NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Padeliporfin for treating localised prostate cancer [ID866]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Padeliporfin for treating localised prostate cancer [ID866]

Contents:

Evidence Review Group report – factual accuracy check – *the company stated that they did not identify any factual inaccuracies in the ERG report*

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

Pre-meeting briefing

Padeliporfin for treating localised prostate cancer [ID866]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

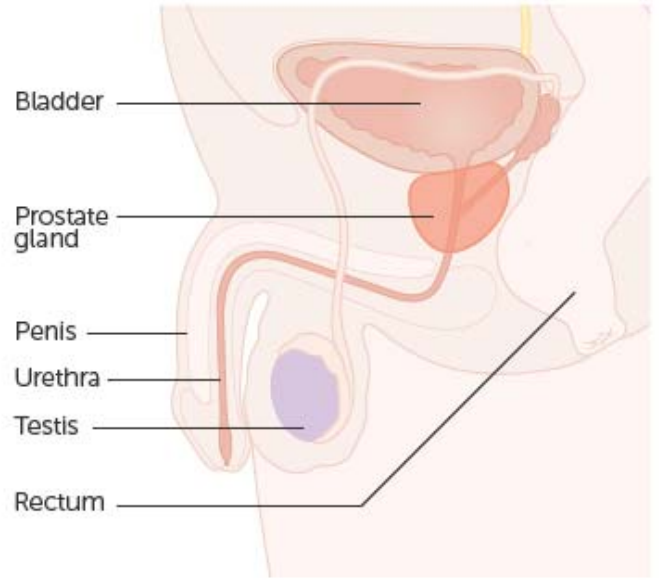
Key issues for consideration
Clinical effectiveness

- Treatment pathway and positioning of padeliporfin
  - relevant comparators (active surveillance or radical treatment)?
- Appropriate outcome definition for ‘disease progression’?
- No long-term evidence
- No evidence of padeliporfin *vs* radical therapy
  - potentially delay effective radical therapy → no evidence of long-term impact of padeliporfin on subsequent radical therapy

Key issues for consideration
Cost effectiveness

- Is the company's assumption that all treatments have the same risk of metastatic progression clinically plausible?
- The company adjusted 'time to metastasis' and 'overall survival' for general population all-cause mortality. Should 'time to radical therapy' also be adjusted?
- Which extrapolation curve for 'time to radical therapy' should be used?
- How should adverse events rates be modelled?
- Should adjuvant and salvage therapies be included in the model?
- What costs should be included for padeliporfin administration? Inpatient or day case?
- Innovation and equality issues

Background



Cancer Research UK

- Prostate
  - small gland near bladder
  - helps to produce semen
- Prostate cancer
  - most common cancer
    - 26% of male cancer diagnoses in UK
    - **17% low risk**, 47% intermediate risk*
    - majority between 65 to 74 years
- Risk factors
  - increasing age
  - black African-Caribbean family origin

Low risk: Prostate-specific antigen (PSA) **<**10ng/mL **&** Gleason score ≤6 **&** Clinical stage T1 to T2a
Intermediate risk: PSA 10–20 ng/ml **or** Gleason score 7 **or** Clinical stage T2b (NICE CG175)

Prostate cancer

disease progression

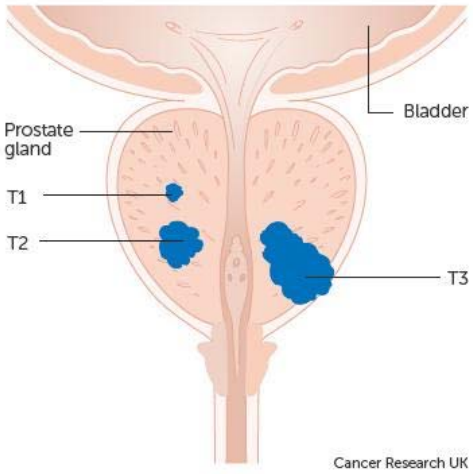
Localised disease

Very-low risk

Low risk

Intermediate risk

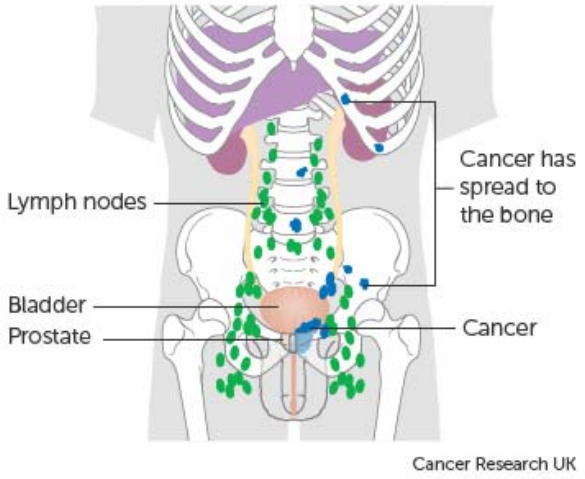
High risk*



Hormone sensitive

Hormone resistant^ – no longer hormone sensitive

Metastatic disease



*can be locally advanced disease

^can be hormone resistant and non-metastatic

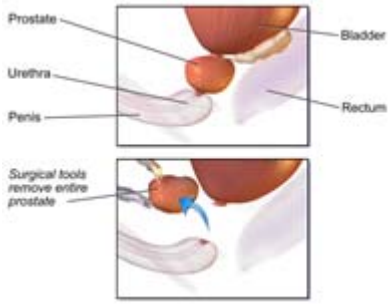
Treatments for localised prostate cancer

Routine options are active surveillance and radical therapy
Focal therapy available by special arrangements or in trials

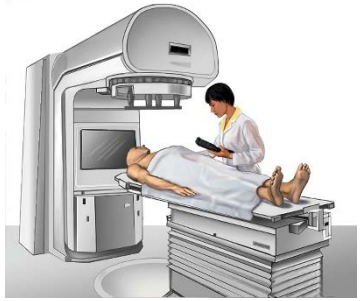
NHS

Active surveillance
- monitors for disease progression
- delays radical therapy

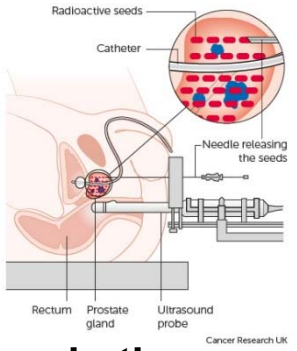
Radical therapy
- treats cancer → affects whole prostate
- risk of side effects → affect quality of life



prostatectomy



external beam radiotherapy



brachytherapy

FOCAL THERAPY

- Treats cancer by targeting main lesion → preserve prostate
- Reduce risk of side effects
- Debate: treating individual cores when disease is multifocal

By special arrangements or in trials:
- NICE IPG423 (cryotherapy)
- NICE IPG424 (high-intensity focused ultrasound)

PADELIPORFIN

- 1st focal therapy assessed in trial
- reduce overtreatment by radical therapy
- intact prostate → future radical therapy possible

Padeliporfin (Tookad), Steba Biotech

*Indication population: unilateral, low-risk prostate cancer (**not** very-low-risk)*
Administered using Vascular-Targeted Photodynamic (VTP) therapy

Marketing authorisation

➢ **monotherapy** for adults with previously **untreated, unilateral, low-risk**, adenocarcinoma of the prostate with a **life expectancy ≥10 years**:

- prostate-specific antigen (PSA) ≤10 ng/mL **&**
- Gleason score ≤ 6 **&**
- Clinical stage **T1c** or T2a **&**
- 3 positive cancer cores (core length no more than 5 mm in any 1 core) or 1-2 positive cores with ≥50% cancer involvement in any 1 core or a PSA density ≥0.15 ng/mL/cm^3

Mechanism of action

- administered using Vascular-Targeted Photodynamic (VTP) therapy
- fibres inserted using hollow tubes into cancer lesions
- padeliporfin is injected
- padeliporfin is activated by laser light → kills cancer cells over several days

Administration and dose

- single dose of 3.66 mg/kg of padeliporfin administered intravenously
- VTP procedure done under general anaesthetic
- retreatment of same lobe or treatment of other lobe not recommended

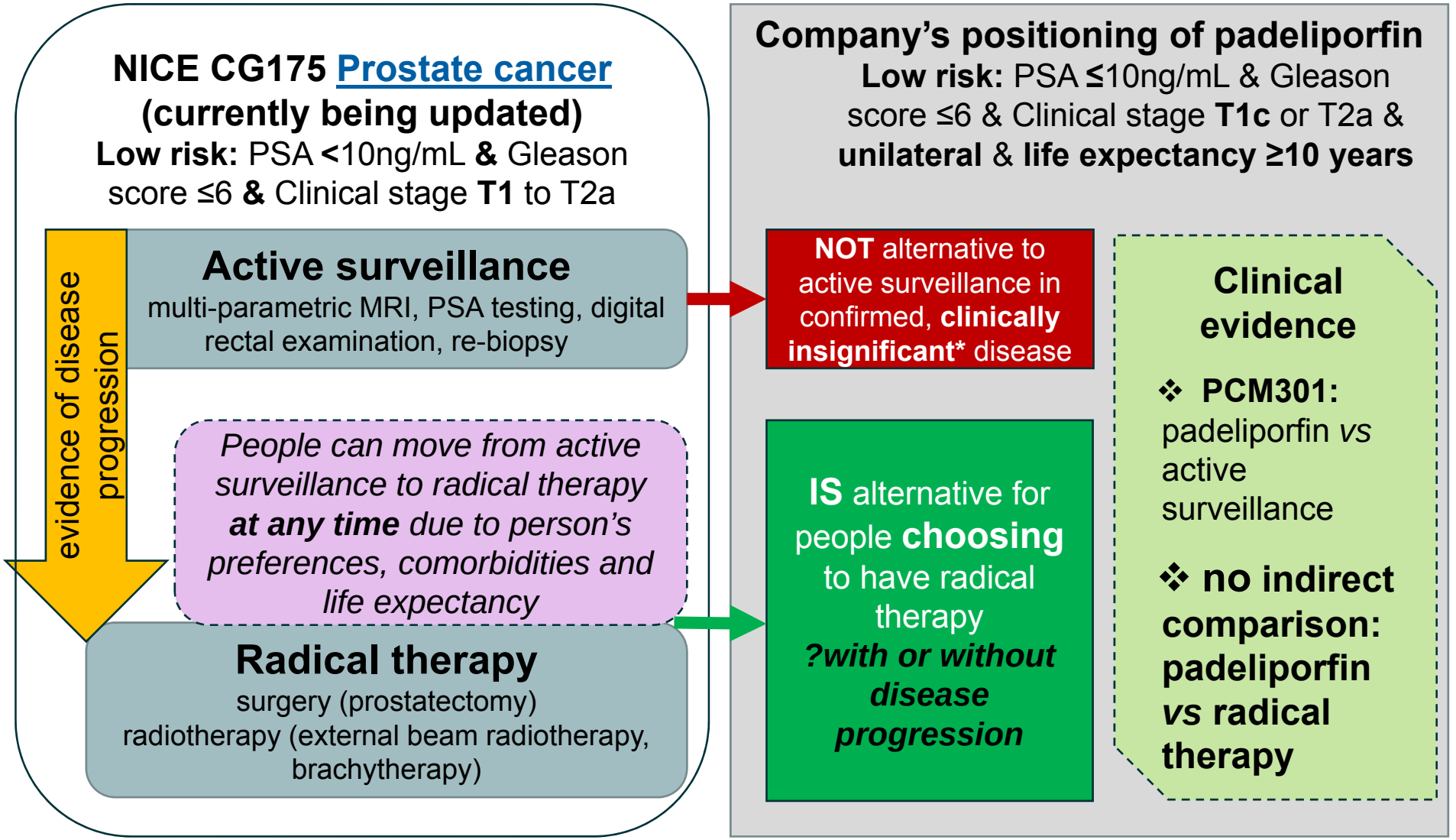
Clinical perspective

Active surveillance is mainly recommended for low-risk disease

- Treatment of localised disease: stop progression outside prostate with few side effects (bowel, urinary and sexual dysfunction)
  - Active surveillance in low and intermediate risk disease: about 1 in 3 men change to radical therapy by 5 years (mainly disease progression; for minority burden of surveillance)
  - 8% of men diagnosed with low-risk disease had radical therapy (National Prostate Cancer Audit 2017 report)
  - Variable access to current focal therapies in the NHS
- Treatment response: absence of any '**clinically significant'** disease on biopsy or MRI
  - different definitions of 'clinically significant': usually at least Gleason 3 + 4 disease (considering maximum cancer core length and grade)
- Risk stratification: thresholds between low and intermediate risk disease not well established e.g. low volume Gleason 3 + 4 may have less risk than high volume Gleason 3 + 3
- Padeliporfin has safe side effect profile
  - option for intermediate risk disease (Gleason 3 + 4 or possibly high volume Gleason 3 + 3)

Treatment pathway and positioning of padeliporfin

Padeliporfin is an alternative to radical therapy



*Index-lesion concept: only dominant lesion drives natural history of disease. Lesions: clinically significant (likely to have an impact on quality and length of life) or clinically insignificant (little to no chance of disease progression in expected lifetime and unlikely to benefit from active treatments) [Valerio 2014]

ERG clinical expert comments on positioning of padeliporfin

Padeliporfin should be compared with radical therapy
Effect of padeliporfin on effectiveness of future radical therapy is unknown

- Agree with company that padeliporfin is not an alternative to active surveillance
  - no place for padeliporfin for low-risk disease
  - treatment at outset not needed
  - if treated, may lead to over-treatment
- To fit in the current pathway, padeliporfin should:
  - be compared with radical therapy (cancer and quality of life outcomes)
  - show better cancer outcomes in people who progress on active surveillance
- Padeliporfin delays or avoids need for radical therapy (effective oncologically) → unclear impact of delay on future radical therapy effectiveness

Decision problem: population and comparators

Company only provides clinical evidence of padeliforin compared with active surveillance

NICE scope	Company submission
Population: adults with unilateral, low-risk localised prostate cancer	✓
Comparators: • Active surveillance • For people who choose radical treatment: radical surgery and radiotherapy	• **Clinical evidence:** active surveillance • **Economic model:** active surveillance, surgery (prostatectomy), radiotherapy (external beam radiotherapy and brachytherapy)

Decision problem: outcomes

*ERG questions the company's non-standard definition of disease progression and whether **notification** of start of radical therapy is similar to time to start of radical therapy*

NICE scope	Company submission, ERG comments
Outcomes: • disease-free survival • progression of disease • need for radical treatment • mortality • adverse effects of treatment (for example, erectile dysfunction or incontinence) • health-related quality of life	**ERG comments:** • disease-free survival (**continuous** outcome): company reports 'absence of definitive cancer' (**dichotomous** outcome) • progression of disease: company reports 'treatment failure' (progression of cancer from low to moderate or higher risk) and 'absence of definitive cancer'. **ERG clinical expert:** questions **non-standard definition** of 'progression' • need for radical treatment: company reports '**notification** of start of radical therapy'. **ERG: unclear** if 'notification' is an **adequate surrogate** for 'time to start of radical therapy'

Key clinical evidence

- **1 Phase 3 randomised controlled trial: PCM301**
  - padeliporfin *vs* active surveillance
  - **subgroup:** unilateral, low-risk (**not** bilateral or very-low-risk)
  - outcomes used in **economic model**: time to start of radical therapy and adverse events (bowel, urinary and sexual dysfunction)

- **NO network meta-analysis of padeliporfin and radical therapy**

PCM301 trial

413 adults with untreated, low-risk disease, diagnosed by biopsy <12 months (Gleason ≤6, 5mm maximum cancer core length)

✓ **Indication population (subgroup): 158** unilateral, low-risk disease (**not** bilateral or very-low-risk)

Padeliporfin (3.66mg/kg infusion & LASER activation)

Phase III, international, multicentre, randomised, open-label, parallel group (2011-2013)

UK sites

Active surveillance (PSA and DRE every 3 months, biopsy every 12 months)

Co-primary endpoints at 24 months

- absence of definite cancer
- treatment failure*

Other key outcomes

- time to start of radical therapy
- adverse events (bowel, urinary, sexual dysfunction)

- Follow-up of **all** patients: biopsy at 12 and 24 months, PSA and DRE every 3 months
- Outcome assessments blinded: Outcomes Review Panel

***Treatment failure:** histological cancer progression from low to intermediate/high risk or prostate cancer-related death. Any of the following: ≥4 positive cancer cores from all follow-up histological results, ≥1 core length >5 mm, any Gleason pattern ≥4, PSA >10ng/mL in 3 consecutive measures, any T3 clinical stage prostate cancer, any metastasis, prostate cancer-related death

DRE, digital rectal examination; PSA, prostate-specific antigen

ERG comments on PCM301

No comparison with radical therapy, no long-term cancer outcomes

- Trial methods not in line with current practice guidelines:
  - accuracy of tumour localisation did not meet focal therapy requirements (highlighted by study investigators)
  - risk of false negatives with biopsy sampling in padeliporfin is not adequately minimised by increasing sampling density
- Only comparator is active surveillance
  - no comparison with radical therapy
- Short-term outcomes (2 years)
  - no long-term oncological outcomes on the clinical effectiveness of padeliporfin

Comments from British Association of Urological Surgeons on PCM301

Patients on active surveillance were treated differently than in NHS
Some criteria in 'treatment failure' less likely to predict long-term clinical outcomes

- For low-risk disease (low volume Gleason 6 and ≤5mm cancer core length on biopsy): active surveillance is most appropriate form of initial management
- PCM301 did not offer men on active surveillance multi-parametric MRI: in NHS, this will routinely be offered to detect more significant disease
  - 44% of men in active surveillance in PCM301 had Gleason pattern 4 disease at the end of study
- PCM301 definition of treatment failure:
  - T3 disease and metastasis are very predictive of poorer long-term clinical outcome
  - Gleason pattern 4 of high burden may predict long-term clinical outcomes
  - Presence of ≥3 positive cores, cancer core length ≥5mm and PSA rise on 3 consecutive measures are less likely to adequately predict long-term clinical outcomes in the presence of Gleason 3 + 3 disease

PSA, prostate-specific antigen

‘Indication’ population: baseline characteristics

Patients were on average 63 years, ‘white’, diagnosed 5 months before and were at clinical stage T1c

Baseline characteristic	Padeliporfin (n=80)	Active surveillance (n=78)
Age (years)	64 (6.3; 48-74)	62 (6.3; 46-73)
Caucasian, n (%)	78 (98%)	78 (100%)
Body mass index (kg/m^2)	26 (3.3; 19-38)	26 (3.4; 19-41)
Time since diagnosis (months)	5 (4.7; 0.6-20)	5 (4.1; 0.2-19)
T1c clinical stage, n (%)	66 (82.5%)	71 (91%)
T2a clinical stage, n (%)	14 (17.5%)	7 (9%)
PSA (ng/mL)	7 (1.8; 1-10)	7 (1.7; 3-10)
Estimated prostate volume (cm^3)	37 (9.7; 25-68)	38 (9.6; 25-66)
Number of positive cores, n (%)		
1	15 (19%)	18 (23%)
2	34 (43%)	33 (42%)
3	31 (39%)	27 (35%)
Total cancer core length (mm)	5.3 (2.6; 0-14)	3.8 (2.7; 0-12)

Data are mean (SD; range) unless otherwise specified; PSA, prostate-specific antigen; SD, standard deviation

‘Indication’ population: co-primary endpoints

Patients on padeliporfin were less likely to have definitive cancer or disease progression at 24 months than patients on active surveillance
*ERG: disease progression in active surveillance **higher** than in other trials*

Outcomes	Padeliporfin	Active surveillance (AS)	Risk ratio (95% CI)
Absence of definitive cancer at 24 months*			
Lobe diagnosed at baseline	71% of 80 patients	15% of 78 patients	4.6 (2.7 to 7.9)
Whole gland	45% of 80 patients	10% of 78 patients	4.4 (2.2 to 8.3)
Absence of disease progression at 27 months			
Lobe diagnosed at baseline	90% of 71 patients	42% of 67 patients	2.2 (1.6 to 2.9)^
Whole gland	64% of 76 patients	25% of 71 patients	NA

*At clarification, company provided adjusted risk ratio using 12 months biopsy results where 24 months biopsy results were missing. **ERG comment:** risk ratios were comparable; ^calculated by **ERG**; CI, confidence intervals; NA, not available

ERG comments

- disease progression in active surveillance is higher than in other trials → may skew effectiveness in favour of padeliporfin
  - ProtecT (UK-based; low & intermediate risk, few high risk; 10 years; n=545 AS): 30%
  - PIVOT (US-based; low, intermediate & high risk; 8 years; n=367 AS): 68%

‘Indication’ population: outcomes used in economic model

ERG: rate of radical therapy in active surveillance higher than in other trials at 10 years

Outcomes at 24 months (unless otherwise stated)	Padeliporfin (n=79, unless otherwise stated)	Active surveillance (n=78, unless otherwise stated)	Padeliporfin *vs* active surveillance
Proportion on radical therapy at 48 months*	28% of 80 patients	57%	HR: 0.3 (95% CI: 0.2 to 0.5)
Bowel dysfunction^[a]	5%	0%	NA
Urinary incontinence^	1%	1%	NA
Erectile dysfunction^	18%	3%	NA

***Criteria to start radical therapy:** Gleason score ≥7, PSA 10ng/mL for 3 consecutive measures, clinical stage progression, >3 positive cores and at least 1 core >5mm; ^Grade 2 or above adverse event needing treatment; [a]includes gastrointestinal hypermotility, gastrointestinal disorder, anal fistula, gastrooesophageal reflux disease, gastritis, abnormal faeces, rectal haemorrhage, anal haemorrhage, haematochezia, and frequent bowel movements; CI, confidence intervals; HR, hazard ratio; NA, not available

ERG comments

- Rate of radical therapy in active surveillance is higher than ProtecT
  - Company’s log-normal base case projects [redacted] will have radical therapy by 10 years *vs* 55% in ProtecT

Company's rationale for difference in rate of radical therapy in PCM301 and ProtecT

PCM301 monitoring schedule and criteria for starting radical therapy was more stringent than ProtecT and patients in ProtecT included very-low-risk disease which is less likely to progress to radical therapy

Criteria	PCM301	ProtecT	Company's conclusion
Monitoring schedule	PSA and DRE every 3 months Biopsy at Month 12 and Month 24	PSA: every 3 months in year 1, every 6 months after (repeat testing if needed) No scheduled re-biopsies	PCM301 scheduled biopsies lead to earlier detection and progression to radical therapy
Criteria for consideration to start radical therapy	Gleason score ≥7, PSA 10ng/mL for 3 consecutive measures, clinical stage progression, >3 positive cores and at least 1 core >5mm	Increase of ≥50% PSA level in previous 12 months: review Management options: continued monitoring or further tests and radical or palliative treatments as required	Criteria to consider starting radical therapy in ProtecT may be based on looser guidelines than in PCM301. PCM301 criteria may have led to more frequent detections and progression to radical therapy
Baseline risk of progression in patients	Unilateral, low-risk disease but not very-low-risk	Mix of very-low-risk, low-risk and intermediate risk disease	Very-low-risk disease is less likely to progress to radical therapy (Godtman 2016)

PSA, prostate specific antigen; DRE, digital rectal examination

Padeliporfin *vs* radical therapy: no network analysis

ERG: agrees with company that a network meta-analysis was not possible

Company:

