment with docetaxel	None	Enzalutamide	800	1199
			Placebo	399	
Sun *et al.* 2016	Patients ≥ 18 years old with mCRPC	None	Abiraterone + Prednisone	143	214
			Placebo + Prednisone	71	
TheraP	Patients with mCRPC who are pre-treated with taxane regimens	One regimen: 70 (71%) Two regimens: 21 (21%) Enzalutamide and/or abiraterone	^{177}Lu vipivotide tetraxetan	99	200
		One regimen: 82 (81%) Two regimens: 9 (9%) Enzalutamide and/or abiraterone	Cabazitaxel	101	
CARD	Patients with progressive mCRPC who had been treated with three or more cycles of docetaxel	One regimen: 129 (100%)* Enzalutamide or abiraterone	Cabazitaxel + Prednisone	129	255
		One regimen: 126 (100%)* Enzalutamide or abiraterone	Enzalutamide or abiraterone + prednisone	126	
VISION	Patients with mCRPC who are pre-treated with taxane regimens	One regimen: 298 (54.1%) Two regimens: 213 (38.7%) > two regimens: 40 (7.3%) Enzalutamide, abiraterone and/or apalutamide	^{177}Lu vipivotide tetraxetan + SOC	551	831
		One regimen: 128 (45.7%) Two regimens: 128 (45.7%) > two regimens: 24 (8.6%) Enzalutamide, abiraterone and/or apalutamide	SOC	280	

Abbreviations: BSC, best supportive care; mCRPC, metastatic castration-resistant prostate cancer; SOC, standard of care.

*Failure within 12 months as an inclusion criterion

The company also argues that it is inconsistent to exclude the TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials on the basis of differences in prior treatments, whilst including the CARD study, because the population in the CARD trial was less heavily pre-treated when compared to the population in the VISION trial (0% vs. 41% had received >2 lines of taxane therapy). In response to clarification question A10,[5] the company presented OS and rPFS for the subgroup of patients who received docetaxel and for the subgroup of patients who received docetaxel and cabazitaxel. [redacted] was observed in OS or rPFS for these two groups of patients (Table 4), suggesting that the number of prior lines of taxane therapy may not be a significant treatment effect modifier.

Table 4: OS and rPFS for patients who had previously received one vs. two taxanes prior entry into the VISION trial

	Patients who previously received docetaxel (95% CI)	Patients who previously received docetaxel and cabazitaxel (95% CI)
OS	[redacted]	[redacted]
rPFS	[redacted]	[redacted]

Abbreviations: OS, overall survival; rPFS, radiographic progression-free survival; CI, confidence interval.

The EAG conducted inconsistency checking for the EAG's rPFS NMA (which contains a feedback loop by including the TheraP trial). The node-split approach shows that no inconsistency between the direct and indirect evidence was observed.

Because there is [redacted] in OS or rPFS in patients who had previously received one and more than one taxanes and no inconsistency when including the direct evidence (the TheraP trial) in the NMA, the EAG believes that it's appropriate to compare cabazitaxel and ^{177}Lu vipivotide tetraxetan using the CARD and VISION trials in the NMA.

(ii) Use of a fixed effect model

The company disagrees with the use of a random effects model with an informative prior to take into account the heterogeneity within the NMA, but opted for a fixed effect modelling approach which assumes that there is no heterogeneity among the trials included in the NMA. This assumption contradicts the company's acknowledgment of inter-trial heterogeneity in the network. The EAG's informative prior is based on analysing 14,886 meta-analyses from Cochrane Database of Systematic Reviews and a constraint assuming that the HR in one study could be no more than 5 times that of the HR in another.[6, 7] This prior represents a realistic distribution for heterogeneity in evidence synthesis in general while taking into account the data in this NMA. The EAG's approach is also in line with NICE's 2022 HTA methods guide[8] in the use of external information to help estimate the heterogeneity in the case of sparse data.