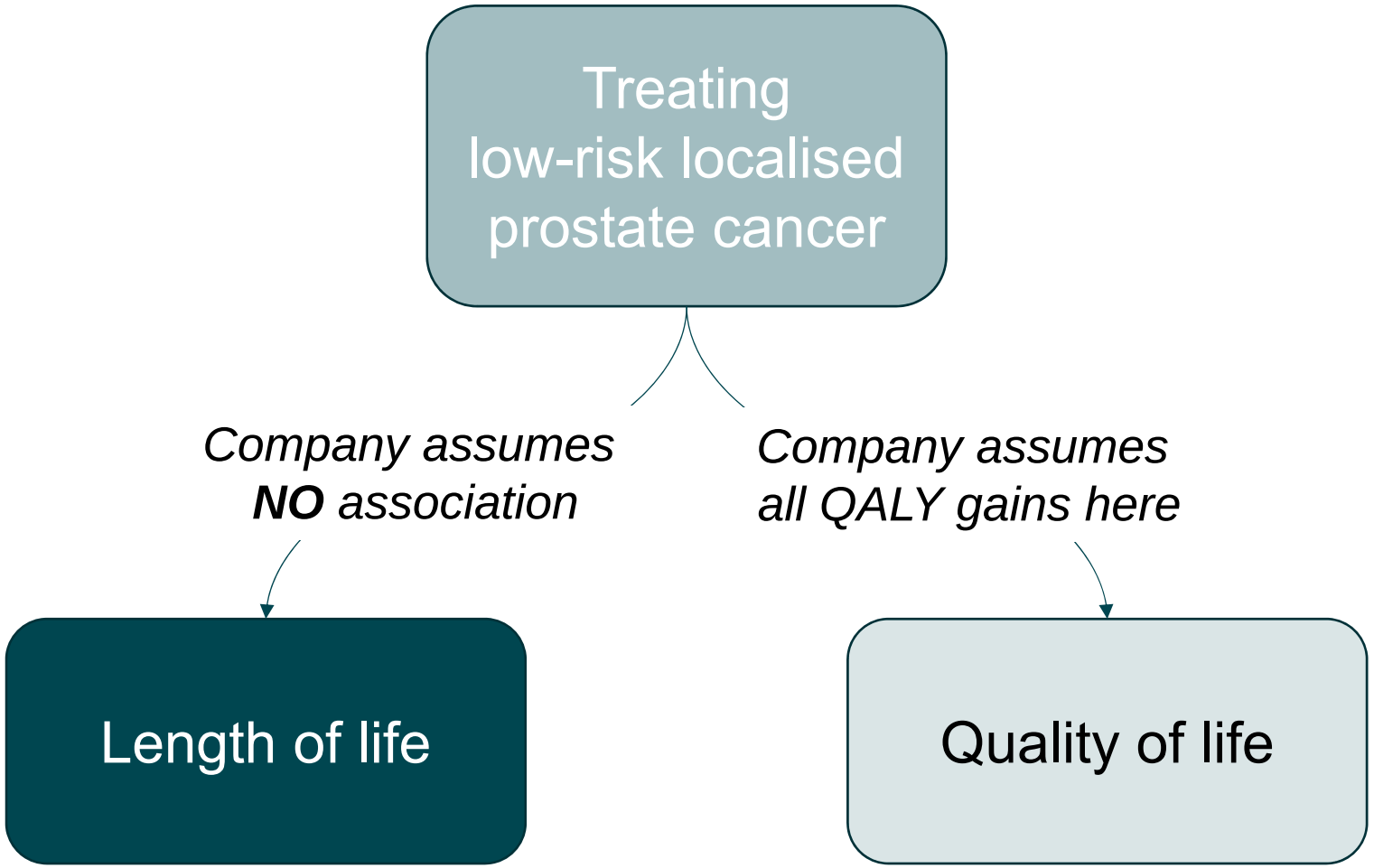
- No appropriate network possible between padeliporfin/active surveillance and radical therapy (prostatectomy, external beam radiotherapy, brachytherapy)
- Different endpoints used in economic model e.g. time to radical therapy

ERG's comments:

- Did not identify any further trials that could have been used
- Broadly agrees that no network meta-analysis could be undertaken given the available evidence

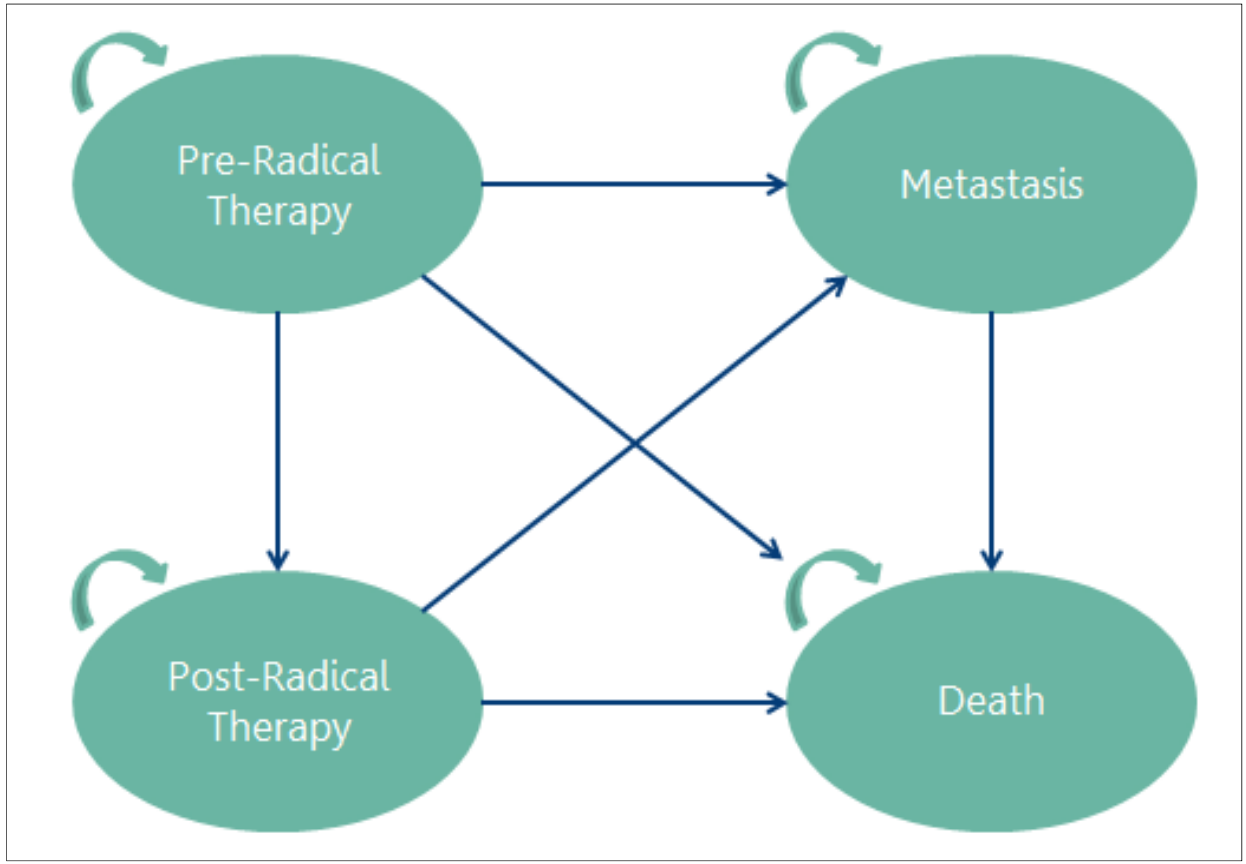
Cost effectiveness

Where do the QALY gains come from?



Increase in QALYs comes from improvement in quality of life associated with adverse events of treatments

Company's model



- Lifetime horizon (37 years; starting age 63 years), 6 monthly cycle
- 3.5% discount, NHS perspective

- Partitioned survival analysis model
- Parametric curves for time to radical therapy (TTRT), time to metastasis (TTM) and overall survival (OS) partition cohorts into 4 states
- Padeliporfin and active surveillance start in pre-radical therapy state (no radical therapy after 75 years old)
- Radical therapy starts in post-radical therapy state
- Company assumed all treatments have equal OS and TTM

Overview of health states

Health state	Utility values	Costs
Pre-radical therapy: patients have active surveillance or padeliporfin	Same health-related quality of life; differences due to adverse events	Active surveillance (AS): monitoring/testing and adverse events Padeliporfin: similar to AS, treatment-related acquisition and administration
Post-radical therapy: patients have immediate radical therapy; patients move from pre-radical to post-radical therapy when they start radical therapy	Same health-related quality of life as pre-radical therapy state; differences due to adverse events	Radical, adjuvant and salvage therapy, follow up surveillance and adverse events
Metastatic disease	Utility value of metastatic disease	Lump sum of treating metastatic disease in cycle 1
Death: absorbing health state	-	One-off end-of-life care

Data sources: PCM301 and ProtecT

- **Time to radical therapy** curves for padeliporfin and active surveillance (AS): based on **PCM301**
- **Time to metastasis** and **Overall survival**: based on **ProtecT** (AS *vs* Surgery and external beam radiotherapy (EBRT); at 10 years, no difference in prostate-cancer-specific survival but higher rate of disease progression in AS)
  - digitally extracted Kaplan-Meier data adjusted for general population all-cause mortality for 'prostate-cancer-specific mortality' and 'freedom from disease progression' (prostate-cancer related death; metastasis; long-term androgen deprivation therapy; clinical T3 or T4 disease; and ureteric obstruction, rectal fistula or need for permanent catheter when not considered to be complication of treatment in trial)
  - Time to metastasis: padeliporfin and AS (AS arm); radical therapies (EBRT arm)
  - Overall survival: all treatments (EBRT arm)

Baseline characteristics of ProtecT

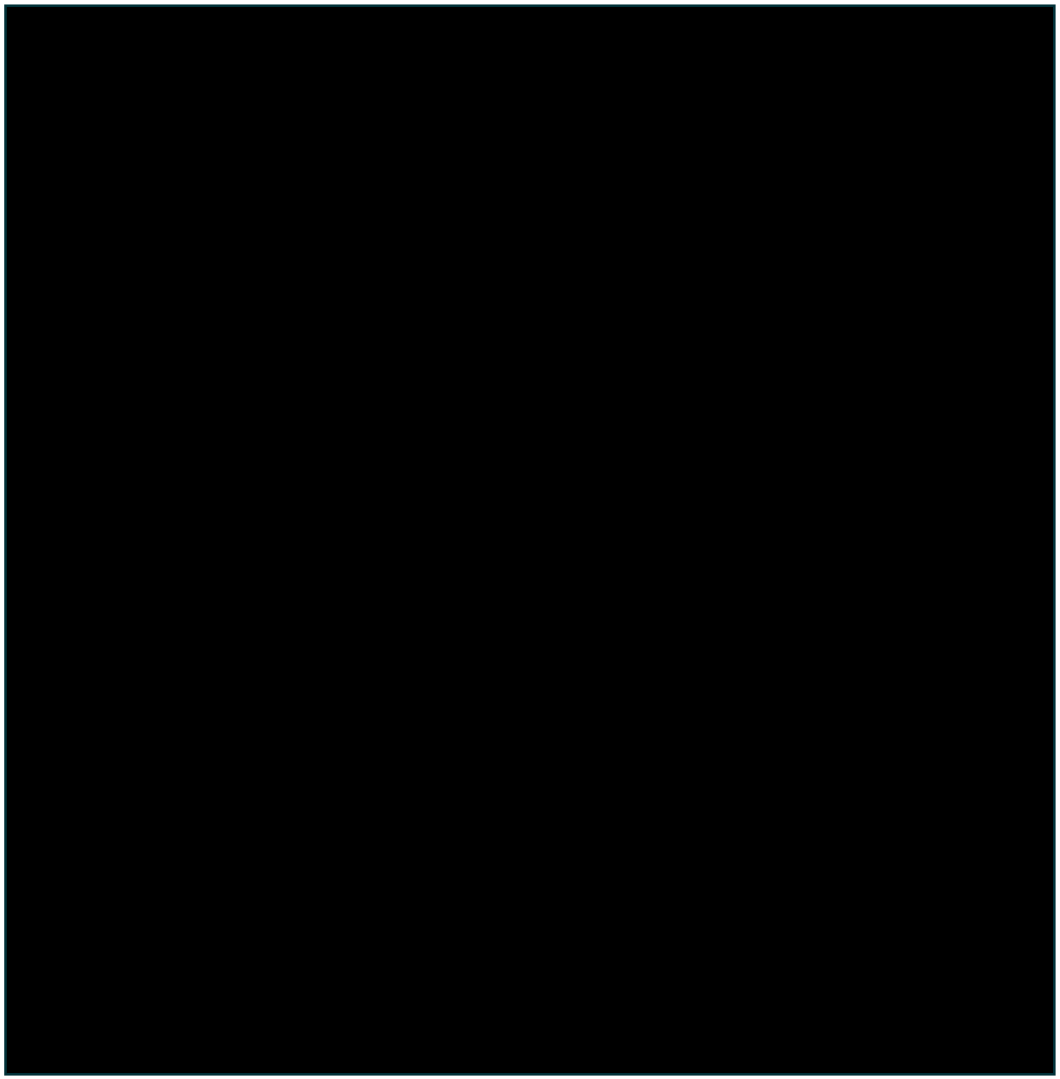
	Active surveillance (n=545)	Surgery (n=553)	Radiotherapy (n=545)
Mean age, years (SD)	62 (5)	62 (5)	62 (5)
Median PSA, ng/ml (IQR)	4.7 (3.7, 6.7)	4.9 (3.7, 6.7)	4.8 (3.7, 6.7)
PSA 10+ ng/ml (%)	57 (10%)	57 (10%)	58 (11%)
Gleason score 6, n (%)	421 (77%)	422 (76%)	423 (78%)
T1c clinical stage, n (%)	410 (75%)	410 (74%)	429 (79%)
T2 clinical stage, n (%)	135 (25%)	143 (26%)	116 (21%)

SD, standard deviation; IQR, inter-quartile range; PSA, prostate-specific antigen

Proportion of patients in health states

- Metastasis health state for padeliporfin and active surveillance: based on overall survival (time to prostate cancer-related death) – time to metastasis curves (adjusted for general population mortality)
- Post-radical therapy health state for padeliporfin and active surveillance: based on time to metastasis (TTM) – time to radical therapy (TTRT) curves
  - patients split into radical therapy type based on market share: 51.3% radical surgery, 24.4% external beam radiotherapy and 24.4% brachytherapy
- **ERG comments:**
  - Company did not adjust TTRT curve for general population mortality → overestimate numbers in pre-radical therapy health state
- **Company assumed all treatments have equal overall survival and time to metastasis**
- **ERG comments:**
  - no long-term data to verify there is equal metastatic progression between:
    - padeliporfin and active surveillance
    - padeliporfin or active surveillance and radical therapy
      - delayed time to radical therapy → poorer long-term outcomes?
  - **only driver in quality-adjusted life year differences: key adverse events**

Extrapolation of time to radical therapy for padeliporfin and active surveillance: PCM301



- **Company preferred log-normal distribution (based on AIC, clinical plausibility)**
- **ERG comments:**
- good fit in active surveillance (AS) arm driving log-normal selection → very little to choose between fitted curves based on AIC and BIC in padeliporfin arm
- extrapolations **uncertain** (affects 11.9 years from baseline as no radical therapy after 75 years) and **impact ICERs** → consider other distributions
- rate in AS is higher than in other trials (see **slides 19 and 20**)

Fit statistics – time to radical therapy

Treatment	Distribution	Akaike information criterion (AIC)	Bayesian information criterion (BIC)
Padeliporfin	Gompertz	194.76	199.52
	Weibull	194.94	199.70
	Log-logistic	195.27	200.03
	Lognormal	**196.35**	**201.11**
	Gamma	196.64	203.78
	Exponential	201.28	203.66
Active surveillance	Gamma	363.91	370.98
	Lognormal	**372.06**	**376.77**
	Log-logistic	375.94	380.65
	Weibull	380.96	385.68
	Gompertz	387.39	392.10
	Exponential	387.56	389.92
(Sum)	Gamma	560.55	574.76
	Lognormal	**568.41**	**577.89**
	Log-logistic	571.20	580.68
	Weibull	575.90	585.38
	Gompertz	582.14	591.62
	Exponential	588.84	593.58

Source: Patient-level data of PCM301 study

Company's rationale for choosing log-normal distribution

- Fit statistics: Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC)
- Visual inspection
- Clinical plausibility: in disease progression and progression to radical therapy after focal therapy:
  - most in-field progressions occur in 1st 2 years after treatment
  - most out-of-field progressions (other lobe) occur after this initial period at a fairly constant rate (typically 1-2% per year)
- ✓Lognormal distribution has a steadier hazard of progression to radical therapy over time after the first few years than generalised gamma distribution

Health-related quality of life: utility values

	Utility value or decrement	Company justification	ERG comments
Baseline utility	0.88	Similar values in PCM301 and Ramsay (2015)	Company did not discuss appropriateness of utility values in 'indication' population from original sources which used different methods to elicit utility values
Metastasis	0.58	Unlikely to differ based on prior treatment	Key assumption: people in pre-radical therapy state with disease progression is not associated with reduced quality of life independent of subsequent radical therapy effect on adverse event rates
Urinary incontinence	-0.05	Active treatment of prostate leads to urinary, erectile and bowel dysfunction, affecting quality of life	• Bowel dysfunction values derived from group of Japanese men applied to UK population using multiplier (Hummel 2003). **Company did not apply multiplier → overestimating original value** • Erectile dysfunction and urinary incontinence: applied as constant decrements rather than age-adjusted multipliers
Erectile dysfunction	-0.04		
Bowel dysfunction	**-0.16**		

Rates of adverse events

- Padeliporfin and active surveillance: PCM301
- Radical therapy: Ramsey (2015) – based on all sources (RCT, non-randomised comparative studies, case series with >10 people) reporting adverse events
  - Short term: median of rates before 6 months
  - Long term: mean of annualised rates after 6 months
- **ERG comments:**
  - not based on meta-analysis of adverse event rates by treatment; naïve indirect comparison, does not control for factors that may affect observed rates e.g. age, baseline prevalence, grade, stage of disease, year of study → uncertainty comparability of adverse events rates applied for radical therapies
  - cross-checked rates against ProtecT (different results) and applied rates for radical prostatectomy and radiotherapy compared to active surveillance from ProtecT (adjusted for baseline)

Short and long-term adverse event rates: company and ERG changes

Treatment	Duration	Proportion of people experiencing adverse event short term (first 6 months) and long term (after 6 months) in each model cycle					
		Urinary incontinence		Erectile dysfunction		Bowel dysfunction	
		Company	ERG	Company	ERG	Company	ERG
Padeliporfin	Short-term	1.3%		1.8%		5%	
	Long-term	0		10%		1.3%	
Active surveillance	Short-term	1.3%		1.3%		0	
	Long-term	0		0.013		0	
Radical prostatectomy	Short-term	24.8%	**45.3%**	64.5%	**47.2%**	4%	**0**
	Long-term	27.8%	**17%**	70.6%	**31.1%**	12.8%	**0**
External beam radiotherapy	Short-term	9.2%	**6.3%**	48.6%	**37.9%**	15.2%	**16.5%**
	Long-term	11.1%	**2.5%**	40.6%	**20.3%**	18.1%	**10%**
Brachytherapy	Short-term	33.2%		26.8%		5.5%	
	Long-term	36.3%		26.2%		11.6%	

Sources: PCM301 **grade 2 or above**; Ramsay 2015 (no explicit mention of severity grade of adverse events, assumed to be grade 2 or above); ProtecT (ERG)
Short-term = first 6 months, Long-term = after 6 months

Costs overview

- Pre-radical therapy and post-radical therapy health state: based on Ramsey (2015) study adjusted for inflation (2017-18 prices)
  - **ERG comments:** Ramsey (2015) used bottom-up costings → low compared to Healthcare Resource Group-based reference costs
- Padeliporfin: acquisition and administration in cycle 1 (secondary care costs for physical examinations and nurse consultations); cycle-specific monitoring costs and second padeliporfin treatment
- Active surveillance: same monitoring cost structure as padeliporfin
- Post-radical therapy health state: costs of radical therapy and monitoring (some receive adjuvant/salvage therapies)
- Monitoring costs for 3 key adverse events
- Metastasis state: one-off cost of treatment and maintenance
- Death state: one-off cost of end-of-life care

Padeliporfin administration costs

- **ERG comments**
  - Unclear if all resources have been measured (e.g. time in theatre, duration of stay, pre-treatment planning) but same issues may apply to other treatments
  - PCM301: pre-treatment multi-parametric MRI, reviewed with biopsy results by team of radiologists and urologists who determined number and positioning of optical fibres; 2 hour theatre allocation and planned overnight stay
    - unclear whether company included multi-parametric MRI costs
    - company cost procedure as day case although PCM301 patients stayed overnight

Adjuvant and salvage therapy costs

- **Adjuvant therapy costs**
  - Company assumes that 22% and 36% of patients having surgery have adjuvant hormone therapy and adjuvant external beam radiotherapy respectively
- **ERG comments**
  - NICE CG175 does not recommend these treatments in low-risk disease
- **Salvage therapy costs**
  - Company assumes 15.5% of people having surgery, 6.2% having external beam radiotherapy and 12.4% having brachytherapy also receive salvage therapy
- **ERG comments**
  - Unclear if these rates are appropriate for 'indication' population
  - Data informing probabilities are from Ramsey (2015) and generalisability to 'indication' population is unclear

Bowel dysfunction costs

- Company derived bowel dysfunction costs from Ramsey (2015) who sourced it from Hummel (2010)
- Company applied cost on an annual basis
- **ERG comments**
  - Costs reported as mean cost per patient, not per patient year → more suitable to apply as a one-off cost to the proportion of patients experiencing bowel dysfunction, rather than an annual basis

Company base case deterministic results – fully incremental analysis with and without active surveillance

ICERs are sensitive to adverse event rates/disutility

Treatment	Total costs (£)	Total QALYs	ICER (£/QALY)
Active surveillance	16,650	12.269	-
External beam radiotherapy	17,522	12.113	Dominated by AS
Surgery	19,334	11.970	Dominated by AS
Brachytherapy	20,554	12.162	Dominated by AS
Padeliporfin	27,652	12.492	**49,415**

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
External beam radiotherapy	17,522	12.113	-	-	-
Surgery	19,334	11.970	1,812	-0.143	Dominated by EBRT
Brachytherapy	20,554	12.162	3,033	0.049	Extendedly dominated
Padeliporfin	27,652	12.492	10,130	0.379	**26,728**

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World with and without padeliporfin: company's base case results

Treatment	World without padeliporfin	World with padeliporfin
Padeliporfin	0%	[redacted]
Active surveillance	51%	[redacted]
Surgery	25%	[redacted]
External beam radiotherapy	12%	[redacted]
Brachytherapy	12%	[redacted]

Company's base case

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
World without padeliporfin	17,889	12.163	-	-	-
World with padeliporfin	20,263	12.301	2,373	0.137	**17,287**

QALY, quality-adjusted life year

ERG exploratory analysis

1) Different proportion of patients receiving surgery, external beam radiotherapy and brachytherapy following active surveillance or padeliporfin in each cycle of the model
2) Adjust time to radical therapy curves on active surveillance and padeliporfin for general population mortality
3) **Reduce utility decrement associated with bowel dysfunction from 0.16 to 0.1**
4) **Remove costs of adjuvant therapies following radical therapy**
5) **Set bowel dysfunction rate in surgery equal to rate in active surveillance**
6) **Set bowel dysfunction rate in surgery equal to rate in padeliporfin**
7) Use adverse event rates in surgery and external beam radiotherapy from ProtecT
8) Include costs for multi-parametric MRI prior to padeliporfin administration and active surveillance; £343.42
9) **Include cost of an overnight stay (£275.59) in the padeliporfin**
10) **Apply cost of treating bowel dysfunction as a one-off to patients experiencing long-term bowel dysfunction**

ERG deterministic results – fully incremental analysis without active surveillance (1)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
Company revised base case (after clarification)					
EBRT	17,522	12.113	-	-	-
Surgery	19,334	11.970	1,812	-0.143	Dominated by EBRT
Brachytherapy	20,554	12.162	3,033	0.049	Extended dominated
Padeliporfin	27,652	12.492	10,130	0.379	**26,728**
Scenario 1 Recalculating the percentage of patients receiving surgery, EBRT and brachytherapy following active surveillance or padeliporfin in each cycle of the model					
EBRT	17,522	12.113	-	-	-
Surgery	19,334	11.970	1,812	-0.143	Dominated by EBRT
Brachytherapy	20,554	12.162	3,033	0.049	Extended dominated
Padeliporfin	27,733	12.492	10,211	0.379	**26,942**
Scenario 2 Adjusting the time to radical therapy curves on active surveillance and padeliporfin for general population mortality					
EBRT	17,522	12.113	-	-	-
Surgery	19,334	11.970	1,812	-0.143	Dominated by EBRT
Brachytherapy	20,554	12.162	3,033	0.049	Extended dominated
Padeliporfin	27,931	12.452	10,409	0.339	**30,673**

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy

ERG deterministic results – fully incremental analysis without active surveillance (2)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
Scenario 3 Using bowel disutility value equal to -0.1					
EBRT	17,522	12.250	-	-	-
Surgery	19,334	12.065	1,812	-0.185	Dominated by EBRT
Brachytherapy	20,554	12.249	3,033	-0.001	Dominated by EBRT
Padeliporfin	27,652	12.530	10,130	0.280	**36,195**
Scenario 4 Removing costs of adjuvant EBRT and HR therapies					
EBRT	17,085	12.113	-	-	-
Surgery	18,242	11.970	1,156	-0.143	Dominated by EBRT
Brachytherapy	20,315	12.162	3,230	0.049	Extended dominated
Padeliporfin	27,248	12.492	10,162	0.379	**26,813**
Scenario 5 Setting bowel dysfunction prevalence of surgery equal to active surveillance (ProtecT)					
Surgery	14,373	12.223	-	-	-
EBRT	17,522	12.113	3,149	-0.110	Dominated by surgery
Brachytherapy	20,554	12.162	6,181	-0.060	Dominated by surgery
Padeliporfin	26,929	12.529	12,555	0.306	**41,036**

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy

ERG deterministic results – fully incremental analysis without active surveillance (3)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
Scenario 6 Setting bowel dysfunction prevalence of surgery equal to padeliporfin					
Surgery	14,930	12.195	-	-	-
EBRT	17,522	12.113	2,592	-0.082	Dominated by surgery
Brachytherapy	20,554	12.162	5,625	-0.032	Dominated by surgery
Padeliporfin	27,012	12.525	12,083	0.330	**36,612**
Scenario 7 Setting the adverse event rates for surgery and EBRT, based on the observed differences compared to active surveillance in ProtecT					
Surgery	12,996	12.479	-	-	-
EBRT	13,590	12.424	594	-0.056	Dominated by surgery
Brachytherapy	20,554	12.162	7,559	-0.317	Dominated by surgery
Padeliporfin	26,455	12.588	13,459	0.108	**124,345**
Scenario 8 Adding one-off cost of a pre-treatment multiparametric MRI scan to the cost of active surveillance and padeliporfin					
EBRT	17,522	12.113	-	-	-
Surgery	19,334	11.970	1,812	-0.143	Dominated by EBRT
Brachytherapy	20,554	12.162	3,033	0.049	Extended dominated
Padeliporfin	28,016	12.492	10,494	0.379	**27,688**

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy

ERG deterministic results – fully incremental analysis without active surveillance (4)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
Scenario 9 Adding 1 inpatient excess bed day (£275.59) to padeliporfin treatment cost					
EBRT	17,522	12.113	-	-	-
Surgery	19,334	11.970	1,812	-0.143	Dominated by EBRT
Brachytherapy	20,554	12.162	3,033	0.049	Extended dominated
Padeliporfin	27,944	12.492	10,423	0.379	**27,500**
Scenario 10 Treatment cost of bowel dysfunction as a one-off long term cost					
EBRT	11,817	12.113	-	-	-
Surgery	15,391	11.970	3,574	-0.143	Dominated by EBRT
Brachytherapy	16,956	12.162	5,139	0.049	Extended dominated
Padeliporfin	26,115	12.492	14,299	0.379	**37,727**
Scenario 11 Applying scenarios 3,4,5,9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
EBRT	12,428	12.250	-	-	-
Surgery	15,167	12.223	2,739	-0.027	Dominated by EBRT
Brachytherapy	16,717	12.249	4,288	-0.001	Dominated by EBRT
Padeliporfin	26,525	12.553	14,097	0.303	**46,544**

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy

ERG deterministic results – fully incremental analysis without active surveillance (5)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
Scenario 12 Applying scenarios 3,4,6,9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
EBRT	12,428	12.250	-	-	-
Surgery	15,277	12.205	2,848	-0.045	Dominated by EBRT
Brachytherapy	16,717	12.249	4,288	-0.001	Dominated by EBRT
Padeliporfin	26,542	12.550	14,114	0.300	**47,016**
Scenario 13 Applying scenarios 1,2,3,4,5,9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
EBRT	12,428	12.250	-	-	-
Surgery	15,167	12.223	2,739	-0.027	Dominated by EBRT
Brachytherapy	16,717	12.249	4,288	-0.001	Dominated by EBRT
Padeliporfin	26,565	12.524	14,137	0.274	**51,543**
Scenario 14 Applying scenarios 1,2,3,4,6,9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
EBRT	12,428	12.250	-	-	-
Surgery	15,277	12.205	2,848	-0.045	Dominated by EBRT
Brachytherapy	16,717	12.249	4,288	-0.001	Dominated by EBRT
Padeliporfin	26,586	12.521	14,158	0.271	**52,235**

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy

Innovation

- First focal therapy with RCT data to support its use
- Unique solution to low-risk prostate cancer that addresses limitations of active surveillance and radical therapy
- Minimally invasive, targeted therapy aimed at area of cancer, preserving normal tissue, controlling disease progression and preserving quality of life (mainly urinary and erectile function)
- Reduce over-treatment:
  - ~17% low risk
  - ~49% elect to have radical therapy
  - Of the 51% electing to have active surveillance, 25 to 60% switch to radical therapy within 5 to 10 years (large proportion stopping active surveillance even in absence of risk upstaging)

Equality issues

- None identified by company or stakeholders

Authors

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  Technical Lead
- **Jasdeep Hayre**
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- with input from the Lead Team (**John Cairns and Sarah Wild**)

Back-up slides

Ongoing studies

- PCM301 FU5 – extension study of PCM301
  - high drop outs
- ‘In-depth biopsy study’ planned
  - Phase IV study PCM401 – 7 year follow up observational cohort study of unilateral low risk localised prostate cancer treated with TOOKAD vascular targeted photodynamic therapy in clinical practice
  - Assess importance of tumour location in relation to toxicity and oncological outcome
  - Only baseline information in next 12 months
  - Data collection planned at 12 months after TOOKAD
- PCM402 – international registry to assess use of TOOKAD for localised prostate cancer
  - Only collects pre-treatment data

Time to metastasis curves

- PIVOT trial (Observation *vs* surgery; 15 year follow up; Wilt 2017)
  - in very-low and low-risk disease, no significant difference in metastatic disease progression between observation and surgery (HR 0.54, 95% CI 0.18 to 1.62)
- Based on these additional data and the differences in populations between PCM301 and ProtecT, company concluded the following for the TTM curves:
  - for radical therapy (surgery, EBRT and brachytherapy), surgery arm of ProtecT is appropriate to describe expected disease progression in a UK, low-risk only population as differences in patient populations do not affect disease progression
  - for active surveillance (and padeliporfin), surgery arm of ProtecT is appropriate to describe expected disease progression in a UK, low-risk only population, taking into account the impact of excluding intermediate-risk patients on disease progression
- UK clinician agreed that radical therapy would have a similar effect on progression among patients with low risk and intermediate risk disease but patients on active surveillance with low risk *vs* intermediate risk would have different risk progression as no treatment is involved

Active surveillance resource use

Year	Resource inputs	NICE CG175 Multi-parametric MRI at start
1	• 4 nurse-led outpatient appointments • 4 PSA tests • 1 DRE • 1 MDT meeting	• 3-4 PSA tests • 1-2 DRE • 1 rebiopsy
2	• 1 biopsy • 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	• 2-4 PSA tests • 1-2 DRE
3	• 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	• 2-4 PSA tests • 1-2 DRE
4	• 1 biopsy • 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	• 2-4 PSA tests • 1-2 DRE
5	• 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	• 2 PSA tests • 1 DRE
Annually thereafter	• 1 practice nurse appointment • 1 PSA test • 1 DRE	• 2 PSA tests • 1 DRE

PSA, prostate-specific antigen; DRE, digital rectal examination; MDT, multidisciplinary team; Source: Ramsay (2015)

Company's original base case and ERG's adjustment for general population all-cause mortality deterministic results – fully incremental analysis without active surveillance

Company's original base case model (before clarification): assumed that active surveillance and padeliporfin follow higher rate of progression to metastasis (active surveillance arm in ProtecT). After clarification, company assumed all treatments have equal time to metastasis and overall survival.

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
EBRT	16,999	11.340	-	-	-
Surgery	18,752	11.185	1,754	-0.155	Dominated by EBRT
Brachytherapy	19,871	11.393	2,873	0.053	Extended dominated
Padeliporfin	26,714	11.643	9,715	0.303	**32,082**

ERG's revision of company's original base case model – adjusted for general population all-cause mortality

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
EBRT	17,522	11.089	-	-	-
Surgery	19,334	10.947	1,812	-0.143	Dominated by EBRT
Brachytherapy	20,554	11.139	3,033	0.049	61,372
Padeliporfin	27,621	11.083	7,067	-0.056	**Dominated by Brachytherapy**

EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

World with and without padeliporfin (1)

- Overall cost effectiveness: ICER of a population where padeliporfin is an option *vs* not

	Proportion of people having		
	Active surveillance	**Surgery**	**Radical radiotherapy**
Newly diagnosed low risk <60 years*	55.9%	27.3%	16.8%
Newly diagnosed low risk 60 – 69 years*	63.7%	16.6%	19.7%
'Indication' population <60 years^	14.8%	17.9%	7.4%
'Indication' population 60-69 years^	22.6%	7.1%	10.3%
Overall market share	51%	25%	24% (12% EBRT, 12% brachytherapy)

*Based on Greenberg (2015), adjusted by the company to exclude people who may have had hormone therapy (4.3%) and reallocated to the 3 treatment options; ^PCM301 distribution: 40% unilateral low risk ('indication' population), 37% unilateral very low risk, 23% bilateral low risk

ERG's exploratory analyses – world with and without padeliporfin (1)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 1 recalculating the percentage of patients receiving surgery, EBRT and brachytherapy following active surveillance or padeliporfin in each cycle of the model					
World without padeliporfin	17,930	12.163	-	-	-
World with padeliporfin	20,327	12.301	2,398	0.137	**17,465**
Scenario 2 Adjusting the time to radical therapy curves on active surveillance and padeliporfin for general population mortality					
World without padeliporfin	17,855	12.157	-	-	-
World with padeliporfin	20,312	12.282	2,457	0.125	**19,596**
Scenario 3 Using bowel disutility value equal to -0.1					
World without padeliporfin	17,889	12.250	-	-	-
World with padeliporfin	20,263	12.371	2,373	0.121	**19,616**

EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

ERG's exploratory analyses – world with and without padeliporfin (2)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 4 Removing costs of adjuvant EBRT and HR therapies					
World without padeliporfin	17,218	12.163	-	-	-
World with padeliporfin	19,712	12.301	2,494	0.137	**18,170**
Scenario 5 Setting bowel dysfunction prevalence of surgery equal to active surveillance (ProtecT)					
World without padeliporfin	15,752	12.272	-	-	-
World with padeliporfin	18,901	12.370	3,148	0.098	**32,183**
Scenario 6 Setting bowel dysfunction prevalence of surgery equal to padeliporfin					
World without padeliporfin	16,000	12.259	-	-	-
World with padeliporfin	19,059	12.362	3,059	0.102	**29,885**

EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

ERG's exploratory analyses – world with and without padeliporfin (3)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 7 Setting the adverse event rates for surgery and EBRT, based on the observed differences compared with active surveillance in ProtecT					
World without padeliporfin	14,355	12.446	-	-	-
World with padeliporfin	17,637	12.510	3,282	0.064	**51,157**
Scenario 8 Adding one-off cost of a pre-treatment multiparametric MRI scan to the cost of active surveillance and padeliporfin					
World without padeliporfin	18,056	12.163	-	-	-
World with padeliporfin	20,538	12.301	2,482	0.137	**18,082**
Scenario 9 Adding a weighted average cost of an inpatient excess bed day (£275.59) to the treatment cost of padeliporfin					
World without padeliporfin	17,889	12.163	-	-	-
World with padeliporfin	20,350	12.301	2,461	0.137	**17,927**

EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

ERG's exploratory analyses – world with and without padeliporfin (4)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 10 Applying cost of bowel dysfunction as a one-off long term cost					
World without padeliporfin	14,284	12.163	-	-	-
World with padeliporfin	17,345	12.301	3,061	0.137	**22,297**
Scenario 11 Applying scenarios 3, 4, 5, 9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
World without padeliporfin	14,309	12.318			
World with padeliporfin	17,561	12.414	3,252	0.096	**33,763**
Scenario 12 Applying scenarios 3, 4, 6, 9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
World without padeliporfin	14,356	12.310			
World with padeliporfin	17,592	12.409	3,236	0.099	**32,661**

EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Prostate cancer (localised) - padeliporfin [ID866]

Document B

Company evidence submission

February 2018

File name	Version	Contains confidential information	Date
ID866_Padeliporfin VTP_ Document B_Company Evidence Submission_2018Feb27_redacted	Final	Yes	Feb 28, 2018

Contents

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List of Abbreviations

3-D CRT	3D conformal radiation therapy
5-ARI	5-α-reductase inhibitor
AE	Adverse event
AIC	Akaike information Criteria
ANCOVA	Analysis of covariance
AS	Active surveillance
AUC	Area under the curve
AUS	Artificial urinary sphincter
BD	Bowel dysfunction
BIC	Bayesian Information Criteria
BT	Brachytherapy
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness Analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPI	Consumer price index
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE	Common Terminology Criteria for Adverse Events
DARE	Database of Abstracts of Reviews of Effects
DRE	Digital rectal exam
DSMB	Data Safety Monitoring Board
DT	Doubling time
EBRT	External beam radiotherapy
eCRF	Electronic case report form
ED	Erectile dysfunction
EED	Economic Evaluation Database
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	EuroQoL 5-Dimension
HEED	Health Economic Evaluations Database
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HT	Hormone therapy
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IGRT	Image-guided radiation therapy

IIEF	International Index of Erectile Function
IMRT	Intensity-modulated radiation therapy
IPSS	International Prostate Symptom Score
ITT	Intention-to-treat
IV	Intravenous
LYG	Life years gained
MAA	Marketing Authorisation
MDT	Multidisciplinary team
mITT	Modified intention-to-treat
MRC	British Medical Research Council
MRI	Magnetic resonance imaging
NA	Not applicable
NA	Not applicable
NC	Not calculated
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ORP	Outcomes Review Panel
OS	Overall survival
OWSA	One-way deterministic sensitivity
PADT	Primary androgen deprivation therapy
PAES	Post-Authorization Efficacy Study
PASS	Post-Authorization Safety Study
PCa	Prostate cancer
PCI	Prostate Cancer Index
PH	Proportional hazard
PP	Per protocol
PSA	Prostate-specific antigen
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality-adjusted life-year
QLQ-C30	Quality of Life Questionnaire—Cancer 30
QLQ-PR25	Quality of Life Questionnaire-Prostate Cancer 25
QoL	Quality of life
RCT	Randomized controlled trial
RP	Radical prostatectomy
RR	Risk ratio
RT	Radical therapy
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error

SF-12	Medical Outcomes Study 12-Iterm Short-Form General Health Survey
SLR	Systematic literature review
TEAE	Treatment-emergent adverse event
TNM	Tumour, nodes, metastasis
TRUS	Transrectal ultrasound
TTM	Time to metastasis
TTRT	Time to radical therapy
UI	Urinary incontinence
UK	United Kingdom
VAS	Visual analogue scale
VTP	Vascular-targeted photodynamic therapy
WTP	Willingness to pay

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

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 unilateral, low-risk localised prostate cancer	As per scope	Not applicable
Intervention	Padeliporfin for use in vascular-targeted photodynamic therapy	As per scope	Not applicable
Comparator(s)	• Active surveillance For people who choose radical treatment: • Radical surgery • Radical radiotherapy	As per scope	Not applicable
Outcomes	The outcome measures to be considered include: • Disease-free survival • Progression of disease • Need for radical treatment • Mortality • Adverse effects of treatment (for example, erectile dysfunction or incontinence) • Health-related quality of life.	As per scope	Not applicable

B.1.2 Description of the technology being appraised

The summary of product characteristics (SmPC) and the European Public Assessment Report (EPAR) have been submitted as part of the reference pack.

Table 2 Technology being appraised

UK approved name and brand name	Approved name: padeliporfin Brand name: TOOKAD®
Mechanism of action[1]	Padeliporfin is retained within the vascular system. When activated with 753 nm wavelength laser light, padeliporfin triggers a cascade of pathophysiological events resulting in focal necrosis within a few days. Activation within the illuminated tumour vasculature, generates oxygen radicals (•OH, $O_2^{\bullet-}$) causing local hypoxia that induces the release of nitric oxide (•NO) radicals. This results in transient arterial vasodilatation that triggers the release of the vasoconstrictor, endothelin-1. Rapid consumption of the •NO radicals, by oxygen radicals, leads to the formation of reactive nitrogen species (RNS) (e.g. peroxynitrite), in parallel to arterial constriction. In addition, impaired deformability is thought to enhance erythrocyte aggregability and formation of blood clots at the interface of the arterial supply (feeding arteries) and tumour microcirculation, results in occlusion of the tumour vasculature. This is enhanced by RNS-induced endothelial cell apoptosis and initiation of self-propagated tumour cells necrosis through peroxidation of their membrane.
Marketing authorisation/CE mark status	The CHMP has adopted a positive opinion on the Marketing Authorisation Application (MAA) for TOOKAD® on 14 September 2017. The European Commission has granted Marketing Authorization for TOOKAD® on 10 November 2017.
Indications and any restriction(s) as described in the summary of product characteristics[1]	TOOKAD® is indicated as monotherapy for adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and: • Clinical stage T1c or T2a, • Gleason Score ≤ 6, based on high-resolution biopsy strategies, • PSA ≤ 10 ng/mL, • 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1-2 positive cancer cores with ≥ 50% cancer involvement in any one core or a PSA density ≥ 0.15 ng/mL/cm^3 TOOKAD® is restricted to hospital use only. It should only be used by personnel trained in the Vascular-Targeted Photodynamic therapy (VTP) procedure.
Method of administration and dosage[1]	<u>Posology</u> • The recommended posology of TOOKAD® is one single dose of 3.66 mg/kg of padeliporfin. • TOOKAD® is administered as part of focal VTP. The VTP procedure is performed under general anaesthesia after rectal preparation. Prophylactic antibiotics and alpha-blockers may be prescribed at the physician's discretion. • Retreatment of the same lobe or sequential treatment of the contralateral lobe of the prostate are not recommended.

	Method of administration TOOKAD® is for intravenous use. *Illumination for photoactivation of TOOKAD®* The solution is administered by intravenous injection over 10 minutes. Then the prostate is illuminated immediately for 22 minutes 15 seconds by laser light at 753 nm delivered via interstitial optical fibres from a laser device at a power of 150 mW/cm of fibre, delivering an energy of 200 J/cm. Planning of optical fibre positioning should be performed at the beginning of the procedure using the treatment guidance software. During the procedure, the number and the length of the optical fibres are selected depending on the shape and the size of the prostate and the optical fibres are positioned transperineally into the prostate gland under ultrasound guidance to achieve a Light Density Index (LDI) ≥ 1 in the targeted tissue. Treatment should not be undertaken in patients where an LDI ≥ 1 cannot be achieved
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment	Anticipated list prices: • Padeliporfin: £3,761 per 183 mg vial • Optical fibre: £254 per fibre • Catheter: £55 per catheter • Rectal probe: £332 per probe • Laser: £620 per procedure Average cost of a course of treatment: • Total acquisition cost: £12,111 per patient (excluding leasing the laser)
Patient access scheme (if applicable)	Not applicable

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

Brief overview of the disease or condition for which the technology is indicated

Clinical presentation

The prostate gland is located at the base of the bladder and is normally about the size of a walnut. It surrounds the first part of the urethra (carrying urine from the

bladder and sperm from the testicles to the penis), and its most important function is the production of a fluid that, together with sperm and fluids from other glands, makes up semen. Because of these anatomical and functional properties, damage to the prostate and surrounding tissues can cause severe urinary problems and erectile dysfunction. As men get older, the prostate often gets bigger, a condition called benign prostatic hyperplasia. This increase in size can cause urinary symptoms but is not cancer and is not a target indication for the current technology.

Among other proteins, the prostate gland produces a protein called prostate specific antigen (PSA). A blood test can measure the level of PSA, and higher levels of PSA can indicate hyperplasia or cancerous growth of the prostate. In the United Kingdom (UK), PSA testing is not offered routinely due to the lack of proven overall benefit of such testing.[2] However, men who experience symptoms, or who for other reasons request to investigate possible presence of prostate cancer, can request to be tested.[3] If the test is positive, follow up examinations and additional tests can show if the growth is cancerous and whether or not any monitoring or treatment activities need to be initiated.[4]

Most prostate cancers start in the outer gland cells of the prostate and are known as acinar adenocarcinomas. Many of these cancers grow extremely slowly and are not likely to spread, but some can grow more quickly.[5] The stage of a prostate cancer provides information about its size and how far it has spread in the body. Clinicians usually rely on the TNM (Tumour, Node, Metastasis) system for classification: T describes the size of the tumour; N describes whether cancer cells are detected in regional lymph nodes; and M describes whether the cancer has metastasized. In the TNM staging system, localised prostate cancer is defined as one of the following: T1/ N0/M0, T2/N0/M0, or T3a/N0/M0.

Based on the TNM classification, the result of the PSA test, and microscopic inspection of tumour biopsies (i.e., the Gleason score), physicians further divide localised prostate cancer into four risk groups:

- Very low risk: T1c and Gleason score ≤6 and PSA<10ng/mL and maximum 2 biopsy cores positive and maximum cancer core involvement ≤50% in any one core and PSA density<0.15mg/mL/g

- Low risk: T1-T2a and Gleason score ≤6 and PSA<10ng/mL
- Intermediate risk: T2b or Gleason score 7 or PSA10-20ng/mL
- High risk: ≥T2c or Gleason score 8-10 or PSA>20ng/mL

Very low and low-risk prostate cancers are unlikely to grow or spread for many years. The approved label of padeliporfin (TOOKAD®) VTP defines the indication population essentially as low, but not very low risk unilateral disease. Specifically padeliporfin VTP is indicated as monotherapy for adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and:

- Clinical stage T1c or T2a,
- Gleason Score ≤ 6, based on high-resolution biopsy strategies,
- PSA ≤ 10 ng/mL,
- 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1-2 positive cancer cores with ≥ 50 % cancer involvement in any one core or a PSA density ≥ 0.15 ng/mL/cm^3.

Epidemiology in England

Prostate cancer is the most common cancer in men and makes up 26% of all male cancer diagnoses in the UK.[6] In 2016, 40,489 cancer diagnoses were registered in England,[7] of which 17% are low risk using estimates from 2011.[8] In the UK, prevalence of prostate cancer was estimated to be 835 per 100,000 males in 2010 and was projected to increase to 1,264 per 100,000 males in 2010.[9] There were 10,016 deaths from prostate cancer in England in 2015.[10] Prostate cancer is predominantly a disease of older men (aged 65–79 years) but around 25% of cases occur in men younger than 65. There is also higher incidence of mortality from prostate cancer in men of black African-Caribbean family origin compared with white Caucasian men. Prostate cancer is usually diagnosed after a blood test in primary care has shown elevated PSA levels. The introduction of PSA testing has significantly reduced the number of men presenting with metastatic cancer since the 1980s. Most prostate cancers are now either localised or locally advanced at diagnosis, with no evidence of spread beyond the pelvis.[8]

Current management of early stage prostate cancer and the rationale for focal therapy

Does it make sense to treat localised, low-risk prostate cancer cores? How and when does early-stage cancer progress to more aggressive forms? Because these questions still lack comprehensive answers and most patients present with multiple cancer foci, there has been some debate about the general usefulness of early-stage treatments of individual cores. If early detection and treatment eliminating individual cores can prevent progression to more aggressive disease,[11] then this strategy holds promise to avoid progression to metastatic disease, which is difficult to treat and has a 5-year survival rate of only 30%.[12] But if treatment of early stages comes with considerable side effects and aggressive cancer cores develop independently of these lesions, then this type of treatment could constitute overtreatment, impairment of quality of life, and waste of healthcare resources.