The EAG also performed goodness of fit checking on the company's updated NMA to assess if the fixed effect model used is a good representation of the data. The results show that the fixed effect model used in the company's updated NMA does not fit the data well: OS NMA model does not fit the CARD trial data well and the rPFS NMA model does not fit the CARD, TROPIC, COU-AA-301 and AFFIRM trials data well.

The EAG notes that the probability sensitivity analysis (PSA) results for the economic analysis is very sensitive to whether heterogeneity was appropriately addressed in the NMA. Using a fixed effect model assuming no heterogeneity would substantially underestimate the PSA incremental cost-effectiveness ratio (ICER).

(iii) Generalisability of the patient population in the CARD trial

The company argues that patients in the CARD trial were required to have experienced progression within 12 months of treatment with first ARPI, and this is likely to bias the relative treatment effect in favour of cabazitaxel in the NMA because no such eligibility criteria were applied in the VISION trial. However, the company did not provide time to progression while treating with ARPI for the VISION trial. The EAG notes that 46.0% of patients in the ^{177}Lu vipivotide tetraxetan arm and 54.3% patients in the SOC arm in the VISION trial have failed on 2 or 3 ARPIs before receiving the trial treatments. These patients may also have ARPI resistance similar to the patient population in the CARD trial. The clinical advice received by the EAG suggests that most mCRPC patients in the trial would progress within 12 months on ARPI. The EAG argues that the eligibility criteria on progression within 12 months of treating with first ARPI in the CARD trial would not be likely to bias the relative treatment effect when comparing cabazitaxel and ^{177}Lu vipivotide tetraxetan in the NMA.

(iv) Exclusion of the TheraP trial

The company excluded the TheraP trial in the updated NMA based on the fact that the compound used was a "home-brew", the dosage was different from the VISION trial and the protocol allowed for treatment suspension in exceptional responders to ^{177}Lu vipivotide tetraxetan which may bias the results of TheraP towards the cabazitaxel treatment arm. The EAG notes that 7% of patients randomised to ^{177}Lu vipivotide tetraxetan arm suspended treatment because of a protocol-defined exceptional PSMA response in the TheraP trial.

The EAG still believes it is important to include the head-to head evidence comparing ^{177}Lu vipivotide tetraxetan against cabazitaxel in the NMA which provides valuable unbiased estimates of the treatment effect of comparing ^{177}Lu vipivotide tetraxetan versus cabazitaxel. However, the EAG also acknowledges the differences raised by the company. An additional exploratory analysis was conducted

excluding the TheraP trial in the EAG's original base case NMA to assess the impact this would have on the cost-effectiveness estimates.

Key issue 4: Concerns regarding OS estimates for cabazitaxel in the model

The company presented a PSW analysis to try to address the population differences between the real-word evidence and the VISION trial. The baseline characteristics included in the PSW analysis were age, ECOG, time from diagnosis, gleason score 8-10 and previous prostatectomy. The adjustment did not make any difference in the point estimate of median OS and hardly made any difference in the 95% confidence internal (CI) (before PSW: [redacted] vs. after PSW: [redacted].

The EAG has concerns regarding the PSW analysis conducted because statistical hypothesis testing was used to identify potential prognostic factors rather than these being based on disease area expertise and a review of the literature. The company's approach highly depends on the data collected and the sample size.

Two other real-world evidence studies on cabazitaxel use in mCRPC in Netherlands and France also show that median OS was lower than the CARD and TROPIC trials (8.7 months for the Netherlands cohort and 11.9 months for the France cohort).[9, 10] Both studies suggest that the most likely reasons for the discrepancy between the real-word study and the clinical trial are due to differences in the patient population (i.e., more healthier patients were enrolled in the clinical trial) and cabazitaxel was used as different lines of treatment in the real-word setting and the clinical trial. It is highly likely that the patient population in the company's RWE analysis have poorer prognosis at baseline compared to the population in the CARD and VISION trials. The EAG believes that the PSW may have failed to include some of the important prognostic factors and hence failed to correct the difference in the patient population between the RWE and the VISION trial as there was no change in the outcome before and after adjustment.