In this context, early stage prostate cancer patients are currently offered two options to manage their disease that are at the opposite ends of the care spectrum:

- Active surveillance, where cancer is left untreated but its possible progression is monitored according to a pre-defined schedule based on PSA testing, rebiopsy, and digital rectal exam (DRE). This approach primarily aims at deferring radical treatment and this way preserving patient's quality of life, but with a greater risk of cancer progression

- Radical therapy, where the cancer is removed by destroying the whole prostate gland either through surgery or external beam radiotherapy (EBRT) or brachytherapy (BT). This approach primarily aims at controlling cancer progression, but with a greater risk of impairing the patient's quality of life through genitourinary and bowel-associated toxicities

As a result, patient preference plays an important role in the selection of treatment for early stage prostate cancer. Roughly 50% of low-risk patients currently elect to radical therapy at diagnosis and 50% elect to active surveillance.[7;13;14] 25 to 60% of active surveillance patients eventually cross over to radical therapy within 5-10 years, with its attendant morbidity.[15-17] In recent years, an intermediate approach of

focal treatment of prostate cancer has been explored – padeliporfin VTP falls under this approach.

Recent results based on whole-genome sequencing have provided support for the clonal expansion theory of prostate cancer foci thus supporting the rationale that early treatment of individual cores can result in long-term avoidance of metastatic disease. A recent study showed, for example, that adjacent lesions of Gleason patterns 3 and 4 were clonal (i.e., derived from a common progenitor) based on multiple shared genomic alterations.[18] This indicates that elimination of the detected Gleason pattern 3 lesion and surrounding cells holds promise to also eliminate those cells that would otherwise develop into more aggressively growing lesions.

In a recent review, Valerio et al. connected the clonal hypothesis to the rationale behind focal therapies as follows:[19]

> "To balance the unfavourable risk/benefit ratio of current standard treatments, new approaches and novel technologies are being explored. Hitherto, prostate cancer therapy has been traditionally directed towards the whole gland rather than to the area of the gland harbouring cancer. It is one of the outliers in terms of cancer therapy with most other solid organ cancers having therapy directed to the tumour and not primarily to the whole organ in the majority of cases. For the prostate, a consequence of whole-gland treatment is that surrounding structures are at risk of damage with consequent urinary, erectile and bowel side effects. However, new evidence has highlighted that only the index lesion – largest by volume and/or grade – typically drives the natural history of the disease despite prostate cancer being multifocal in most men.[20-22] Thus, a new approach delivering treatment only to the area of the gland affected by significant disease might be a reasonable approach and the best way to preserve function while retaining the benefits of cancer control. This approach has been called 'focal therapy'."[23;24]

In summary, there is a strong biological rationale for focal treatment, but prostate cancer has not seen the same choices of radical versus tumour-targeted treatment that, for example, breast cancer has seen with the introduction of lumpectomy as an alternative to radical mastectomy.[25] As was the case when lumpectomy was

introduced in the breast cancer treatment pathway, there is some remaining uncertainty regarding long-term outcomes. Patients who would be willing to accept this uncertainty are, however, facing additional hurdles because of the current restrictions on the use and reimbursement of focal therapies.

Early detection and stage migration: potential for benefit and harm

In the case of prostate cancer, “stage migration” refers to the increased number of patients diagnosed at an early stage mainly after introduction of PSA testing.[3] In contrast to other cases, caused by reclassification of patients between stages, which do not affect the total numbers, stage migration caused by earlier detection of prostate cancer has led to a substantial increase in the total number of diagnosed patients. Earlier diagnosis holds promise to reduce the currently 22% of patients diagnosed at the metastatic state,[26] which is difficult to treat and has a five-year survival rate of only 30%.[27] The disadvantage of early detection lies in the increased number of patients who receive a diagnosis but who would have lived normal lives and died of other causes if they had not been tested.

Clarification of terminology for surveillance strategies

The terms “active surveillance” and “watchful waiting” refer to cautious management approaches at different stages in the disease. Active surveillance implies close monitoring of patients who are eligible for radical therapies and can switch over to active treatment when certain conditions are met (e.g., disease progression, increase in PSA levels, patient choice).[28] Watchful waiting usually refers to the avoidance of treatment at the palliative stage and often implies choices of non-curative treatment approaches such as hormonal therapy.[29] Because both approaches evolved from a similar philosophy of “first, do no harm,” the two terms are often used in the medical literature as if they were synonymous. Because our application focuses on a low-risk prostate cancer population that is eligible for active treatment options with curative intent, we consistently use the term “active surveillance” herein to describe the deferment of active treatments in patients eligible for radical therapies.

Clinical pathway of care showing the context of the proposed use of the technology

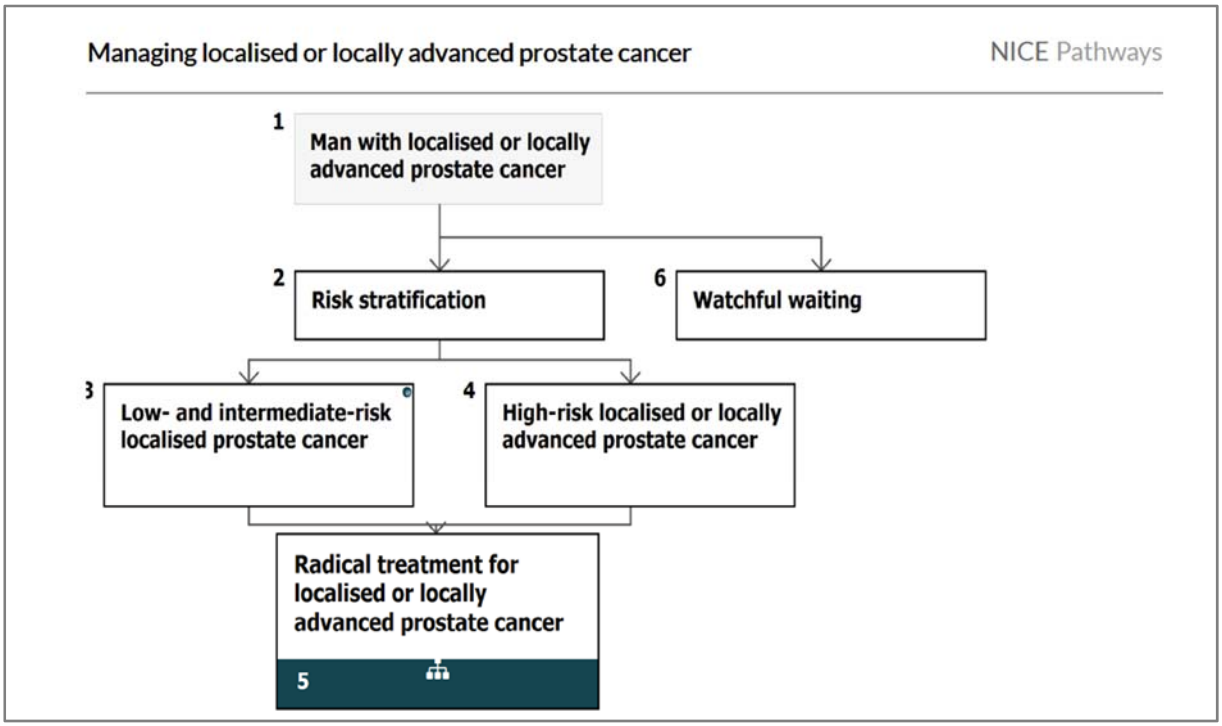
Current treatment pathway

The current National Institute for Health and Care Excellence (NICE) treatment pathways shown in **Figure 1** and **Figure 2** below illustrate the dilemma that patients with low-risk prostate cancer face when opting for active treatment. Because the field of localised, low-risk prostate cancer lacks a clear standard of care, patient-directed National Health Service (NHS) treatment recommendations consistently emphasize patient preference as the most important determinant of treatment choice.[30] This choice, however, is limited by the current lack of routine reimbursement of focal therapies. Patients who choose active treatment are thus faced with a choice between several radical treatments, each of which comes with its own set of potentially severe side effects. Patients concerned about erectile dysfunction or urinary symptoms usually opt for radiation treatments, which have milder urogenital side effects but come with increased risk for severe bowel impairment. Evidence from RCTs shows that there is little to no difference between the available treatment choices in terms of overall survival after at least 10 years of follow up.[11;15;16;31]

The subsequent treatment pathway (**Figure 2**) offers "interventions not recommended outside of clinical trials" as potential alternative options. The fact that these treatments are "not recommended" puts an additional burden on the patient, because opting for them usually implies participation in a clinical trial.[32] Patients who would be willing to accept the uncertainty of long-term outcomes with newer focal therapies thus face additional hurdles of finding a centre that runs a trial and being accepted as a participant.

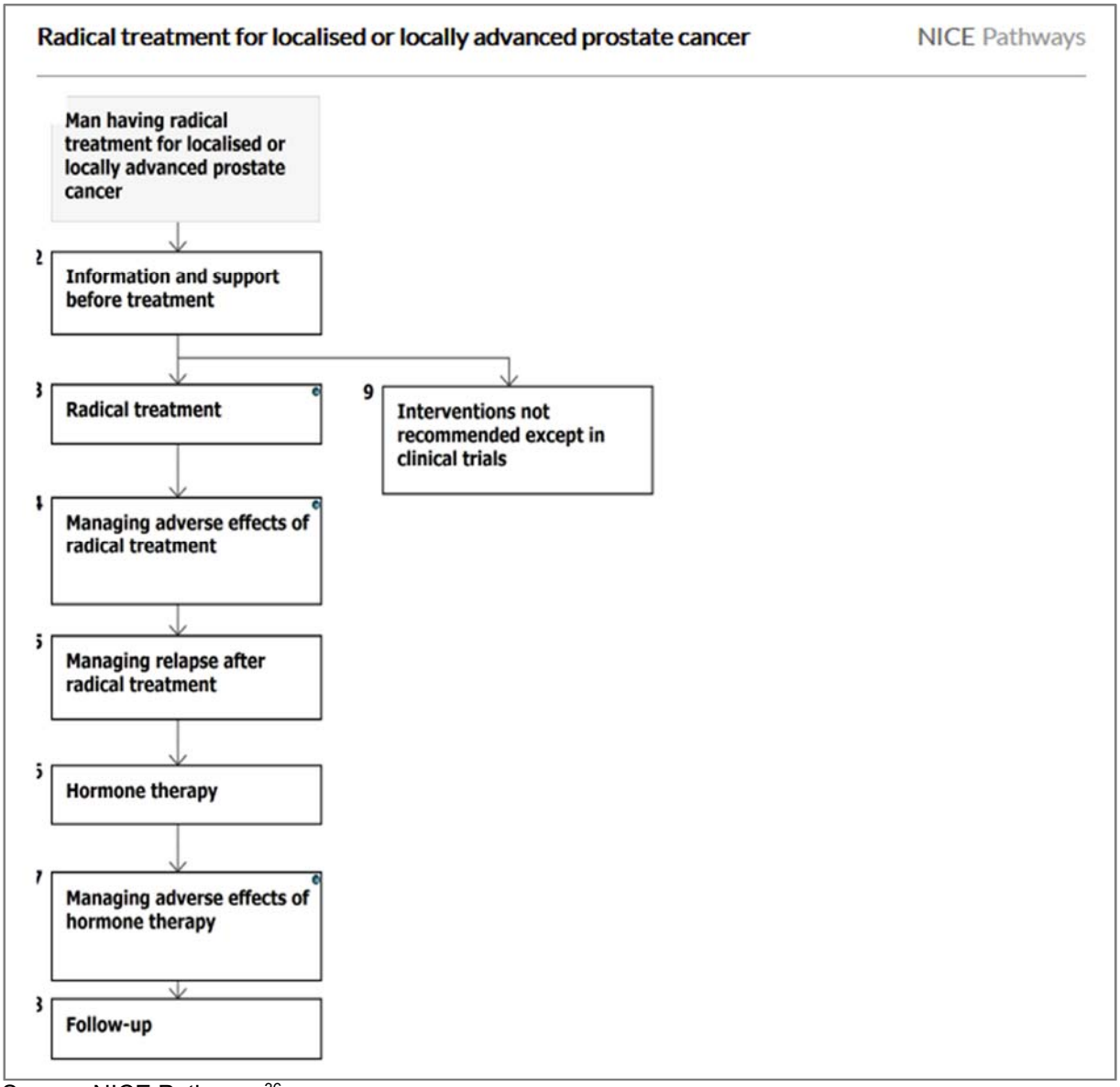
While the UK is a world-wide leader in adult clinical trial participation rates,[33] too few patients still opt to participate, and the failed PREFERE trial initiated by the German healthcare decision makers in cooperation with German payers has shown the substantial difficulties that can be encountered when aiming to recruit large numbers of patients into trials that, at any point, might restrict their autonomy in making decisions about their own care.[34;35]

Figure 1 Current NICE pathway in localised prostate cancer



Source: NICE Pathways[36]

Figure 2 Current NICE pathway in localised prostate cancer for radical treatment



Source: NICE Pathways[36]

Intended treatment pathway incorporating the new technology

The role and position of padeliporfin VTP is indicated in an updated/edited pathway chart in **Figure 3**. It is of utmost importance to clarify that we agree with leading clinicians who do not see focal therapy as an alternative to active surveillance in patients with confirmed, clinically insignificant, low-risk disease.[3] Nonetheless, in the pivotal trial of padeliporfin VTP (PCM301) and in its cost-effectiveness evaluation, active surveillance with deferred radical therapy provides the most relevant reference to assess the benefit of padeliporfin VTP on the reduction of the burden of treatment

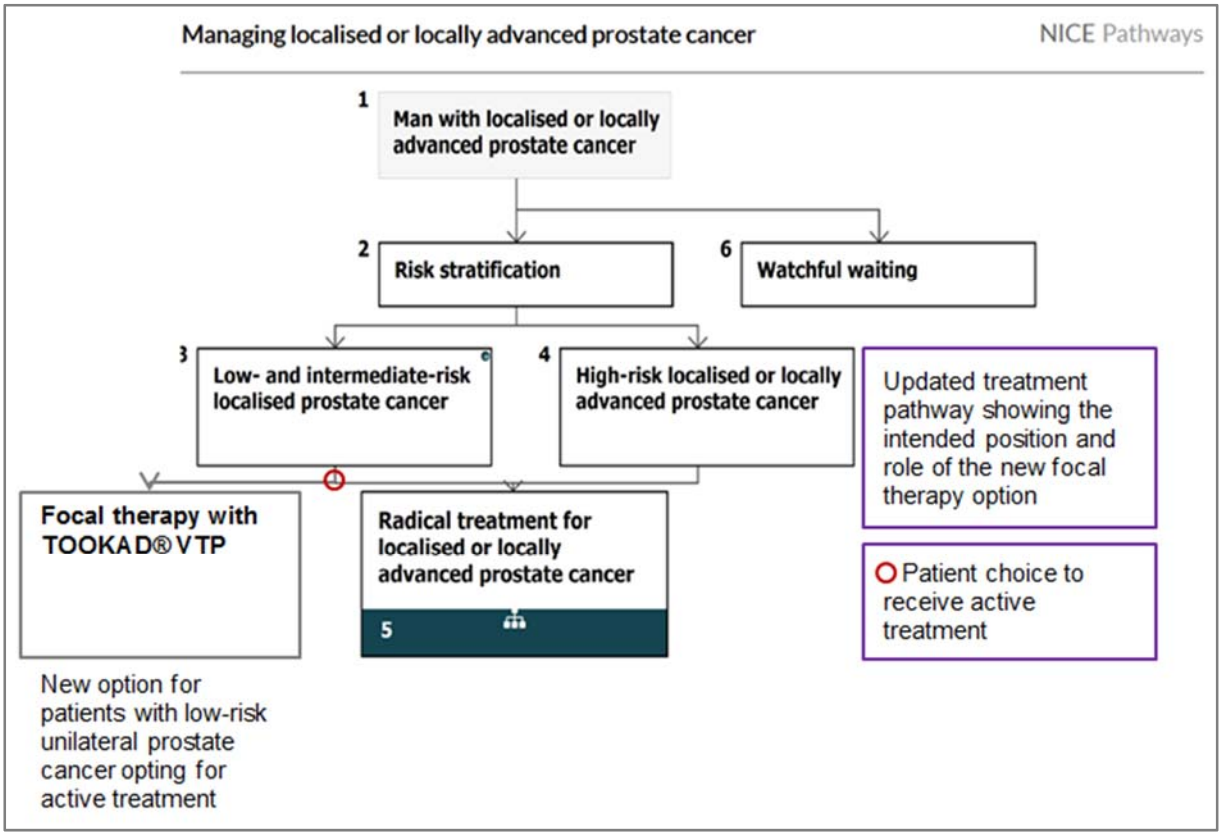
toxicities, which was a conclusion made after careful deliberation with the European Medicines Agency (EMA).

We seek to provide padeliporfin VTP as an alternative to radical therapy for patients who choose active treatment either because of experienced symptoms, clinical indicators, clinician recommendation, or psychological factors (e.g., family history, other negative experiences, risk aversion). For these patients, focal treatment with padeliporfin VTP can reduce overtreatment by radical therapies and provide HRQoL benefits (for more details on HRQoL deterioration due to side effects associated with radical therapies, see Ramsay et al 2015,[37] our systematic literature review and our model).

A recent trial (Godtman 2016) showed that patients with low-risk prostate cancer on active surveillance progressed to radical therapy more frequently than those with very-low risk prostate cancer and in a fashion similar to patients with intermediate-risk prostate cancer.[15] This indicates that the approved indication for padeliporfin VTP of low-risk, but not very-low risk patients would restrict the use of padeliporfin VTP by clinicians to those patients who benefit the most from it to avoid radical treatments and their morbidities.

Because the prostate gland is largely intact after VTP treatment, this treatment option does not exclude the possibility of further treatment with radical therapy (surgery or radiotherapy) later on, should long-term outcomes require additional, more radical interventions.

Figure 3 Updated NICE pathway indicating the intended position and benefit of the new technology



Regarding the outcomes of interest for the consideration of this new technology, three large studies (PIVOT[11;31], ProtecT[16], Swedish study by Godtman et al.[15]) have shown equivalence of currently available treatment approaches (i.e., active surveillance and different radical treatments) with regard to overall survival. An economic analysis by Hayes et al.[38] based the hazard ratio for overall survival on one of these studies (the PIVOT trial) and thus assumed longer overall survival (OS) for patients on active surveillance than for radical treatment. This was criticized by others, because the differences in overall survival in the trial were small, and the confidence intervals were large.[39] The rationale, however, to use this hazard ratio was based on the fact that sensitivity analyses showed that very minor differences found in the large trials in survival estimates had only very minor effects on the overall economic analysis.

Thus, Hayes et al. 2013[38] demonstrated that the main benefit of active surveillance (AS) against radical therapies lies in the avoidance of severe side effects and the associated increase in QoL. In our rationale for focal therapy with padeliporfin VTP,

clinical analysis and economic model, we follow this example and focus on the gain of quality of life by means of avoidance of serious side effects as the measurable difference between padeliporfin VTP and radical treatments. This connects our model and economic rationale to the intended position in the treatment pathway shown in **Figure 3**: to prevent overtreatment and HRQoL detriment in those patients who have made a decision to undergo active treatment.

B.1.4 Equality considerations

We do not anticipate that the use of padeliporfin VTP will be associated with any equality issues.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Search strategy

Patients with low-risk prostate cancer have a very limited risk of dying from their prostate cancer and a limited risk of progressing to metastasis. Recent randomized controlled studies have shown that there is no significant difference in prostate-specific survival and a borderline significant increase in the risk of metastasis between patients who elect to active surveillance and those who elect to radical therapy.[11;16] In this context, the main expected benefit of new treatment options for low-risk prostate cancer is to reduce the use of radical therapies and their related toxicities. This benefit was used by the EMA as the primary criterion for the evaluation of padeliporfin. We have focused our search strategy and documentation of the clinical effectiveness on this same benefit.

Two separate systematic literature reviews were designed to identify studies with 1) clinical evidence for patients with low-risk prostate cancer on active surveillance or treated with padeliporfin vascular-targeted photodynamic therapy (including identification of randomized, controlled, comparative studies that provide information on rate of radical therapy and/or “time to metastasis”) and of 2) the safety/toxicity profile of radical therapy for prostate cancer with a focus on urinary incontinence, erectile dysfunction and radiation-induced enteropathy. These literature searches were conducted in November 2017 using various relevant bibliographic electronic databases (**Table 3**).

Table 3 Electronic databases searched

Database / information source	Interface / URL	Date of Search
MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE <1946 to Present>	Ovid SP	Nov. 10, 2017
Embase	Ovid SP	Nov. 10, 2017
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library / Wiley	Nov. 11, 2017
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library / Wiley	Nov. 11, 2017
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library / Wiley	Nov. 11, 2017
Health Technology Assessment Database (HTA	Cochrane Library / Wiley	Nov. 11, 2017

Database / information source	Interface / URL	Date of Search
Database)		

Study Selection

The full eligibility criteria applied to the identified records are presented in **Table 4** for search strategy #1 and in **Table 5** for search strategy #2.

Table 4 Eligibility criteria used in search strategy #1

	Details
Population	Low-risk localised prostate cancer
Intervention	Padeliporfin Active Surveillance
Comparator	> No Restriction
Outcomes	**Systematic Search:** > Rate of Radical Treatment (events per patient year) > Adverse Effects **Specific outcome for pragmatic search within the overall search:** > Time to metastasis
Study Design	**Systematic Search:** > RCTs (prospective and cross-over) > Non-RCTs (non-randomised and non-controlled studies) /observational studies > Systematic reviews, meta-analyses and HTAs for screening reference lists to identify additional, relevant studies > **Specific study types for pragmatic search within the overall search:** > RCTs and comparative studies only

Table 5 Eligibility criteria used in search strategy #2

	Details
Population	Low-risk localised prostate cancer
Intervention	> Radical therapies o Radical prostatectomy (= removal of the entire prostate gland and lymph nodes by open surgery or a keyhole technique (laparoscopic or robotically assisted laparoscopic prostatectomy)) o Radical radiotherapy – external beam radiotherapy (EBRT) – brachytherapy
Comparator	> No Restriction
Outcomes	> Specific Adverse Effects: o Urinary Incontinence o Erectile Dysfunction

	o Radiation-Induced Enteropathy
Study Design	> RCTs (prospective and cross-over) > Non-RCTs (non-randomised and non-controlled studies) /observational studies > Systematic reviews, meta-analyses and HTAs for screening reference lists to identify additional, relevant studies
Time Frame	> Publication date for journal articles, HTA reports etc.: 2008-2017/8 > Publication date conference abstracts: 2014-2017

Table 6 Number of records retrieved from each information source

Database / information source	Records identified	
	Search strategy #1	Search strategy #2
MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE <1946 to Present>	1386	1286
Embase	2396	1866
Cochrane Library (CCTR, CDSR, DARE, HTA)	203	292
Total number of combined records retrieved (including duplicates)	**3985**	**3443**
Total number of records (excluding duplicates)	**2618**	**2176**

B.2.2 List of relevant clinical effectiveness evidence

Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial (**Table 7**)[40] is the pivotal Phase 3 RCT evaluating the efficacy and safety of padeliporfin VTP in adult men with low-risk, localised prostate cancer. In this study, the clinical efficacy and safety of padeliporfin VTP were directly compared to active surveillance.

Since one of the main objectives of focal treatments like padeliporfin VTP is to reduce the need for radical therapy and its subsequent toxicity, the only acceptable comparator for this clinical study was active surveillance, as it was the only recognized patient management strategy to defer radical therapy. However, VTP should not necessarily be viewed as a direct comparator against active surveillance, but rather as an alternative option to primary active treatment (**Figure 3**).

Details of the study are presented in **Table 7**.

Table 7 Clinical effectiveness evidence

Study	CLIN1001 PCM 301[41]; Azzouzi *et al*. 2016[40]		
Study design	Multicentre, randomised, controlled phase 3 trial		
Population	Men with low-risk, localised prostate cancer (Gleason pattern 3) who had received no previous treatment		
Intervention(s)	3.66 mg/kg padeliporfin intravenously over 10 min and optical fibres inserted into the prostate to cover the desired treatment zone and subsequent activation by laser light 753 nm with a fixed power of 150 mW/cm for 22 min 15 s		
Comparator(s)	Active surveillance		
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	PCM 301 was used in the economic model because it is the trial on which the regulatory submission is based, and it is the only phase 3 trial of padeliporfin VTP compared against active surveillance in the population stated above. The economic model was based on the regulatory analyses as published in the European Public Assessment Report for the indication population, which is a subgroup of the overall PCM 301 trial patient population.		
Reported outcomes specified in the decision problem	Disease-free survival, progression of disease, **need for radical treatment**, mortality, **adverse effects (for example, erectile dysfunction or incontinence)**, health-related quality of life *Marked in bold the outcomes that are incorporated into the model		
All other reported outcomes	Not applicable		

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

The clinical efficacy and safety of padeliporfin VTP was evaluated in a Phase 3 RCT in adult men with low-risk, localised prostate cancer, conducted in 47 university centres and community hospitals in ten European countries (Belgium, Finland,

France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the United Kingdom). Subjects were recruited from March 8, 2011, to April 30, 2013.

A total of 413 subjects were randomised 1:1 to receive either VTP (4 mg/kg padeliporfin administered intravenously over 10 minutes and optical fibres inserted into the prostate to cover the desired treatment zone and subsequent activation by laser light; n=206) or remain on active surveillance (n=207).

Male subjects aged 18 years or older were eligible for enrolment in the study if they met the following criteria:

1. Low-risk prostate cancer diagnosed with 1 existing transrectal ultrasound (TRUS)-guided biopsy using from 10 to 24 cores performed less than 12 months prior to enrolment and showing the following:
    - Gleason 3 + 3 prostate adenocarcinoma, as a maximum
    - 2 to 3 cores positive for cancer (subjects with only 1 positive core could be included provided they had at least 3 mm of cancer core length.)
    - A maximum cancer core length of 5 mm in any core
2. Cancer clinical stage up to T2a (pathological or radiological up to T2c disease permitted)
3. Prostate-specific antigen (PSA) of 10 ng/mL or less (5 ng/mL or less for subjects using a 5-α-reductase inhibitor [5-ARI])
4. Prostate volume ≥ 25 cc and < 70 cc

As patients' performance status was not considered a criterion for study inclusion, men were required to have a predicted life expectancy of 10 years or more and had to be free of any medical condition deemed to be a contraindication to general anaesthesia.

Upon consideration of feedback received from some of the experts of the Scientific Advisory Group Oncology, a reassessment of the efficacy and safety of VTP was done in a proposed restricted indication population which only included unilateral ablation. This restricted population included 158 participants with 80 assigned to the VTP arm and 78 assigned to the active surveillance arm. The following exclusion criteria were applied to this indication population:

1. Patients with bilateral disease (as they would require two VTP procedures; a second VTP treatment is not recommended after detection of residual cancer, either in the ipsilateral or in the contralateral lobe, even in absence of progression)
2. Very low risk patients with 1 or 2 positive cores and a PSA density ≤0.15 ng/mL/cm^3 (as they have a lower likelihood of upstaging or progression, especially with modern biopsy technique)

The pre-specified co-primary efficacy endpoints for both populations were:

A. Absence of definite cancer: absence of any histology result definitely positive for cancer at Month 24, and;
B. Treatment failure: histological progression of cancer from low to moderate or high risk or prostate cancer-related death during 24 months' of follow-up.

Treatment was deemed a failure if a patient met any of the following criteria:

- 4 cores or more positive for cancer when considering all histological results during follow-up
- At least one cancer core length greater than 5 mm
- Any Gleason primary or secondary pattern 4 or more
- PSA >10ng/mL in 3 consecutive measures
- Any T3 stage prostate cancer
- Any metastasis
- Prostate cancer-related death

All 413 and 158 randomised participants from the intention-to-treat (ITT) and indication populations were included in the efficacy analyses. Pre-specified secondary objectives were the proportion of patients who underwent radical therapy; the total number of positive prostate core samples; the frequency of severe prostate cancer-related events (cancer progression to T3, metastasis, prostate cancer-related death); the frequency of adverse events; and the proportion of patients with significant changes in patient satisfaction scores of the International Prostate Symptom Score (IPSS) questionnaire for lower urinary tract symptoms or the

International Index of Erectile Function (IIEF) questionnaire for erectile function and EuroQoL 5-Dimension (EQ-5D) questionnaire for general quality of life.

Of the 206 men randomly assigned to VTP, nine did not receive the procedure: three withdrew consent, three were excluded because of exclusion criteria (bladder cancer discovered on pre-treatment MRI, Gleason 3+4 score on previous biopsy, history of transurethral prostate resection), one was withdrawn by the investigator because of noncompliance, one had a myocardial infarction, and one was claustrophobic and therefore unable to undergo the pre-treatment MRI.

A full summary of the study design is provided in **Table 8**. Details on the demographic and baseline characteristics of study participants are presented in **Table 9** for the indication population and in **Table 10** for the ITT population.

Table 8 Comparative summary of trial methodology

	CLIN1001 PCM301[41]
Location	Subjects were enrolled in 47 university centres and community hospitals in 10 European countries (Belgium, Finland, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the United Kingdom).
Trial design	Phase 3, multicentre, randomised, open-label clinical trial Subjects were randomised in a 1:1 ratio by use of a web-based randomisation system generated by the sponsor and stratified by centre with balanced blocks of variable size (2 or 4 men).
Eligibility criteria for participants	Key inclusion criteria were men with previously untreated low-risk localised prostate cancer diagnosed by TRUS-guided biopsy showing 2 to 3 cores positive for cancer, a Gleason score of 3 + 3 as a maximum and a maximum cancer core length of 5 mm in any core, cancer clinical stage up to T2a, PSA of ≤ 10 ng/mL, and prostate volume ≥ 25 cc and < 70 cc (Subjects with only 1 positive core could be included provided they had at least 3 mm of cancer core length.) Key exclusion criteria were contraindication to MRI (e.g., cardiac pacemaker), factors excluding accurate reading of pelvic MRI (e.g., bilateral hip replacements), or any disorder or history of illness or surgery that might have posed an additional risk to men undergoing the vascular-targeted photodynamic therapy procedure. The restricted indication population had the following additional exclusion criteria: patients with bilateral disease and very low risk patients with 1 or 2 positive cores and a PSA density ≤0.15 ng/mL/cm3.

	A complete list of inclusion and exclusion criteria is provided in **Appendix D.**
Settings and locations where the data were collected	The trial was conducted in 47 university centres and community hospitals in Belgium, Finland, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the United Kingdom
Trial drugs	VTP arm (n=206): a single IV infusion of 4 mg/kg padeliporfin over 10 min and optical fibres inserted into the prostate to cover the desired treatment zone and subsequent activation by laser light 753 nm with a fixed power of 150 mW/cm for 22 min 15 s Active surveillance arm (n=207): active surveillance was done according to best practice at the time of study design, and consisted of a protocol-directed biopsy at 12-month intervals and PSA measurement coupled with a digital rectal examination at 3-month intervals. No therapeutic intervention was included as part of active surveillance. In the indication population, the VTP arm (n=80) and the active surveillance arm (n=78) only included patients with unilateral disease. Men randomly assigned to VTP underwent pre-treatment multiparametric MRI, which was centrally reviewed with the biopsy results by a committee composed of radiologists and urologists who made detailed recommendations on the number, length, and position of interstitial optical fibres using treatment guidance software.
Permitted and disallowed concomitant medication	Disallowed medications or treatments: • any prior or current treatment for prostate cancer, including surgery, radiation therapy (external or brachytherapy), or chemotherapy • any surgical intervention for benign prostatic hypertrophy • receipt of an investigational product within 1 month of study entry • hormonal manipulation (excluding 5-ARIs) or androgen supplements within the previous 6 months • medications which have potential photosensitising effects (such as tetracyclines, sulphonamides, phenothiazines, sulfonylurea hypoglycaemic agents, thiazide diuretics, griseofulvin and amiodarone) from 10 days before to 3 days after VTP • anticoagulant drugs or antiplatelet drugs (e.g., warfarin, aspirin) from 10 days before to 3 days after VTP Because 5-ARIs are known to decrease serum PSA levels after prolonged use, a subject who had been using a 5-ARI for more than 6 months was not to adjust 5-ARI therapy during the study. Enrolment of a subject who had started 5-ARI therapy within 6 months of randomisation was to be discussed with the Medical Monitor before randomisation.

	Prophylactic measures were taken to avoid the risk of thromboembolic events, which are known to be increased after general anaesthesia, especially when it is associated with pelvic surgery for cancer. The choice of the measures for the prevention of thromboembolism was left to the discretion of the Investigator as per local clinical standards.
Primary outcomes (including scoring methods and timings of assessments)	Co-primary endpoint A: Absence of definitive cancer: Absence of any histology result definitively positive for cancer at 24 months Co-primary endpoint B: Treatment failure: Progression of cancer from low to moderate or higher risk over the 24 months of follow-up. Moderate or higher risk is defined as the observation of 1 of the following events: • More than 3 cores definitively positive for cancer when considering all histological results available during follow-up in the study • Any Gleason primary or secondary pattern of 4 or more • At least 1 cancer core length > 5 mm • PSA > 10 ng/mL in 3 consecutive measures • Any T3 prostate cancer • Metastasis • Prostate cancer-related death
Other outcomes used in the economic model/specified in the scope	Used in economic model and specified in the scope • Notification of initiation of radical therapy (any radical treatment for prostate cancer other than the treatment to which the subject was randomised, including surgery, radiotherapy [external beam, brachytherapy, focused], high-intensity focused ultrasound, cryotherapy, hormonal therapy for cancer, or chemotherapy for cancer) • Frequency of adverse events Specified in the scope • Total number of cores positive for cancer • Proportion of subjects with a severe prostate cancer-related event: cancer extension to T3, metastasis, or prostate cancer-related death • Proportion of patients with significant changes in scores of the IPSS questionnaire or the IIEF questionnaire and EQ-5D Long-term follow-up was assessed in a 5-year open-label extension study for the following outcomes at 36, 48, 60, 72 and 84 months: • Serum Prostate Specific Antigen (PSA) data (number of patients with PSA tests performed since last visit, PSA results and number of patients with “disease progression” according to PSA values) • Prostate biopsies (number of patients with ≥1 prostate biopsy

	performed since last visit, number of prostate biopsies performed in patients, patients with Gleason score<6 or ≥7, number of positive cores, number of patients with ≥3 positive cores, number of patients with at least one core length>5 mm, and maximal length of positive cancer cores) • Prostate cancer extension, according to TMN score (number of patients with local, regional extension and/or metastasis, and number of patients with "disease progression" according to the TNM score) • Cancer therapies initiated since last visit (number of patients who initiated a radical, and/or other active, and/or palliative therapy, and type of therapy in patients) All randomised participants were included in the efficacy analyses according to assigned treatment (intention-to-treat & indication populations). All men randomly assigned to VTP who received any padeliporfin or initiated any study treatment-related procedure and all men randomly assigned to active surveillance were included in the safety analyses.
Pre-planned subgroups	A pre-planned subgroup efficacy analysis was performed by disease status at baseline (unilateral or bilateral disease) in the intention-to-treat population. A post-hoc subgroup analysis was conducted in subjects with unilateral low risk disease excluding very low risk, which was ultimately the approved indication.
5-ARI: 5-α-reductase inhibitor; EQ-5D: EuroQol 5-Dimension; IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom Score; IV: intravenous; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; TNM: tumour, nodes, metastasis; TRUS: transrectal ultrasound; VTP: vascular-targeted photodynamic therapy Sources: Azzouzi et al., 2016[40]; CLIN1001 PCM301 Clinical Study Report[41]; PCM301-FU5 Interim Analysis Report[42]; EMA Assessment Report Tookad[43]	

Table 9 Characteristics of participants in the CLIN1001 PCM301 study across treatment groups (indication population)

Baseline characteristic	VTP (N=80)	Active surveillance (N=78)
Age (years)*	63.9 (6.27; 48-74)	62.3 (6.32; 46-73)
Race, n (%)		
Caucasian	78 (97.5)	78 (100)
Black	1 (1.3)	0
Asian	0	0
Other	1 (1.3)	0

Body mass index (kg/m^2)	26.05 (3.328; 18.8-37.5)	26.47 (3.360; 19.3-40.6)
Time since diagnosis (months)†	4.92 (4.656; 0.6-20.3)	4.81 (4.106; 0.2-18.9)
TNM staging, n (%)		
T1a	0	0
T1c	66 (82.5)	71 (91.0)
T2a	14 (17.5)	7 (9.0)
PSA (ng/mL)	6.98 (1.796; 1.0-10.0)	7.12 (1.704; 3.1-10.0)
Estimated prostate volume (cm^3)‡	37.2 (9.67; 25-68)	37.6 (9.63; 25-66)
Disease status, n (%)		
Unilateral disease	80 (100)	78 (100)
Bilateral disease	0	0
Total number of pre-treatment biopsy cores	13.8 (3.64; 10-24)	14.3 (4.06; 10-26)
Total number of positive pre-treatment biopsy cores§	2.2 (0.74; 1-3)	2.1 (0.76; 1-3)
Number of positive cores, n (%)		
1	15 (18.8)	18 (23.1)
2	34 (42.5)	33 (42.3)
3	31 (38.8)	27 (34.6)
Total cancer core length (mm)	5.3 (2.64; 0¶-14)	3.8 (2.72; 0¶-12)

Data are mean (SD; range) unless otherwise specified

PSA: prostate-specific antigen; SD: standard deviation; TNM: tumour, nodes, metastasis

* *P* = 0.126 from Student t test

† 3 subjects diagnosed for more than 2 years before randomization were removed from the main analysis of the indication population – the mean time since diagnosis when including these patients was 5.99 months (SD=7.50).

‡ *P* = 0.800 from Student t test

§ *P* = 0.477 from Student t test

¶ Some of the subjects included on the basis of 2 biopsies at the beginning of the study had 1 of those 2 biopsies negative

Source: EMA Assessment Report Tookad[43]

Table 10 Characteristics of participants in the CLIN1001 PCM301 study across treatment groups (ITT population)

Baseline characteristic	VTP (N=206)	Active surveillance (N=207)
Age (years)	64.2 (6.70; 45-85)	62.9 (6.68; 44-79)
Race, n (%)		
Caucasian	202 (98.1)	206 (99.5)
Black	3 (1.5)	0
Asian	0	1 (0.5)
Other	1 (0.5)	0
Body mass index (kg/m^2)	26.47 (3.337; 18.8-38.6)	27.34 (3.947; 18.8-44.8)
Time since diagnosis (months)	6.34 (8.536; 0.2-54.2)	6.02 (7.887; 0.2-47.4)
TNM staging, n (%)		
T1a	1 (0.5)	0
T1c	177 (85.9)	180 (87.0)
T2a	28 (13.6)	27 (13.0)
PSA (ng/mL)	6.19 (2.114; 0.1-10.0)	5.91 (2.049; 0.5-10.0)
Estimated prostate volume (cm^3)	42.5 (12.49; 25-70)	42.5 (11.76; 25-70)
Disease status, n (%)		
Unilateral disease	157 (76.2)	163 (78.7)
Bilateral disease	49 (23.8)	44 (21.3)
Total number of pre-treatment biopsy cores	13.6 (3.31; 10-25)	13.6 (3.55; 10-26)
Total number of positive pre-treatment biopsy cores	2.1 (0.68; 1-3)	2.0 (0.72; 1-3)
Number of positive cores, n (%)		
1	39 (18.9)	52 (25.1)
2	110 (53.4)	100 (48.3)
3	57 (27.7)	55 (26.6)
Total cancer core length (mm)*	4.3 (2.31; 0-14)	3.8 (2.40; 0-11)

Data are mean (SD; range) unless otherwise specified

PSA: prostate-specific antigen; SD: standard deviation; TNM: tumour, nodes, metastasis

* Some of the subjects included on the basis of 2 biopsies at the beginning of the study had a negative result for one of those 2 biopsies.

Source: Azzouzi et al., 2016[40]; CLIN1001 PCM301 Clinical study report[41]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The statistical analyses used in CLIN1001 PCM301 are summarised in **Table 11**.

Table 11 Summary of statistical analyses, CLIN1001 PCM301

Hypothesis	
Analysis populations	All efficacy analyses were carried out in the intent-to-treat (ITT) population, defined as all randomised patients. Patients were analysed according to their assigned treatment arm. In addition, the modified ITT (mITT), defined as all subjects in the ITT population randomised to the VTP group who received any amount of padeliporfin VTP or initiated any study treatment-related procedure (including initiation of pre-procedure anaesthesia) and all subjects in the ITT population randomised to the active surveillance group, and per-protocol population, defined as all subjects in the ITT population, randomised to either group, who had no major protocol violations, were used for primary efficacy endpoint analyses. Safety analyses were carried out in the safety population, defined as all subjects randomised to the VTP treatment group who received any amount of padeliporfin VTP or initiated any study treatment-related procedure (including initiation of pre-procedure anaesthesia) and all subjects randomised to the active surveillance group. Patients were analysed according to actual treatment received. Reassessment of the efficacy and safety of VTP was done in a proposed restricted indication population which only included unilateral ablation. The following exclusion criteria were applied to this indication population: 1. Patients with bilateral disease (as they would require two VTP procedures; a second 2nd VTP treatment is not recommended after detection of residual cancer, either in the ipsilateral or in the contralateral lobe, even in absence of progression) 2. Very low risk patients with 1 or 2 positive cores and a PSA density ≤0.15 ng/mL/cm3 (as they have a lower likelihood of upstaging or progression, especially with modern biopsy technique)
Sample size and power calculation	The sample size required for co-primary endpoint B (progression to moderate- or higher risk cancer) is 400 subjects (200 subjects per group), and at least 40 events (subjects with progression of cancer) need to be observed for the final analysis to take place. With this number of subjects, the comparison of the 2 randomised groups will have extremely high power (> 99.9%) to detect the expected difference for co-primary endpoint A (absence of any histology result definitively positive for cancer at 24 months). The following assumptions were made to calculate the sample size for co-primary endpoint B: 15% and 5% of patients will experience treatment failure at 2 years in the active surveillance and the VTP groups, respectively; the 2-sided significance level was set to 0.025 to account for the fact that 2 co-primary endpoints were to be tested but each co-primary endpoint was analysed at the 0.05 significance level using the Hochberg procedure to control for multiplicity and the power

	required for each co-primary endpoint is 80%.
Statistical analysis of primary outcome	The co-primary endpoint A was analysed as a dichotomous outcome, i.e., success (absence of any histology result definitely positive for cancer) or failure (presence of at least 1 result definitely positive for cancer). The percentage of subjects with observed success was compared between the 2 treatment arms using a 2-sided Pearson's chi-square test. In addition, the crude odds ratio and the risk ratio at 24 months, comparing VTP versus active surveillance and the associated 95% confidence interval (CI), were presented. The co-primary endpoint B was treatment failure (progression of cancer from low to moderate or higher risk over the 24 months of follow-up). The Kaplan-Meier method was used to estimate the progression rates and associated 95% confidence intervals (CIs). Time to progression was compared between the 2 treatment groups using the log-rank test. The crude hazard ratio at 24 months comparing VTP versus active surveillance and the associated 95% CI was presented, using a Cox proportional hazards regression model. The Hochberg procedure was used to adjust for multiplicity of the 2 co-primary endpoints.
Statistical analysis of other outcomes	**Time to initiation of radical therapy** The Kaplan-Meier method was used to estimate the time to initiation of radical therapy and associated 95% confidence intervals (CIs). The log-rank test was used to compare the time to initiation of radical therapy between the 2 treatment groups. Subjects who did not initiate any radical therapy were censored at the time of study completion. **Total number of positive cores** The total number of positive cores observed during follow-up was calculated for each biopsy by adding the number of positive cores observed in each of the right and left lobes. The mean total number of cores positive for cancer was compared between the 2 treatment groups using a Student *t* test.
Interim analyses	Using the cut-off date of August 30, 2017, the first interim analyses included the same primary endpoints in Germany but the following long-term efficacy outcomes were included in the other countries: disease progression, from low-risk prostate cancer to moderate or higher-risk prostate cancer in men randomized to VTP compared to men randomized to active surveillance, use of prostate cancer therapy and prostate cancer-related death.
Treatment of missing data	Time-to-progression data were interval-censored. As a result, additional sensitivity analyses of time to progression were conducted using parametric models (Weibull, exponential, and log-logistic models) to account for this interval censorship. No other imputation process was undertaken for missing data.

Source: CLIN1001 PCM301 Clinical Study Report[41]; PCM301-FU5 Interim Analysis Report[42]; EMA Assessment Report Tookad[43]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

CLIN1001 PCM301 was conducted in accordance Good Clinical Practice and in full compliance with the Declaration of Helsinki.

Selection bias

Patients were randomized in a 1:1 ratio to receive VTP or to be followed by standard active surveillance, a validated therapeutic method that consists of deferral of active treatment and periodic monitoring with prostate-specific antigen (PSA) tests, physical examinations, and repeated prostate biopsy. Central randomization was stratified by centre using balanced blocks of variable size using an independent web-based allocation system.

Baseline characteristics of the two treatment groups were well balanced (see **Table 10**) supporting the absence of bias in the selection of patients. Similarly, the demographic characteristics of the population targeted by the indication, which represents 38% of the overall trial population is also well balanced between the two treatment groups and remain comparable to the overall trial population (**Table 9**).

Treatment bias

Although VTP treatment in the study relied on the MRI-based treatment guidance, the MRI was not considered for diagnostic of prostate cancer. This treatment guidance only occurred after initial diagnosis based on a TRUS-guided biopsy and randomization to either VTP or active surveillance, provided the patient met the inclusion criteria, and therefore did not influence prostate cancer management in order to not introduce work-up bias into any one group of the study. The investigator used the MRI to accurately evaluate the volume/shape of the prostate of each patient in order to determine the number and type of laser fibres required and their placement in the lobe to be treated. In the event that the investigator detected more positive cancer cores than expected by the TRUS-guided biopsy, only an additional biopsy would enable a definitive diagnosis (but this was not included in this study).