The company argues that patients in real-world clinical practice receiving SOC would experience shorter OS than that observed in the VISION trial because additional patient monitoring received in the trial setting would be greater for patients in the control arms. The VISION trial compares ^{177}Lu vipivotide tetraxetan+SOC against SOC. Both treatment arms received the "enhanced" SOC. The randomised setting in the VISION trial would ensure that the treatment effect estimated for ^{177}Lu vipivotide tetraxetan is due to the treatment itself. The EAG believes that the relative treatment effect obtained from the VISION trial represents an unbiased estimate of the treatment effect for ^{177}Lu vipivotide tetraxetan in the population included in the trial. Similarly, the EAG believes that the relative treatment effect obtained from the CARD trial represents an unbiased estimate of the treatment effect

for cabazitaxel in the population included in the trial. The indirect treatment effect (^{177}Lu vipivotide tetraxetan vs. cabazitaxel) generated from the NMA in turn benefits from using the unbiased treatment effects estimated in these trials. Using the RWE for cabazitaxel and ^{177}Lu vipivotide tetraxetan from the VISION trial is associated with the very strong assumption that the PSW analysis, which adjusted for age, ECOG, time from diagnosis, gleason score 8-10 and previous prostatectomy, has controlled for all effect modifiers and prognostic factors.

Together with issue 3 on NMA, the EAG would like to point out to the committee that it is likely that the effect of cabazitaxel may be associated with treatment sequencing and prior ARPI response. An alternative approach is to use the RWE on cabazitaxel as the reference group and apply the HR from the NMA in the economic model to estimate OS and rPFS curves for cabazitaxel and ^{177}Lu vipivotide tetraxetan in the population currently receiving cabazitaxel in UK clinical practice. In addition, it would be useful if the company could use the RWE to determine the lines of treatment for which cabazitaxel was used in UK clinical practice and time to ARPI progression for patients in UK clinical practice. Given this information, the relative effect of cabazitaxel could be modelled more appropriately in the NMA.

Key issue 5: Use of pre-progression utility values for cabazitaxel that are equivalent to standard of care and use of post-progression utility values for cabazitaxel that are lower than for both standard of care and ^{177}Lu vipivotide tetraxetan

The company re-analysed VISION EQ-5D data to address the issue that categorisation of an individual's progression status may be inaccurate at the time EQ-5D was measured due to the assessment timepoints for EQ-5D-5L and rPFS being different in the trial. The company excluded the following EQ-5D-5L data in the analysis:

1. EQ-5D measurements recorded after last progression assessment in which the patients remained progression-free
2. EQ-5D measurements recorded directly before a rPFS assessment in which the patient demonstrated radiographic progression
3. Patients with no HRQoL assessment with progression data, or only 1 visit

The EAG disagrees with the company's approach because it would introduce informative censoring with criterion 3, and exclude progression-free utility data when there are multiple HRQoL assessments between rPFS assessments using criteria 1 and 2 which would introduce bias as well. The EAG notes that they have previously raised the issue of the potential for informative censoring in the EQ-5D analysis due to the higher baseline utilities in both treatment arms for patients who dropped out compared to those who remained in the study and the higher rate of drop out in the SOC arm (see Table 9 of company's response to clarification question B15[5] and Section 4.2.4.4 of the EAG report[2]).

Psychological burden on patients receiving cabazitaxel post-docetaxel

Clinical advice received by the EAG suggests that there would be some psychological distress for some patients receiving cabazitaxel post-docetaxel. However, it is difficult to quantify the level of this psychological burden because it would be influenced by many other factors (e.g., whether the patient is responding to treatment, baseline performance status, significant treatment related toxicities and prior experience and toxicities with docetaxel). As previously mentioned in the EAG report (Section 4.3.4: (5) Issues relating to HRQoL, page141), the EQ-5D values presented by Bahl *et al.* (2015)[11] (a quality of life data analysis for patients with mCRPC treated with cabazitaxel in the UK Early Access Programme [UK EAP]) suggests that utility values may be relatively stable during and after cabazitaxel treatment in patients who have previously progressed on docetaxel.