Observation bias

Although subjects and investigational site staff were not blinded to study treatment, objective measures (histologic and biochemical changes) were used for assessment of efficacy and safety to minimize observation bias associated with an open-label study:

- central reading of post-treatment TRUS-guided biopsy samples
- the co-primary efficacy endpoints were determined by the Outcomes Review Panel (ORP) who were blinded to treatment assignment to minimise the potential bias associated with an open-label study design
- central laboratory for standardisation of PSA results
- ongoing, independent review of safety data by the Data Safety Monitoring Board (DSMB)
- statistical inferences for efficacy based on the ITT population, a conservative approach, which included 10 subjects who received no VTP

Table 12 Quality assessment – CLIN1001 PCM301 study

Trial number (acronym)	CLIN1001 PCM301
Was randomisation carried out appropriately?	Yes. Patients were randomly assigned (1:1) to vascular-targeted photodynamic therapy or active surveillance. Randomisation was done by a web-based allocation system stratified by centre with balanced blocks of two or four patients.
Was the concealment of treatment allocation adequate?	Yes. Randomisation was done by a web-based allocation system stratified by centre with balanced blocks of two or four patients, a method recognised for sufficiently concealing treatment allocation.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographic and baseline disease characteristics were well balanced between the two groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No. Treatment was open-label (participants and investigational site staff were not masked to study treatment), but investigators assessing primary efficacy outcomes were masked to treatment allocation.
Were there any unexpected imbalances in drop-outs between groups?	No. More men in the AS group (n=18) than in the VTP group (n=10) withdrew consent before study completion. Although unwillingness to accept randomisation to either group was an exclusion criterion, the sponsor anticipated that men randomised to active surveillance might withdraw because they had entered the study to receive active treatment; however, the number of such withdrawals was

	less than expected. Otherwise, the number of men who completed the study and reasons for withdrawal were similar between the two groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. There is no evidence that the authors measured more outcomes than they reported.
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. Analysis was by intention to treat. All randomised participants were included in the efficacy analyses (intention-to-treat population). Missing data were not imputed.
Did the authors of the study publication declare any conflicts of interest?	Yes. 'Declaration of interests' was reported in the study.
Source: CLIN1001 PCM301 Clinical Study Report[41]	

B.2.6 Clinical effectiveness results of the relevant trials

The CLIN1001 PCM301 trial endpoints at 24 months are presented in this section. All randomised subjects were included in the intention-to-treat (ITT) population, which was the primary population for the efficacy analyses.[41] Where available, data from the follow-up visits at 36 and 48 months are presented. At the time of the database cut-off (August 30th 2017), only 2 patients had reached their Month 84 visit. Thus, no description was given for Month 84 in the Interim Analysis Report.[42] No data for Months 60 or 72 will be presented, as follow-up is insufficient.

Data are also presented for the proposed indication population at various time points where available.

Co-primary endpoint A: Absence of definitive cancer

The study met its co-primary efficacy endpoint of absence of definitive cancer at 24 months.

In the indication population, 65.0% of subjects in the VTP group had a negative biopsy in the lobe diagnosed at baseline compared to 14.1% of subjects in the active surveillance group. Hence subjects in the VTP group were 4.61 times more likely to have a negative biopsy in the lobe diagnosed at baseline compared to subjects in

the active surveillance group. The difference between the two treatment groups is greater in the indication population than the overall trial population, where this figure was 3.24.[43]

Additionally, in the indication population, subjects in the VTP group were 4.39 times more likely to have a negative biopsy in both lobes compared to subjects in the active surveillance group. Here again, the difference between the two treatment groups is greater in the indication population than the overall trial population, where this figure was 3.62.[43] Results of the primary analysis for absence of positive histology results by treatment group in the proposed indication population are summarized in **Table 13**.

The proportion of subjects with a negative biopsy result at Month 24 was significantly higher in the VTP group than in the active surveillance group in the ITT population (adjusted risk ratio 3.67, 95% CI 2.53–5.33; *P* value <.0001; **Table 16**)

Table 13 Absence of positive histology results at Month 24 based on lobe diagnosed at baseline (indication population)

Number of Subjects with	**VTP N = 80**	**AS N = 78**	**VTP vs. AS**
Negative biopsy in lobe diagnosed at baseline, n (%)	52 (65.0)	11 (14.1)	RR=4.61 (95% CI=2.60-8.16)*
Negative biopsy in both lobes, n (%)	36 (45.0)	8 (10.3)	RR=4.39 (95%CI=2.18-8.83)*
Positive biopsy in lobe diagnosed at baseline (patients without radical therapy before Month 24), n (%)	17 (21.3)	33 (42.3)	
No biopsy – Radical Therapy prior to Month 24, n (%)	6 (7.5)	27 (34.6)	
No biopsy for other reasons†, n (%)	5 (6.3)	7 (9.0)	

AS: active surveillance; CI: confidence interval; RR: risk ratio; VTP: vascular-targeted photodynamic therapy.

* p-values<0.001 from Pearson's chi-square test for observed success

† Study withdrawal, medical reason, subject refusal

Source: EMA Assessment Report Tookad[43]

Co-primary endpoint B: Treatment failure: Progression of cancer from low to moderate or higher risk

The study met its co-primary efficacy endpoint of progression of cancer at 24 months.

In the indication population, the proportions of patients with no disease progression in the initially treated lobe were substantially higher in the VTP than in active surveillance arm, with 95% vs. 55% of patients without ipsilateral disease progression at Month 15 respectively and 90% vs. 42% at Month 27 (**Table 14**). Hence, the difference between the two arms at Month 15 was 40% and increased to 48% at Month 27.[43]

When considering the whole gland, the proportions for absence of progression were lower with 73% and 36% at Month 15 for VTP and active surveillance respectively and 64% and 25% at Month 27 (**Table 15**). The difference between the two arms at Month 15 was 37%, which is comparable to the one observed for ipsilateral progression only. The difference increased minimally at Month 27 (39%) and was somewhat lower than the one observed for ipsilateral progression only.[43]

In conclusion, this analysis confirms the significant reduction in progression of disease and need for radical therapy, which had been reported previously based on the review of hazard ratios in Kaplan-Meier analyses.[43]

Table 14 Absence of disease progression at Month 15 and Month 27 in initially diagnosed lobe (indication population)

	Absence of progression at Month 15		Absence of progression at Month 27	
Subjects with	**VTP**	**Active Surveillance**	**VTP**	**Active surveillance**
Available biopsy or progression at prior biopsy, n	79	73	71	67
Absence of disease progression, n (%)	75 (95)	40 (55)	64 (90)	28 (42)
Source: EMA Assessment Report Tookad[43]				

Table 15 Absence of disease progression at Month 15 and Month 27 in whole gland (indication population)

	Absence of progression at Month 15		Absence of progression at Month 27	
Subjects with	**VTP**	**Active surveillance N=73**	**VTP N=71**	**Active surveillance N=67**
Available biopsy or progression at prior biopsy, n	79	73	76	71
Absence of disease progression, n (%)	58 (73)	26 (36)	49 (64)	18 (25)
Source: EMA Assessment Report Tookad[43]				

The proportion of participants who had disease progression at Month 24 in the ITT population was significantly lower in the VTP group than in the active surveillance group (adjusted hazard ratio 0.34, 95% CI 0.24–0.46; *P* value <.0001; **Table 16**).

The distribution of predefined progression criteria showed that VTP was efficacious against the individual criteria for progression (**Table 16**).

Median time to progression was statistically significantly greater in the VTP group than in the active surveillance group (28.3 months, 95% CI 26.0-30.6, vs 14.1 months, 95% CI 12.9-23.8, *P* value <.001).[40]

Table 16 Co-primary efficacy endpoints at Month 24*

	VTP (n=206)	**Active surveillance (N=207)**	**Hazard ratio (95% CI)**	***P* value**
Progression at Month 24	58 (28.2)	120 (58.0)	0.34 (0.24-0.46)†	<.0001‡
Criteria for progression§				
Gleason pattern ≥4	49 (23.8)	91 (44.0)	NC	<.0001¶
>3 positive cores	23 (11.2)	58 (28.0)	NC	<.0001¶
Cancer core length >5 mm	25 (12.1)	51 (24.6)	NC	.001¶
PSA >10 ng/mL in 3 consecutive measures	3 (1.5)	14 (6.8)	NC	.007¶
Any T3 prostate cancer	0	4 (1.9)	NC	NA
Metastasis	0	0	NC	NA
Prostate cancer-related death	0	0	NC	NA

Negative biopsy result at Month 24	101 (49.0)	28 (13.5)	3.67 (2.53-5.33)**	<.0001¶

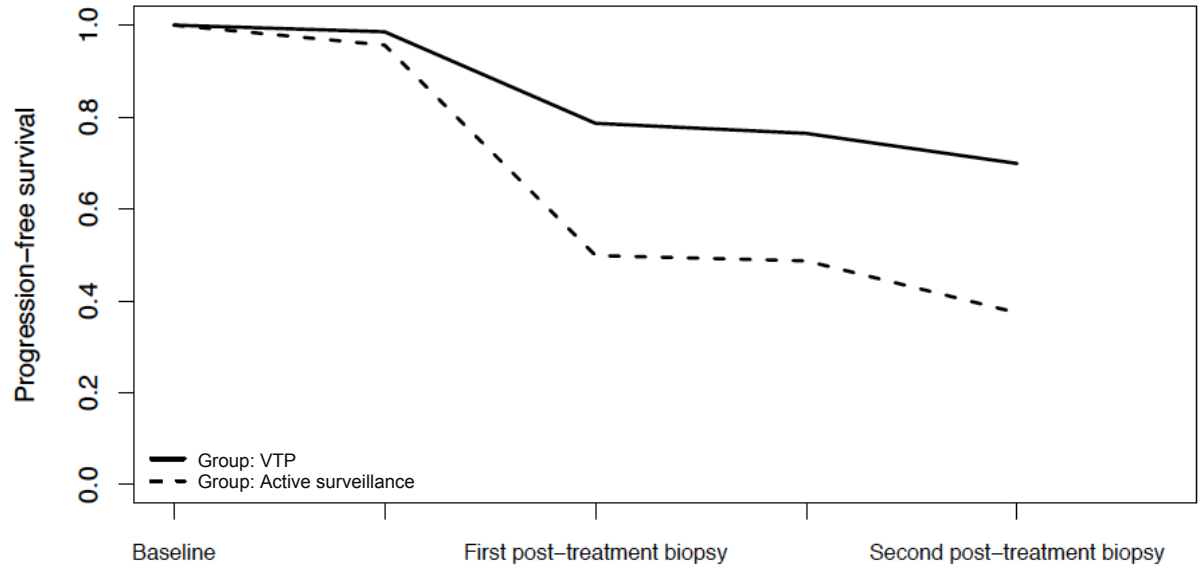
Data are n (%) unless otherwise specified

CI: confidence interval; NA: not applicable; NC: not calculated; PSA: prostate-specific antigen; VTP: vascular-targeted photodynamic therapy.

* The Hochberg procedure was used to adjust for multiplicity of the two co-primary endpoints. †Adjusted hazard ratio. Cox proportional hazards model with treatment as fixed effect and baseline age, number of positive cores, prostate volume, and disease status (unilateral/bilateral) as covariates. ‡From the log-rank test of equality of survival curves across treatment groups Cox proportional hazards model with treatment as fixed effect and baseline age, number of positive cores, prostate volume, and disease status (unilateral/bilateral) as covariates. §A participant might have met more than one criterion for progression. ¶From Pearson's χ^2 test for observed success. **Adjusted risk ratio. Logistic regression model with treatment as fixed effect and baseline age, number of positive cores, prostate volume, and disease status (unilateral/bilateral) as covariates.

Source: Azzouzi et al., 2016[40], CLIN1001 PCM301 Clinical Study Report[41]

Figure 4 Kaplan-Meier analysis of time to progression by Month 24 (ITT population)



Subjects at Risk

Time interval (months)	0	0 to 9	9 to 15	15 to 21	> 21
Vascular-targeted photodynamic therapy	206	189	148	143	128
Active surveillance	207	193	89	84	62

Source: CLIN1001 PCM301 Clinical Study Report[41]

The proportion of patients with at least one PSA level found superior to 10 ng/mL was superior in the AS group, compared to the VTP group, although no statistical test was performed.[42]

Secondary endpoints

Notification of initiation of radical therapy

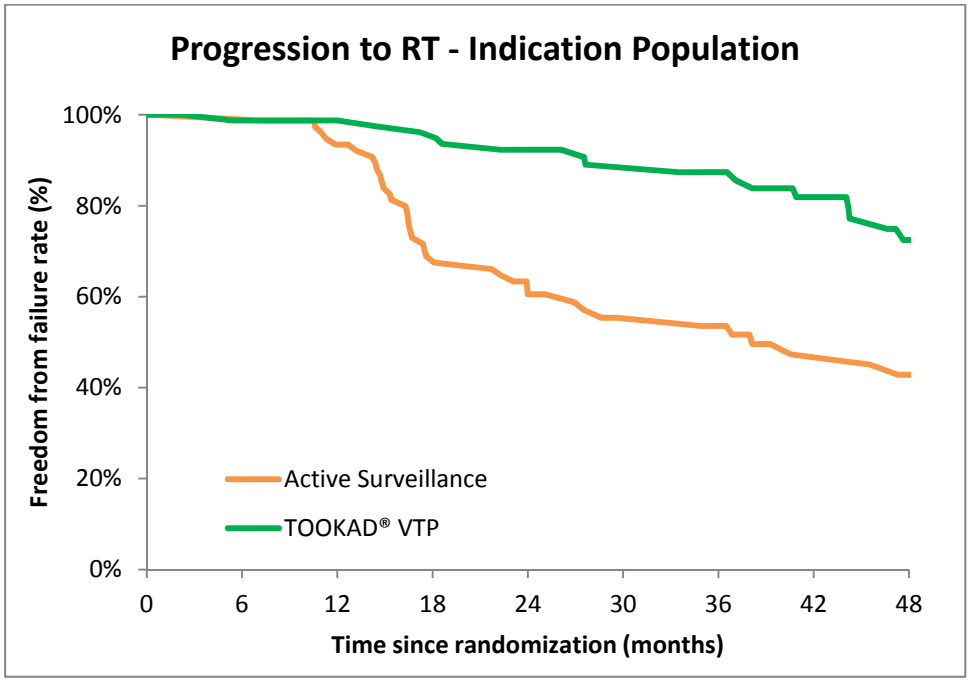
In the indication population, by Month 24 39% of patients under active surveillance had initiated radical therapy vs 8% of VTP patients. By Month 48, these proportions were 57% and 28%, respectively. The hazard ratio for VTP vs active surveillance was 0.293 (p <0.0001) (**Table 17** and **Figure 5**).

Table 17 Time to initiation of radical therapy by treatment group – Kaplan-Meier Analysis (indication population)

		Indication population (N=158)			
		M0 - M12	M12 - M24	M24 - M36	M36 - M48
Active surveillance	N at risk at period start	78	71	43	30
	N radical therapies in the period	5	24	4	5
	% RT at end of period (cumulative)	7%	39%	46%	57%
VTP	N at risk at period start	80	78	68	52
	N radical therapies in the period	1	5	3	7
	% RT at end of period (cumulative)	1%	8%	13%	28%
Absolute risk difference at end of period		6%	31%	33%	29%
Hazard ratio (95%CI) of VTP vs AS		**0.293 (0.163, 0.527) (p-value<0.0001)**			

AS: active surveillance; RT: radical therapy; VTP: vascular-targeted photodynamic therapy.
Source: to be included in revised version of EPAR assessment report

Figure 5 Time to initiation of radical therapy by treatment group – Kaplan-Meier Analysis (indication population)



Source: to be included in revised version of EPAR assessment report

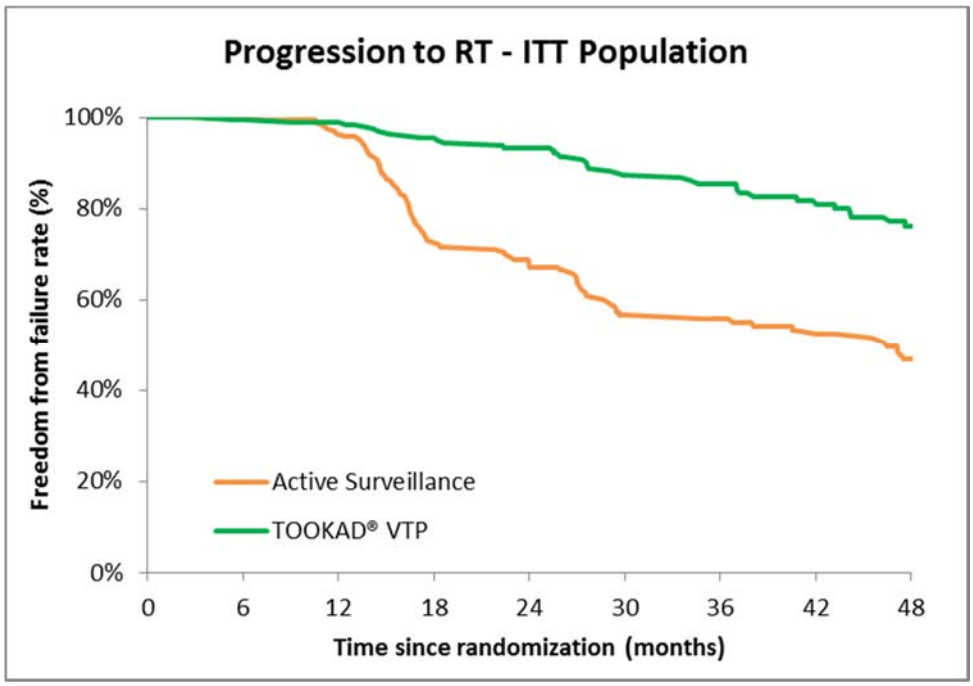
Substantially fewer subjects in the VTP group than in the active surveillance group underwent radical therapy (11 [7.0%] vs 55 [33.0%]) by Month 24 in the ITT population. By Month 48, these proportions were 24% and 53%, respectively. The hazard ratio for VTP vs active surveillance was 0.305 (p <0.0001). It should be noted that 1 subject in the VTP group and 8 subjects in the active surveillance group underwent radical therapy without meeting the co-primary endpoint B definition for progression.[41] Time to initiation of radical therapy for the ITT population is presented in **Table 18** and **Figure 6**.

Table 18 Time to initiation of radical therapy by treatment group – Kaplan-Meier Analysis (ITT population)

		Entire trial population (N=413)			
		M0 - M12	M12 - M24	M24 - M36	M36 - M48
Active surveillance	N at risk at period start	207	189	117	76
	N radical therapies in the period	7	55	16	10
	% RT at end of period (cumulative)	4%	33%	44%	53%
VTP	N at risk at period start	206	195	177	128
	N radical therapies in the period	2	11	12	11
	% RT at end of period (cumulative)	1%	7%	14%	24%

Absolute risk difference at end of period	**3%**	**26%**	**30%**	**29%**
Hazard ratio (95%CI) of VTP vs AS	**0.305 (0.207, 0.450) (p-value<0.0001)**			
AS: active surveillance; RT: radical therapy; VTP: vascular-targeted photodynamic therapy. Source: to be included in revised version of EPAR assessment report				

Figure 6 Time to initiation of radical therapy by treatment group – Kaplan-Meier Analysis (ITT population)



Source: to be included in revised version of EPAR assessment report

Proportion of subjects with a severe prostate cancer-related event

By Month 24, few subjects had experienced a severe prostate cancer-related event; all except one of these subjects were in the active surveillance group. Local cancer extension was reported in 1 VTP-treated subject and 11 subjects in the active surveillance group, while metastasis was observed for 1 subject in each treatment arm. No prostate cancer-related deaths were reported in either treatment group.[41]

The proportion of subjects experiencing a severe prostate cancer-related event is summarized in **Appendix D**.

Criteria for disease progression were evaluated during the 5-year follow-up. In the VTP arm, metastasis occurred in 1 patient at Month 36. Among subjects in the active surveillance arm, metastasis occurred in 1 patient each at Month 36 and Month 48.[42] There were no prostate-cancer related deaths in either arm of the ITT population.[41]

B.2.7 Subgroup analysis

A post-hoc subgroup analysis was conducted in subjects with unilateral low risk disease excluding very low risk. Since this ultimately became the approved indication, the data for this subgroup analysis are reported in the main efficacy and safety outcomes sections.

Pre-planned analyses of absence of definitive cancer, progression rate and time to progression in the other analysis populations (modified intention-to-treat (mITT) and per protocol (PP)) and in the disease status subgroups (unilateral or bilateral disease at baseline) were undertaken to demonstrate the consistency of the efficacy results across analysis populations and disease status at baseline.

The mITT population includes all subjects in the ITT population randomised to the VTP group who received any amount of padeliporfin or initiated any study treatment-related procedure (including initiation of pre-procedure anaesthesia) and all subjects in the ITT population randomised to the active surveillance group. The subjects were analysed as randomised.

The PP population includes all subjects in the ITT population, randomised to either group, who had no major protocol violations. The PP population will consist of all subjects who met the following criteria:

- Complied with the protocol for inclusion and exclusion criteria and follow-up
- Received the appropriate dose of padeliporfin and energy delivered and underwent the VTP consistently with guidance
- Had no major protocol deviations as defined in the Evaluability Plan. The list of all major protocol violations was defined in the Evaluability Plan, which was prepared before database lock. The list of subjects excluded from the PP

population was identified during the data review meeting and approved before database lock.

The disease status subgroups included subjects who, at selection, had unilateral disease or bilateral disease.

These analyses showed similar results to those in the ITT population at Month 24. The consistency of results across all three analysis populations and two subgroups demonstrates the robustness of these outcomes. The results of these subgroup analyses are presented in **Appendix E**.

In addition, both co-primary endpoints were evaluated using only data from assessments performed on the treated lobe(s) for the VTP group and lobe(s) with disease at baseline for the active surveillance group. As with the primary analyses, results of these exploratory analyses were presented on a by-subject basis. The results of these exploratory analyses are presented in **Appendix E.**

B.2.8 Meta-analysis

A meta-analysis was not carried out for padeliporfin VTP because only one trial was identified.

B.2.9 Indirect and mixed treatment comparisons

No indirect or mixed treatment comparisons were performed as no appropriate network could be established due incongruence of key endpoints used in the cost-effectiveness model, e.g. time to radical therapy, between padeliporfin VTP/AS and radical therapies (i.e., RP, EBRT and brachytherapy).

B.2.10 Adverse reactions

Safety data are presented from the CLIN101 PCM301 study for the 25 June 2015 data cut-off (24 months), primarily capturing adverse events (AEs) that occurred until the crossover to radical therapy, which was considered treatment failure. For each of the follow-up evaluations at months 36 and 48, the numbers of AEs occurring since the previous study visit are reported.[42] Follow-up beyond 2 years is poor in this study, with partial follow-up of patients up to 48 months (62% of patients). However,

this study was not designed to provide data beyond that time point. There are inconsistencies in the reports of the numbers of patients that received radical therapy

Treatment exposure

In the ITT population of the CLIN1001 PCM301 study, 196 subjects received a first treatment of padeliporfin VTP. A total of 62 subjects received the VTP procedure in the contralateral lobe by the end of the study (contralateral treatment): 33 of whom received a sequential bilateral treatment before the Month 12 biopsy (at a mean of 7.9 months [range: 5.8 to 12.4 months] between the first and second procedure), 27 of whom had unilateral disease at study enrolment and had the contralateral lobe treated after Month 12 (after a positive biopsy in the contralateral non-treated lobe), and 2 of whom had bilateral disease at Selection and had the lobe treated that had not been previously treated after Month 12 (contralateral treatment). Of the 196 subjects who received treatment before Month 12, 11 had the same lobe treated after Month 12 (retreatment); two of these subjects who had unilateral disease at Selection had treatment in both lobes after Month 12 (treatment of the contralateral untreated lobe and retreatment of the previously treated lobe) (**Table 19**).

In the indication population, 79 subjects received a first unilateral treatment of padeliporfin VTP before Month 12 and 1 did not (reason: consent withdrawal) (**Table 19**). A total of 22 subjects received an additional VTP treatment after Month 12. Of these, 17 subjects received a VTP treatment in the contralateral lobe (contralateral treatment), 4 received a treatment in the previously treated lobe (retreatment), and 1 received a bilateral treatment (treatment of the contralateral untreated lobe and retreatment of the previously treated lobe).

The two most noteworthy differences when comparing the treatment characteristics to of the ITT and indication populations are the lower share of patients who did not receive treatment (1.3% vs. 4.9%) and the higher percentage of patients who received a treatment in the untreated contralateral lobe after Month 12. This is due to the exclusion of patients with bilateral disease at baseline from the indication population. The proportion of patients who received either a treatment in the previously treated lobe or a bilateral treatment after Month 12 was similarly low (6.3% in both populations).

Table 19 Treatment with padeliporfin VTP (ITT & indication populations)

Category	ITT population			Indication population N = 80 n (%)
	Disease Status at Selection			
	Unilateral N = 157 n (%)	Bilateral N = 49 n (%)	Total VTP N = 206 n (%)	
Did not receive any treatment	6 (3.8)	4 (8.2)	10 (4.9)	1 (1.3)
Received a unilateral treatment before Month 12	151 (96.2)	12 (24.5)	163 (79.1)	79 (98.7)
Received contralateral treatment before or after Month 12	27 (17.2)	35 (71.4)*	62 (30.1)	
Received a sequential bilateral treatment before Month 12	0	33 (67.3)	33 (16.0)	0
Received a treatment in previously untreated contralateral lobe after Month 12	27 (17.2)	2 (4.1)*	29 (14.1)	17 (21.3)
Received a treatment in previously treated lobe after Month 12	7 (4.5)	4 (8.2)*	11 (5.3)	4 (5.0)
Received a treatment in both lobes after Month 12	2 (1.3)	0	2 (1.0)	1 (1.3)

VTP: vascular-targeted photodynamic therapy.

* The second procedure for subject 25039-27 was incorrectly recorded in the eCRF as retreatment when it actually was a contralateral treatment. The results in this table include this procedure as contralateral treatment.

Source: CLIN1001 PCM301 Clinical Study Report[41]; EMA Assessment Report Tookad[43]

Adverse events

Month 24

An overview of randomisation-emergent adverse events (AEs) in the overall safety population of the study is presented in **Table 20** by treatment group. A total of 301 (74.5%) subjects in the safety population experienced at least one of the 1,246 AEs reported in this study. Among these AEs, 113 events occurring in 81 (20.0%) subjects met at least one of the criteria for serious adverse events (SAEs).

Events related to the drug, device or procedure account for the differences between the two groups in number of subjects experiencing AEs and SAEs. The two AEs leading to study discontinuation in the VTP group were myocardial infarction (n=1) and anaphylactic reaction (n=1); in the active surveillance group, the single AE leading to study discontinuation was regional ureteric cancer. The AE in the VTP group leading to death was a myocardial infarction approximately 9.5 months after VTP, which the investigator assessed as being unrelated to the study drug, device, or VTP procedure.

Table 20 Overview of adverse events (safety population)

Category	VTP N = 197		Active Surveillance N = 207	
	Subjects n (%)	Events n	Subjects n (%)	Events n
All AEs	187 (94.9)	939	114 (55.1)	307
Drug, device, or VTP procedure-related AE	155 (78.7)	551	NA	NA
All SAEs	60 (30.5)	88	21 (10.1)	25
Drug, device, or VTP procedure-related SAE	30 (15.2)	39	NA	NA
AE leading to study discontinuation	2 (1.0)	2	1 (0.5)	1
AE leading to death	1 (0.5)	1	0	0

AE: adverse event; NA: not applicable; SAE: serious adverse event; VTP: vascular-targeted photodynamic therapy.

Note: AEs/SAEs with assessments of very likely, probable, or possible or with missing relationship are considered related.

Source: CLIN1001 PCM301 Clinical Study Report[41]

An overview of randomisation-emergent adverse events (AEs) in the indication safety population is presented in **Table 21** by treatment group. 344 AEs have been reported in the VTP group and 98 in the Active Surveillance group with 74 VTP subjects (93.7%) and 39 Active Surveillance subjects having experienced at least 1 AE reported in the study. Among those AEs, 32 events occurring in 21 VTP subjects (26.6%) and 7 events occurring in 7 Active Surveillance subjects (9.0%) met at least 1 of the criteria for SAEs.

Events related to the drug, device, or procedure account for the majority of the differences between the 2 groups in number of subjects experiencing AEs and SAEs. The incidences of AEs and SAEs related to drug, device, or VTP procedure are similar in the indication population and the overall safety population (AEs: 79.7% vs. 78.7%; SAEs: 13.9% vs. 15.2%). However, unlike in the overall safety population, no AEs led to either study discontinuation or death within the indication population.

Table 21 Overview of adverse events (indication population)

	VTP N = 79		Active surveillance N = 78	
Category	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**
All AEs	74 (93.7)	344	39 (50.0)	98
Drug, device, or VTP procedure-related AE	63 (79.7)	194	NA	NA
All SAEs	21 (26.6)	32	7 (9.0)	7
Drug, device, or VTP procedure-related SAE	11 (13.9)	14	NA	NA
AE leading to study discontinuation	0	0	0	0
AE leading to death	0	0	0	0

AE: adverse event; NA: not applicable; SAE: serious adverse event; VTP: vascular-targeted photodynamic therapy.

Note: AEs/SAEs with assessments of very likely, probable, or possible or with missing relationship are considered related.

Source: EMA Assessment Report Tookad[43]

Subjects in the VTP group experienced greater frequency and severity of treatment-emergent AEs (TEAEs) compared to those in the active surveillance group in the overall safety population (**Table 22**).[40] The most common TEAEs in the VTP group compared with the active surveillance group were erectile dysfunction (38% vs 11%), haematuria (28% vs 3%), dysuria (26% vs 2%), urinary retention (17% vs 1%), perineal pain (15% vs <1%), micturition urgency (11% vs <1%), urinary tract infection (11% vs 4%) and pollakiuria (abnormal, frequent urination; 10% vs 3%) (**Table 22**).

Adverse events of grade 3 or 4 were reported in 21.8% of subjects in the VTP arm, compared to 9.7% of subjects in the active surveillance arm.[41] The most common

grade 3/4 AEs in the VTP arm compared to the active surveillance group were inguinal hernia (2% vs 0%), rectal haemorrhage (2% vs 0%), urinary retention (2% vs <1%) and prostatitis (2% vs <1%) (**Table 22**).

Table 22 Treatment-emergent adverse effects by treatment arm (safety population)

	VTP (N=197)*			Active surveillance (N=207)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Blood and lymphatic system disorders						
Thrombocytopenia	0	1 (<1%)	0	0	0	0
Cardiac disorders						
Angina unstable	0	0	1 (<1%)	0	0	0
Atrial fibrillation	0	1 (<1%)	0	1 (<1%)	0	0
Myocardial infarction	0	1 (<1)	0	0	2 (<1%)	1 (<1%)
Endocrine disorders						
Hyperthyroidism	1 (<1%)	1 (<1%)	0	0	0	0
Eye disorders						
Cataract	0	2 (1%)	0	0	0	0
Gastrointestinal disorders						
Abdominal pain	4 (2%)	1 (<1%)	0	1 (<1%)	0	0
Gastrointestinal haemorrhage	0	0	0	0	1 (<1%)	0
Inguinal hernia	4 (2%)	4 (2%)	0	1 (<1%)	0	0
Rectal haemorrhage	4 (2%)	4 (2%)	0	0	0	0
General disorders and administration site conditions						
Device failure	0	1 (<1%)	0	0	0	0
Pyrexia	4 (2%)	0	0	2 (<1%)	1 (<1%)	0
Immune system disorders						
Anaphylactic reaction	0	0	1 (<1%)	0	0	0
Drug hypersensitivity	1 (<1%)	2 (1%)	0	0	0	0
Infections and infestations						
Epididymitis	4 (2%)	1 (<1%)	0	0	0	0
Liver abscess	0	0	0	0	1 (<1%)	0
Otitis externa	0	0	0	0	1 (<1%)	0
Orchitis	6 (3%)	1 (<1%)	0	0	0	0
Staphylococcal infection	1 (<1%)	0	0	0	1 (<1%)	0

Urinary tract infection	19 (10%)	2 (1%)	0	7 (3%)	2 (<1%)	0
Injury, poisoning, and procedural complications						
Accident	0	1 (<1%)	0	0	0	0
Craniocerebral injury	0	1 (<1%)	0	0	0	0
Procedural pain	2 (1%)	0	0	2 (<1%)	1 (<1%)	0
Investigations						
Fibrin D-dimer increased	2 (1%)	2 (1%)	0	0	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	3 (2%)	2 (1%)	0	4 (2%)	0	0
Osteoarthritis	2 (1%)	2 (1%)	0	3 (1%)	1 (<1%)	0
Nervous system disorders						
Headache	3 (2%)	1 (<1%)	0	2 (<1%)	0	0
Neoplasms benign, malignant, and unspecified						
Ear neoplasm	0	0	0	0	1 (<1%)	0
Neuroendocrine carcinoma	0	1 (<1%)	0	0	0	0
Tongue cancer recurrent	0	0	0	0	1 (<1%)	0
Tonsillar neoplasm	0	1 (<1%)	0	0	0	0
Ureteric cancer metastatic	0	0	0	0	1 (<1%)	0
Ureteric cancer regional	0	0	0	0	1 (<1%)	0
Nervous system disorders						
Cerebrovascular accident	0	2 (1%)	0	0	0	0
Transient ischaemic attack	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0
Psychiatric disorders						
Depression	4 (2%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0
Renal and urinary disorders						
Dysuria	51 (26%)	0	0	5 (2%)	0	0
Haematuria	55 (28%)	1 (<1%)	0	6 (3%)	0	0
Micturition urgency	21 (11%)	0	0	2 (<1%)	0	0
Pollakiuria	20 (10%)	0	0	6 (3%)	0	0
Urinary incontinence	17 (9%)	2 (1%)	0	9 (4%)	1 (<1%)	0
Urinary retention	29 (15%)	3 (2%)	0	1 (<1%)	1 (<1%)	0
Reproductive system and breast disorders						

Ejaculation failure	14 (7%)	2 (1%)	0	1 (<1%)	0	0
Erectile dysfunction	72 (37%)	2 (1%)	0	21 (10%)	3 (1%)	0
Perineal pain	29 (15%)	1 (<1%)	0	1 (<1%)	0	0
Prostatic pain	5 (3%)	1 (<1%)	0	0	0	0
Prostatitis	7 (4%)	3 (2%)	0	9 (4%)	1 (<1%)	0
Urethral stenosis	1 (<1%)	1 (<1%)	0	0	0	0
Respiratory, thoracic, and mediastinal disorders						
Bronchospasm	0	0	1 (<1%)	0	0	0
Skin and subcutaneous tissue disorders						
Purpura	0	1 (<1%)	0	0	0	0
Surgical and medical procedures						
Cataract operation	2 (1%)	1 (<1%)	0	1 (<1%)	0	0
Facial operation	0	1 (<1%)	0	0	0	0
Knee arthroplasty	0	1 (<1%)	0	0	0	0
Vascular disorders						
Phlebitis	0	0	0	2 (<1%)	1 (<1%)	0
Thrombosis	1 (<1%)	0	0	0	1 (<1%)	0

VTP: vascular-targeted photodynamic therapy.

Data are n (%). Grade 1–2 (when the event occurred in ≥10% of the patients in at least one group) and all grade 3 and 4 treatment-emergent adverse events that occurred during the study period. The worst grade reported for each patient is listed. Events are listed by preferred terms (Medical Dictionary for Regulatory Activities version 18·0), and graded by National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). One patient in the VTP group died due to myocardial infarction during mountain climbing about 8 months after completing treatment; the death was assessed to be not related to treatment.

*Nine men randomly assigned to VTP did not receive treatment and were excluded from the safety analysis.

Source: Azzouzi et al., 2016[40]

Table 23 presents the distribution of patients according to the severity grade of their AEs for each treatment group in the indication population. About twice as many subjects in the VTP group as in the Active Surveillance group experienced AEs of Grades 2 or 3. For both Grade 2 and 3 events, the drug, device, or VTP procedure are likely to be the main driver of the increased frequency compared to the Active Surveillance group. There was only 1 subject with reported Grade 4 event in each arm. The event was not related to the drug, device or procedure in the VTP arm.

The results of the Active Surveillance group are quite consistent in both the overall and indication safety populations. For the VTP group, there is a 6.4% reduction in

the frequency of Grade 3 events and an 8.0% increase in the frequency of Grade 2 events. When focusing only on the drug, device of procedure related events, the frequencies of the different severity grades are similar with an increase of 4.7% in Grade 2 events and a decrease of 3.3% for Grade 3 events.

Table 23 Adverse events (AEs) by severity (indication population)

Number of Subjects with AE in Category	VTP N = 79 n (%)	VTP drug, device or VTP procedure related N = 79 n (%)	Active surveillance N = 207 n (%)
Subjects with only Grade 1 (mild) AEs	18 (22.8)	22 (27.8)	13 (16.7)
Subjects with Grade 2 (moderate) AEs	44 (55.7)	36 (45.8)	19 (24.4)
Subjects with Grade 3 (severe) AEs	11 (13.9)	5 (6.3)	6 (7.7)
Subjects with Grade 4 (life-threatening) AEs	1 (1.3)	0	1 (1.3)
Subjects with Grade 5 (death) AEs	0	0	0
AE: adverse event; VTP: vascular-targeted photodynamic therapy Source: EMA Assessment Report Tookad[43]			

Serious AEs occurred three times more frequently in VTP-treated subjects than in subjects receiving active surveillance in the overall safety population (**Table 20**). Among the 60 subjects in the VTP group experiencing at least one SAE, 30 experienced SAEs related to the drug, the device, or the VTP procedure. The most frequent event was urinary retention (15 cases), and the only other events occurring in more than one subject were urinary tract infection (3 cases), orchitis (2 cases), and prostatitis (2 cases) (**Table 24**). No death related to the drug, device, or procedure was reported. The single death that occurred, due to myocardial infarction, was deemed to be unrelated to the study drug, device, or procedure.

Table 24 Serious adverse events related to study drug, device, or procedure (safety population)

	VTP N = 197	
	Subjects n (%)	Events n

	VTP N = 197	
All SAEs related to study drug, device, or procedure	30 (15.2)	39
Gastrointestinal disorders	1 (0.5)	2
Nausea	1 (0.5)	1
Vomiting	1 (0.5)	1
Infections and infestations	5 (2.5)	5
Orchitis	2 (1.0)	2
Urinary tract infection	3 (1.5)	3
Injury, poisoning and procedural complications	1 (0.5)	1
Surgical procedure repeated	1 (0.5)	1
Investigations	2 (1.0)	2
Body temperature increased	1 (0.5)	1
Residual urine volume increased	1 (0.5)	1
Nervous system disorders	1 (0.5)	1
Transient global amnesia	1 (0.5)	1
Renal and urinary disorders	22 (11.2)	23
Dysuria	2 (1.0)	2
Haematuria	3 (1.5)	3
Urethral stenosis	2 (1.0)	2
Urinary incontinence	1 (0.5)	1
Urinary retention	15 (7.6)	15
Reproductive system and breast disorders	3 (1.5)	3
Penile pain	1 (0.5)	1
Prostatitis	2 (1.0)	2
Respiratory, thoracic and mediastinal disorders	1 (0.5)	1
Bronchospasm	1 (0.5)	1
Vascular disorders	1 (0.5)	1
Haematoma	1 (0.5)	1

SAE: serious adverse event; VTP: vascular-targeted photodynamic therapy.

Note: SAEs with assessments of very likely, probable, or possible or with missing relationship are considered related.

Source: CLIN1001 PCM301 Clinical Study Report[41]

The SAEs related to study drug, device, or procedure reported in the indication safety population are summarized in **Table 25**. There were 14 SAEs reported by 11 patients (13.9%) with the most frequently observed being temporary urinary retention (6 cases). Five of those retentions occurred less than 10 days after the procedure in all the subjects and one occurred 14 months after the procedure. Four of those six SAEs were assessed as moderate in severity (CTCAE Grade 2 definition: urinary, suprapubic, or intermittent catheter placement indicated), one was mild, and the other one was severe (CTCAE Grade 3 definition: elective operative or radiologic intervention indicated). Two cases resolved in less than 2 weeks and the other four in less than 1.5 months.

Table 25 Serious adverse events related to study drug, device, or procedure (indication population)

	VTP N = 79	
System Organ Class Preferred Term	**Subjects n (%)**	**Events n**
All SAEs related to study drug, device, or procedure	11 (13.9)	14
Infections and infestations	3 (3.8)	3
Orchitis	1 (1.3)	1
Urinary tract infection	2 (2.5)	2
Nervous system disorders	1 (1.3)	1
Transient global amnesia	1 (1.3)	1
Renal and urinary disorders	7 (8.9)	8
Dysuria	1 (1.3)	1
Haematuria	1 (1.3)	1
Urinary retention	6 (7.6)	6
Reproductive system and breast disorders	2 (2.5)	2
Penile pain	1 (1.3)	1
Prostatitis	1 (1.3)	1

SAE: serious adverse event; VTP: vascular-targeted photodynamic therapy.
Note: SAEs with assessments of very likely, probable, or possible or with missing relationship are considered related.
Source: EMA Assessment Report Tookad[43]

Month 36

At Month 36, 51 subjects had experienced at least one AE, 20 subjects in the VTP group and 31 in the active surveillance group. These are detailed in **Appendix F.** Most AEs were reported more frequently in the active surveillance group. The most common AEs occurring more frequently in the VTP group were urinary incontinence (3.4% vs 3.1%), pollakiuria (2.7% vs 1.6%) and dysuria (2.0% vs 1.6%).[42]

Of the 20 subjects in the VTP group who had experienced at least one AE at Month 36, one patient had dysuria which was considered as probably related to the study drug, the study device and the VTP procedure; one patient had radiation rectitis, which was considered as possibly related to the VTP procedure; one patient had urethral stricture, which was considered as possibly related to the VTP procedure. None of these AEs were considered serious.[42]

Grade 3/4 AEs occurred in seven subjects (3 in the VTP group, 4 in the active surveillance group). One AE resulted in death in a subject receiving VTP, while two subjects receiving active surveillance experienced AEs resulting in death.[42] Serious AEs were experienced by three VTP-treated subjects and four subjects in the active surveillance group.[42]

Month 48

Twenty five (25) subjects in the VTP group experienced at least one AE at the Month 48 visit, compared to 20 in the active surveillance group. Compared to the active surveillance group, the most common AEs in the VTP group were erectile dysfunction (4.1% vs 1.7%), pollakiuria (2.0% vs 1.7%), prostatitis (1.4% vs 0.8%), congenital, familial and genetic disorders (1.4% vs 0%) and hydrocele (1.4% vs 0%) (**Appendix F**).[42]

At Month 48, one patient reported urinary incontinence which was considered possibly related to the VTP procedure, and one patient reported ejaculation failure which was considered very likely to be related to the VTP procedure. The remaining AEs were deemed to be unrelated to the study drug, device, or VTP procedure. None of the reported AEs were considered serious.[42]

Grade 3/4 AEs were reported by four subjects receiving VTP and six subjects in the active surveillance group; the only two fatal AEs occurred in VTP-treated subjects.[42] Five (5) subjects each in the VTP and the active surveillance arms reported SAEs at Month 48.[42]

Limitation

Although the safety profile appears to favour active surveillance, it is important to take into account that AEs occurring after radical therapy have not been reported consistently across all patients because radical therapy was considered a failure in the PCM301 trial, which led to discontinuation of follow-up in some cases.

Adverse events of special interest in the context of early stage prostate cancer

The numbers of patients who experience erectile dysfunction (ED), urinary incontinence (UI) or bowel dysfunction (BD) in the PCM301 trial are presented in **Table 26** and **Table 27** by treatment group for the overall population and indication population, respectively.

Table 26 Adverse events of special interest in the context of early stage prostate cancer (safety population)

Adverse event of special interest	VTP (N=197) n (%)			AS (N=207) n (%)		
	Any grade AEs	Grade 2 and above AEs	Grade 2 and above AEs reported prior to RT	Any grade AEs	Grade 2 and above AEs	Grade 2 and above AEs reported prior to RT
Erectile dysfunction	74 (38)	34 (17)	32 (16)	24 (12)	12 (6)	5 (2)
Urinary incontinence	19 (10)	7 (4)	4 (2)	10 (5)	5 (2)	1 (0)
Bowel dysfunction*	15 (8)	5 (3)	5 (3)	1 (0)	0 (0)	0 (0)

* Includes gastrointestinal hypermotility, gastrointestinal disorder, anal fistula, gastrooesophageal reflux disease, gastritis, abnormal faeces, rectal haemorrhage, anal haemorrhage, haematochezia, and frequent bowel movements.
VTP, vascular targeted photodynamic therapy; AS, active surveillance; AEs, adverse events; RT, radical therapy
Source: PCM301 post-hoc analysis[14]

Table 27 Adverse events of special interest in the context of early stage prostate cancer (indication population)

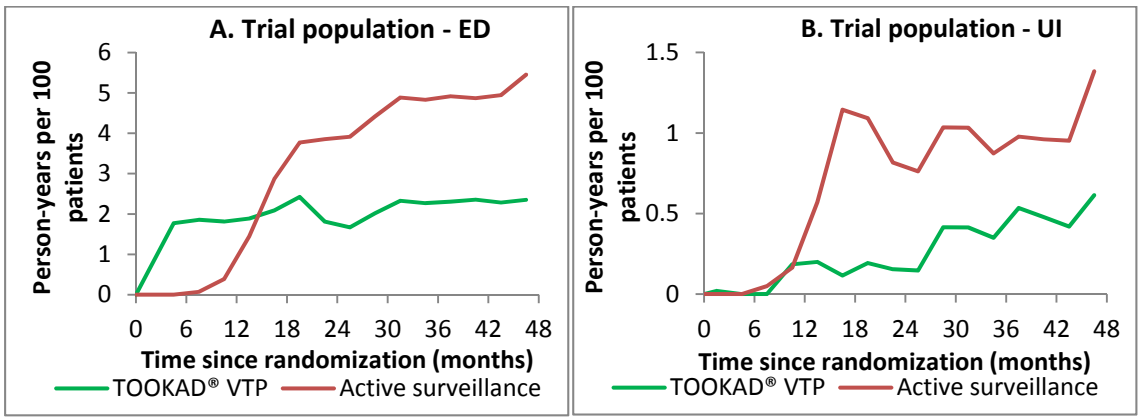
Adverse event of special interest	VTP (N=79) n (%)			AS (N=78) n (%)		
	Any grade AEs	Grade 2 and above AEs	Grade 2 and above AEs reported prior to RT	Any grade AEs	Grade 2 and above AEs	Grade 2 and above AEs reported prior to RT
Erectile dysfunction	28 (35)	16 (20)	14 (18)	10 (13)	6 (8)	1 (3)
Urinary incontinence	8 (10)	3 (4)	1 (1)	6 (8)	3 (4)	1 (1)
Bowel dysfunction*	11 (14)	4 (5)	4 (5)	0 (0)	0 (0)	0 (0)

* Includes gastrointestinal hypermotility, gastrointestinal disorder, anal fistula, gastrooesophageal reflux disease, gastritis, abnormal faeces, rectal haemorrhage, anal haemorrhage, haematochezia, and frequent bowel movements.
VTP, vascular targeted photodynamic therapy; AS, active surveillance; AEs, adverse events; RT, radical therapy
Source: PCM301 post-hoc analysis[14]

Time with genitourinary toxicity

The time with either ED or UI toxicities in each treatment group for the overall trial population is presented in **Figure 7**. The ED toxicities are more prevalent in the VTP group up to ~15 months and then become more prevalent in the active surveillance group, with a gap that increases over time. For UI toxicities, they start to increase in each treatment group around ~9 months, but at a faster pace in the active surveillance arm. It is noteworthy that the maximum toxicity level is reached at 48 months in the active surveillance arm for both ED and UI, with a ~4 fold greater level of toxicity for ED.[43]

Figure 7 Time with genitourinary toxicities (safety population). A. Erectile dysfunction; B. Urinary incontinence



Source: EMA Assessment Report Tookad[43]

The ratios of areas under the curve between VTP and Active Surveillance for each type of toxicity and their total, calculated over 24 and 48 months are summarized in **Table 28**. The analysis over 48 months is restricted to those patients have completed the 48-month follow-up. The overall ratio for the relative time with toxicity for VTP compared to active surveillance is 0.93 (95% CI= 0.47-1.03); 1.15 (95% CI= 0.47-1.03) for ED and 0.23 (95% CI= 0.13-0.45) for UI. Therefore, the overall toxicity is slightly reduced at Month 24 and ED toxicity is slightly increased at Month 24 but without statistically significant differences. The UI toxicity is substantially reduced with a statistically significant difference.[43]