The EAG report previously described that the TheraP trial did report lower incidences of some troublesome symptoms for ^{177}Lu vipivotide tetraxetan versus cabazitaxel and clinically meaningful differences in favour of ^{177}Lu vipivotide tetraxetan for some EORTC QLQ-C30 domains (diarrhoea, fatigue, insomnia and social functioning; it should be noted that the latter was previously incorrectly reported as being in favour of cabazitaxel in the EAG report). The EAG notes that no significant differences were identified in the emotional functioning domain which might be expected to be affected by any psychological impact of being offered cabazitaxel after previous docetaxel treatment. In addition, all of the trouble symptoms reported as being significantly worse for cabazitaxel were physical in nature and there were no significant differences in the troublesome symptoms which might be expected to capture any such psychological impact (anxiety, depression, irritability, mood, emotional well-being, inconvenience of treatment, problems coping with treatment or thought of actually having treatment).

The EAG is willing to accept that utility values for ^{177}Lu vipivotide tetraxetan may be higher than for cabazitaxel based on the head-to-head comparison provided by TheraP which has identified some differences in favour of ^{177}Lu vipivotide tetraxetan. But the company was not able to perform any analysis to estimate the magnitude of these utility differences based on the direct comparison provided by TheraP [redacted]. The EAG maintains that their preferred approach to estimating utilities, which uses treatment independent utilities for the pre- and post-progression health states and adjusts these to account for AEs and SSEs, has the potential to capture important differences in utility that are driven by treatment toxicity. However, the EAG acknowledges that differences in AEs and SSEs may not capture all differences that might be captured by a more comprehensive quality of life tool. Furthermore, patients with a particular psychological aversion to being treated with cabazitaxel following docetaxel treatment may have chosen not to enrol in the CARD or TheraP trials or may have withdrawn early as these trials were open-label. The EAG also believes that there will be a psychological burden of being offered SOC in the knowledge that this option will not prevent progression and therefore it is unlikely that cabazitaxel utility values would be

worse than SOC utility values after accounting for the impact of AEs associated with cabazitaxel toxicity.

The EAG has therefore conducted an exploratory analysis which uses the treatment specific utility values for ^{77}Lu vipivotide tetraxetan and SOC and assumes that the utility values for cabazitaxel fall half-way between these values. However, the EAG does not adopt this as their preferred approach. **Error! Reference source not found.** summarises the different values for pre- and post-progression utilities and QALY losses due to AE and SSEs adopted in each of the analyses developed by the company and the EAG.

Table 5: Utility values for pre- and post-progression health states and QALY losses used in the different analyses

	Company's original approach (CS)			EAG-preferred approach			Company's updated approach (TE)			EAG's new exploratory analysis		
	^{177}Lu	SOC	Cabazitaxel	^{177}Lu	SOC	Cabazitaxel	^{177}Lu	SOC	Cabazitaxel	^{177}Lu	SOC	Cabazitaxel
Utility: Pre-progression state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Post-progression state	[redacted]	[redacted]	0.627	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.627	[redacted]	[redacted]	[redacted]
QALY losses due to AE (one-off)	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
QALY losses due to SSEs (one-off at the point of progression)	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-

Abbreviations: ^{177}Lu, Lutetium-177 vipivotide tetraxetan; AE, adverse events; CS, company submission; EAG, External Assessment Group; QALY, quality-adjusted life year; SSE, symptomatic skeletal event; TE, technical engagement.

5. Results of updated economic analyses including the PAS for ^{177}Lu vipivotide tetraxetan

The EAG has not changed its position regarding the EAG's preferred base case analysis, which remains the same as in the EAG report. The EAG undertook additional exploratory analyses using the previous EAG-preferred version of the model as follows:

Exploratory analysis 1 (TE-EA1): EAG preferences for cabazitaxel pre-medications and concomitant medications

The EAG replaced the previous estimate of treatment duration for G-CSF of 5 days to 7 days per 21-day cycle of cabazitaxel treatment. The remaining pre-medications/concomitant medications remained as in the EAG-preferred analysis.

Exploratory analysis 2 (TE-EA2): Alternative rPFS HR estimates for cabazitaxel

The EAG explored the impact of changing the HR estimate for rPFS for cabazitaxel using the EAG's original base case NMA but excluding the TheraP trial (see Table 26 of the EAG report). The median rPFS HR for ^{177}Lu vipivotide tetraxetan versus cabazitaxel is 0.98 in this scenario versus 0.74 in the EAG's base case. The EAG notes that the HR for OS is unchanged as TheraP did not contribute to the NMA for OS. The remaining assumptions and data sources were kept as in the EAG-preferred analysis.

Exploratory analysis 3 (TE-EA3): Alternative approach for health state utility values

Within this scenario, the EAG explored the approach used in the company's original submission whereby the utility values for the health states were based in the treatment specific utilities generated from the original utility analysis presented by the company, and excluded additional utility decrements applied for AEs and SSEs. For the estimates for cabazitaxel in each heath state, the EAG applied the average between the correspondent values for ^{177}Lu vipivotide tetraxetan and SOC (see **Error! Reference source not found.**).

Table 6 presents the results of the company's original and updated base case analyses, the EAG's preferred analyses, and the EAG's TE exploratory analyses. The results for ^{177}Lu vipivotide tetraxetan against SOC are presented in Table 7. The EAG notes that TE exploratory analysis 1 and 2 do not apply for the comparison of ^{177}Lu vipivotide tetraxetan against SOC, since it impacts only on the results for cabazitaxel. The results of the analyses including the cPAS discounts for comparators are presented in a separate confidential appendix.

Table 6: Company's original and updated base case, EAG's preferred analysis and EAG's TE exploratory analyses of ^{177}Lu vipivotide tetraxetan versus cabazitaxel

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's original base case (deterministic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's original preferred analysis (deterministic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's original preferred analysis (probabilistic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's updated base case (deterministic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TE-EA1: EAG's preferred analysis + 7 days of G-CSF treatment (deterministic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TE-EA2: EAG's preferred analysis + EAG's NMA excluding Thera-P study (deterministic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TE-EA3: EAG's preferred analysis + treatment-specific utilities + alternative utilities for cabazitaxel (deterministic)							
Cabazitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Undiscounted

Abbreviations: ^{177}Lu, Lutetium-177 vipivotide tetraxetan; LYG, life year gained; QALY, quality-adjusted life year; Inc., incremental; ICER, incremental cost-effectiveness ratio; EA, exploratory analysis; EAG, External Assessment Group; EA, exploratory analysis.

Table 7: Company's original and updated base case, EAG's preferred analysis and EAG's TE exploratory analyses of ^{177}Lu vipivotide tetraxetan versus SOC

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's original base case (deterministic)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred analysis (deterministic)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred analysis (probabilistic)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's updated base case (deterministic)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TE-EA3: EAG's preferred analysis + treatment-specific utilities (deterministic)							
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
^{177}Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Undiscounted

Note: TE-EA 1 and 2, where the changes reflected only the number of days of G-CSF treatment and/or the HR estimates for cabazitaxel for OS and rPFS do not apply to the analysis against SOC.

Abbreviations: ^{177}Lu, Lutetium-177 vipivotide tetraxetan; SOC, standard of care; LYG, life year gained; QALY, quality-adjusted life year; Inc., incremental; ICER, incremental cost-effectiveness ratio; EA, exploratory analysis; EAG, External Assessment Group; EA, exploratory analysis.

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