Due to the stable reduction in risk of RT between Month 24 and Month 48, the ratio of relative time with toxicity in the overall safety population is greater at Month 48 compared to Month 24: 0.58 overall (95% CI: 0.27-0.64), with 0.63 for ED (95% CI: 0.28-0.69) and 0.36 for UI (95% CI: 0.16-0.47). Hence, it appears that at Month 48, both the ED and UI toxicities are significantly reduced in the VTP arm compared to the active surveillance group.[43]

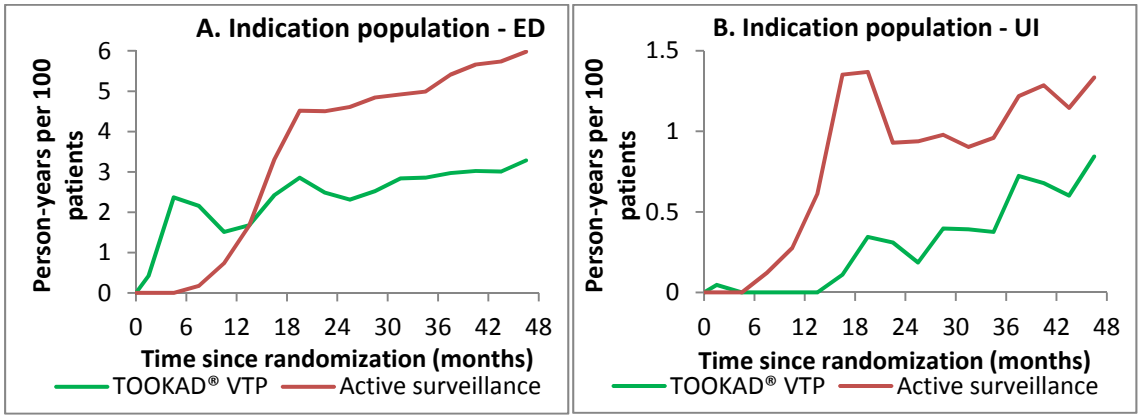
Table 28 Time with genitourinary toxicity ratios (safety population)

	Ratio over 24 months (95% CI)	Ratio over 48 months (95% CI)
Total (ED+UI)	0.93 (0.47-1.03)	0.58 (0.27-0.64)
Erectile dysfunction (ED)	1.15 (0.57-1.29)	0.63 (0.28-0.69)
Urinary incontinence (UI)	0.23 (0.13-0.45)	0.36 (0.16-0.47)

The ratio of the area under the curve (AUC) for the VTP group to that of active surveillance group.
Source: EMA Assessment Report Tookad[43]

The analysis of time with genitourinary toxicities (ED and UI) in the indication population by treatment group is presented in **Figure 8** and **Table 29**. At Month 24, the overall toxicity ratio was 0.85 (95% CI=0.37-1.18), with 1.07 for ED (95% CI=0.49-1.60) and 0.17 for UI (95% CI=0.05-0.44). At Month 48, the overall toxicity ratio was 0.62 (95% CI=0.23-0.83), with 0.68 for ED (95% CI=0.23-0.91) and 0.37 for UI (95% CI=0.14-0.58). As a result, the reduction in time with toxicity was comparable to the overall trial population, with reductions slightly greater at Month 24 and slightly lower at Month 48.[43]

Figure 8 Time with genitourinary toxicities (indication population). A. Erectile dysfunction; B. Urinary incontinence



Source: EMA Assessment Report Tookad[43]

Table 29 Time with genitourinary toxicity ratios (indication population)

	Ratio over 24 months (95% CI)	Ratio over 48 months (95% CI)
Total (ED+UI)	0.85 (0.37-1.18)	0.62 (0.23-0.83)
Erectile dysfunction (ED)	1.07 (0.49-1.60)	0.68 (0.23-0.91)
Urinary incontinence (UI)	0.17 (0.05-0.44)	0.37 (0.14-0.58)

The ratio of the area under the curve (AUC) for the VTP group to that of active surveillance group.
Source: EMA Assessment Report Tookad[43]

International Prostate Symptom Score (IPSS)

The International Prostate Symptom Score (IPSS) is an 8-item questionnaire focused on urinary symptoms with one general question about urinary symptoms. The questions relate to the following areas: sensation of bladder emptying; frequency of urination; stops when urinating; difficulties to postpone urination; urinary steam; beginning of urination; night urination, and the quality of life due to urinary symptoms. Patients were asked to give their response to each of the areas using a 6-point scale (the higher the scale, the worse the state). The potential range of scores for IPSS Questions 1 to 7 is 0 to 35, and a decrease corresponds to an improvement in urinary symptoms. IPSS is indicative of patient satisfaction, but cannot be used for QALY calculation.

In the indication population, the change in IPSS scores (Questions 1 to 7) from baseline to Month 24 are presented in **Table 30** and **Figure 9**. At Month 24, the mean score for the VTP group was decreased compared to baseline (6.0 vs 6.6, mean change from baseline of -0.7), whereas the mean score increased in the active surveillance group (8.0 vs 6.2, mean change from baseline of 1.8). These data indicate that urinary symptoms improved in the VTP group, and worsened for subjects in the active surveillance group. Change from baseline, analysed using an ANCOVA model with treatment group as the fixed effect and baseline IPSS score as a covariate, was statistically significant between the VTP and active surveillance groups (P=0.004).

Table 30 International Prostate Symptom Scores and change from baseline at Month 24 (indication population)

Statistic	**VTP N = 80**	**Active surveillance N = 78**
Observed Cases		
Baseline mean (SD)	6.6 (5.42)	6.2 (4.40)
Month 24 mean (SD)	6.0 (5.46)	8.0 (5.80)
Mean change from baseline (SD)	-0.7 (5.36)	1.8 (5.21)
Imputed Cases		
Adjusted change from Baseline		
N*	79	78

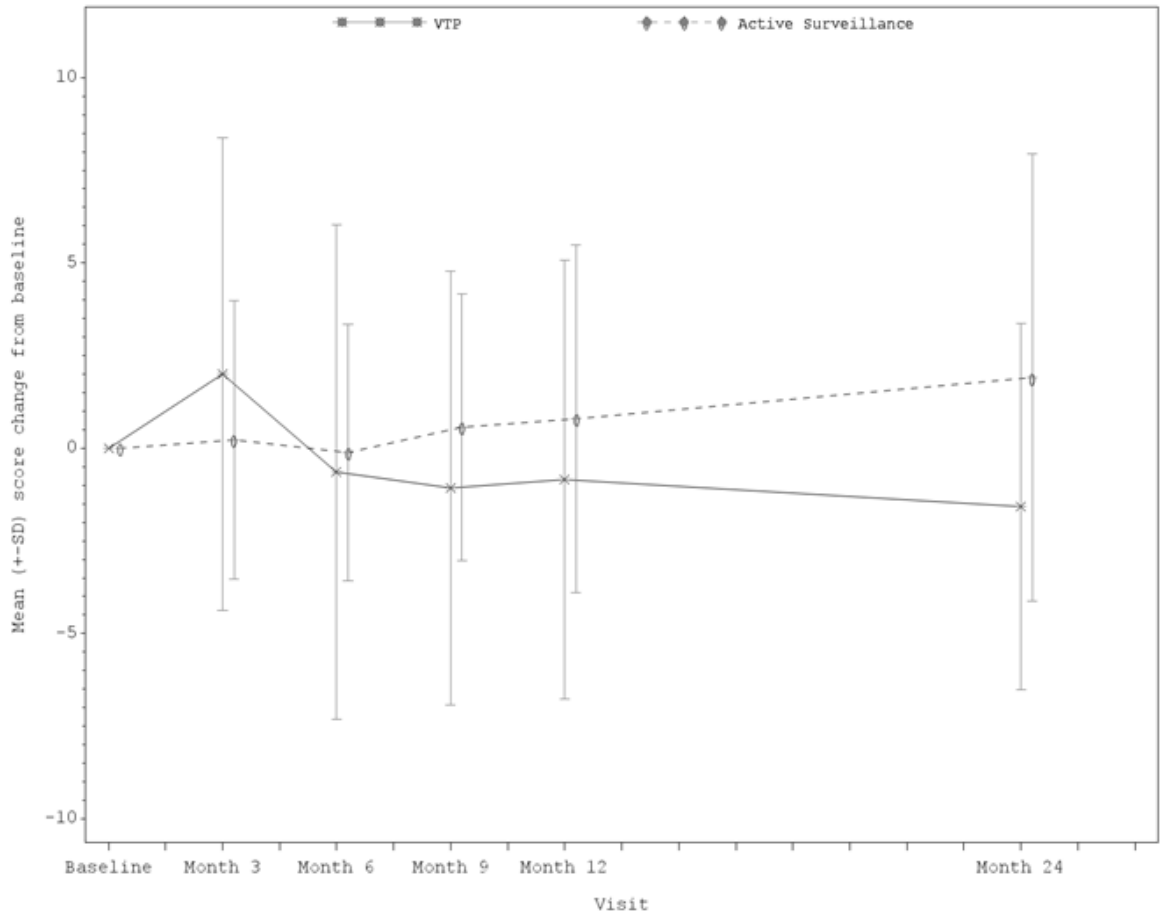
Statistic	VTP N = 80	Active surveillance N = 78
Mean (SE)	-0.6 (0.55)	1.7 (0.55)
95% 2-sided CI	-1.7, 0.5	0.6, 2.8
Difference in adjusted change from baseline vs active surveillance		
Mean (SE)	-2.3 (0.78)	
95% 2-sided CI	-3.8, -0.8	
P value vs active surveillance	0.004	

CI: confidence interval; SD: standard deviation; SE: standard error; VTP: vascular-targeted photodynamic therapy.

* Number of subjects with non-missing Baseline and Month 24 (imputed) values in the safety population. Missing scores are imputed using the Markov Chain Monte Carlo method.

Source: [Data on file]. Additional analysis of PCM301 trial data.

Figure 9 International Prostate Symptom Scores (Questions 1 to 7) mean change from baseline* (and standard deviation) over time (observed cases) (indication population)



SD: standard deviation; VTP: vascular-targeted photodynamic therapy.
Source: [Data on file]. Additional analysis of PCM301 trial data.

Table 31 and **Figure 10** present change in IPSS scores (Questions 1 to 7) from baseline to Month 24 by treatment group in the overall safety population. At Month 24, the mean score in the VTP group (6.6) is slightly lower than the mean score at Month 24 in the active surveillance group (8.2) as well as the mean score at baseline in the VTP group (7.6), indicating a slight decrease in urinary symptoms associated with VTP at Month 24. Mean adjusted change from baseline indicates a decrease in urinary symptoms compared to the active surveillance group as observed with the 14% decrease in the mean IPSS score at Month 24 from baseline in the VTP group compared to the 24% increase in the active surveillance group.

Table 31 International Prostate Symptom Scores and change from baseline at Month 24 (safety population)

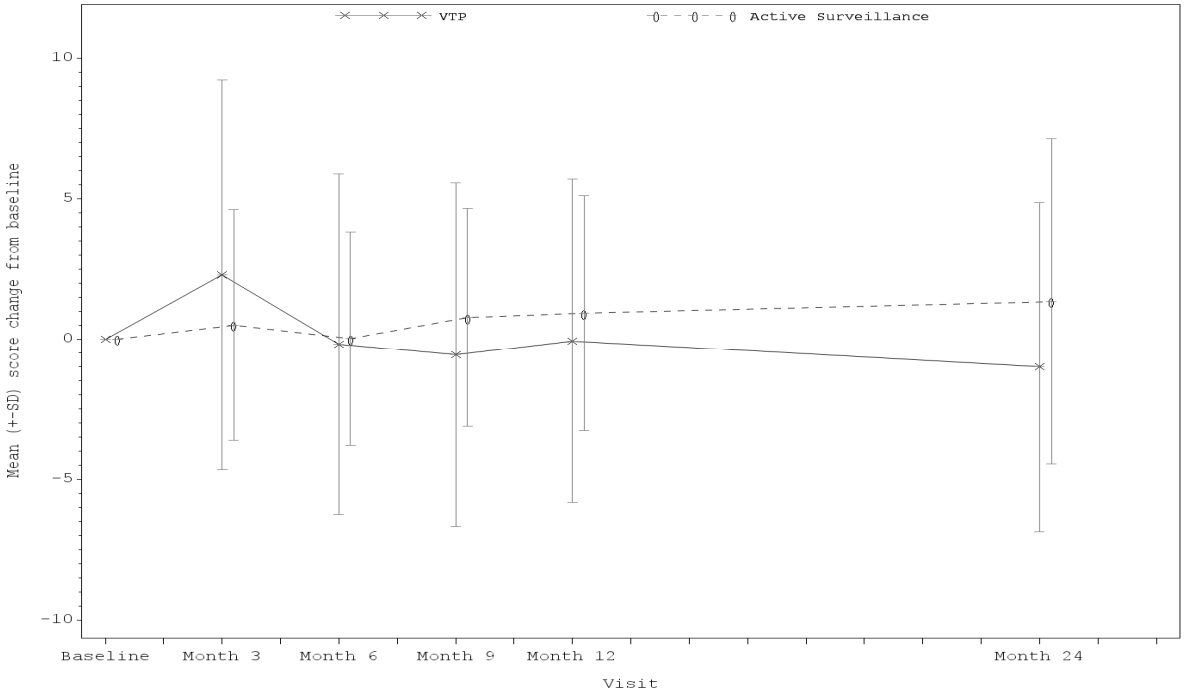
Statistic	VTP N = 197	Active surveillance N = 207
Observed Cases		
Baseline		
Number of observations	179	185
Mean (SD)	7.6 (6.09)	6.6 (5.30)
Month 24		
Number of observations	165	154
Mean (SD)	6.6 (5.47)	8.2 (6.47)
Change from Baseline		
Number of observations	151	138
Mean (SD)	-1.0 (5.86)	1.3 (5.80)
Imputed Cases		
Adjusted change from Baseline		
N*	196	204
Mean (SE)	-0.2 (0.35)	1.0 (0.35)
95% 2-sided CI	-0.9, 0.5	0.3, 1.7
Difference in adjusted change from baseline vs active surveillance		
Mean (SE)	-1.2 (0.50)	
95% 2-sided CI	-2.2, -0.3	
P value vs active surveillance	0.013	

CI: confidence interval; SD: standard deviation; SE: standard error; VTP: vascular-targeted photodynamic therapy.

* Number of subjects with non-missing Baseline and Month 24 (imputed) values in the safety population

Source: CLIN1001 PCM301 Clinical Study Report[41]

Figure 10 International Prostate Symptom Scores (Questions 1 to 7) mean change from baseline* (and standard deviation) over time (observed cases) (safety population)



SD: standard deviation; VTP: vascular-targeted photodynamic therapy.
* Potential range of change in scores: from -35 (best) to +35 (worst).
Source: CLIN1001 PCM301 Clinical Study Report[41]

International Index of Erectile Function (IIEF)

Table 32 and **Figure 11** present change in erectile function scores from baseline to Month 24 by treatment group in the indication population. The potential range of scores for the erectile function domain of the IIEF-15 is 1 to 30, and a decrease corresponds to a worsening in erectile function. Both VTP and active surveillance groups reported mean decreases in erectile functions scores compared to baseline. Change from baseline, analysed using an ANCOVA model with treatment group as the fixed effect and baseline erectile function score as a covariate, indicates no difference in change of erectile function compared to the active surveillance group (P=0.979). IIEF is indicative of patient satisfaction but cannot be used for QALY calculation.

Table 32 Erectile function scores and change from baseline at Month 24 (indication population)

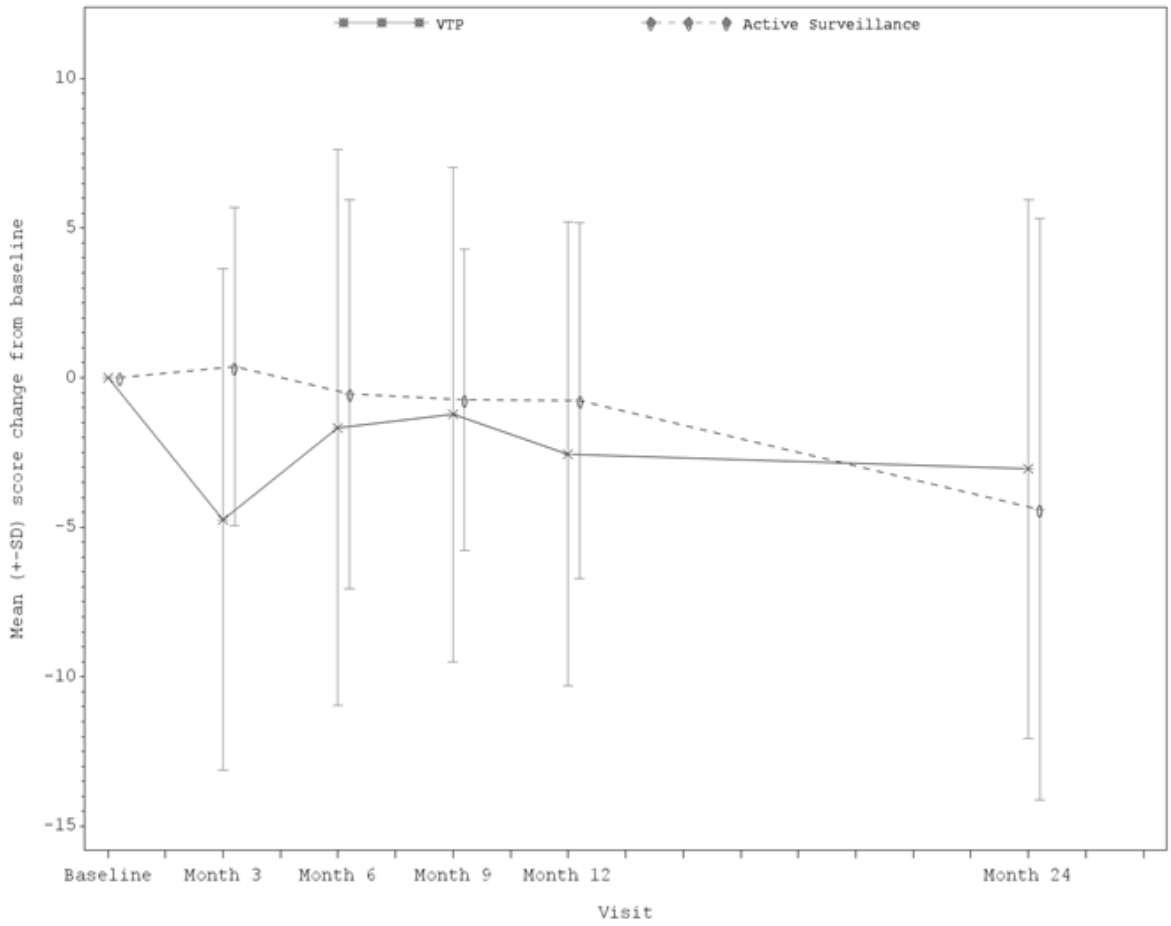
Statistic	VTP N = 80	Active surveillance N = 78
Observed Cases		
Baseline mean (SD)	18.3 (10.07)	20.8 (9.83)
Month 24 mean (SD)	15.3 (10.07)	16.9 (9.67)
Mean change from baseline (SD)	-3.0 (8.53)	-3.9 (8.47)
Imputed Cases		
Adjusted change from Baseline		
N*	79	78
Mean (SE)	-3.5 (0.87)	-3.4 (0.87)
95% 2-sided CI	-5.2, -1.7	-5.1, -1.7
Difference in adjusted change from baseline vs active surveillance		
Mean (SE)	0.0 (1.23)	
95% 2-sided CI	-2.5, 2.4	
P value vs active surveillance	0.979	

CI: confidence interval; SD: standard deviation; SE: standard error; VTP: vascular-targeted photodynamic therapy.

* Number of subjects with non-missing Baseline and Month 24 (imputed) values in the safety population. Missing scores are imputed using the Markov Chain Monte Carlo method.

Source: [Data on file]. Additional analysis of PCM301 trial data.

Figure 11 International Index of Erectile Function - Erectile Function Domain - mean change from baseline* (and standard deviation) over time (observed cases) (indication population)



SD: standard deviation; VTP: vascular-targeted photodynamic therapy.
Source: [Data on file]. Additional analysis of PCM301 trial data.

Change in erectile function scores from baseline to Month 24 for the overall safety population is presented in **Table 33** and **Figure 12**. The change from baseline at Month 24 shows a slight deterioration of erectile function in both treatment groups. Change from baseline indicates no difference in change of erectile function compared to the active surveillance group.

Table 33 Erectile function scores and change from baseline at Month 24 (safety population)

Statistic	VTP N = 197	Active surveillance N = 207

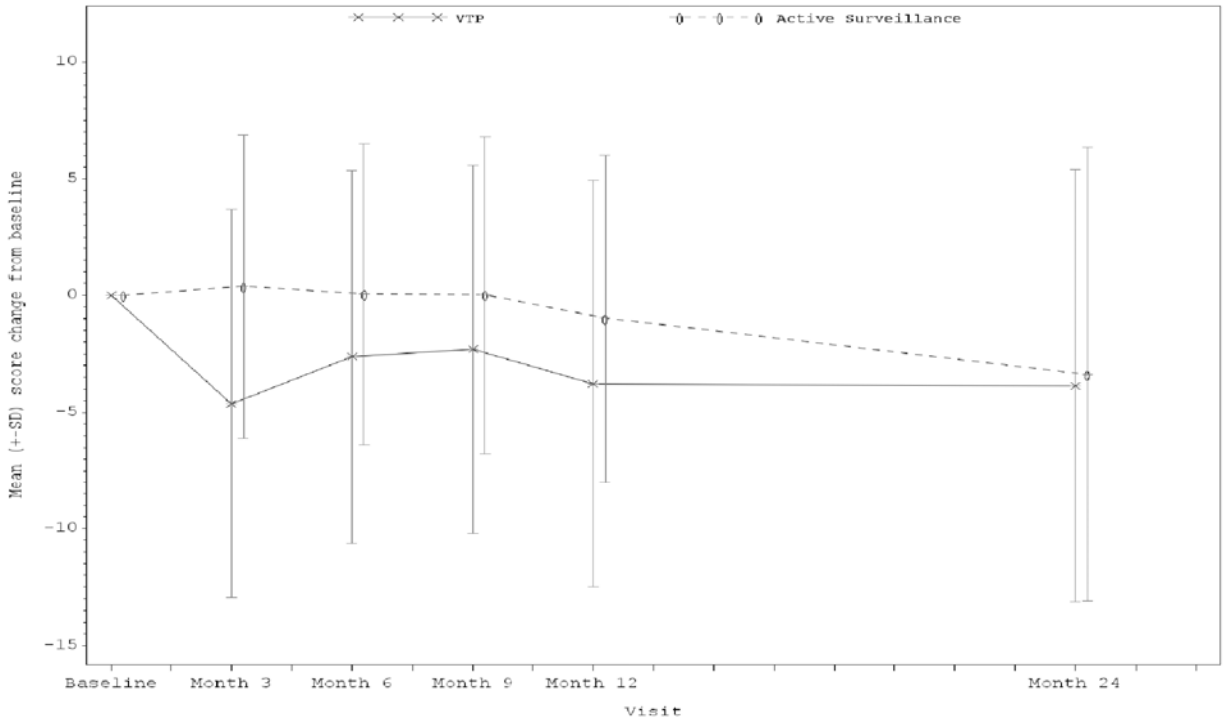
Statistic	VTP N = 197	Active surveillance N = 207
Observed Cases		
Baseline		
Number of observations	184	188
Mean (SD)	18.6 (10.22)	20.6 (9.92)
Month 24		
Number of observations	159	152
Mean (SD)	15.0 (10.70)	16.8 (11.17)
Change from Baseline		
Number of observations	150	140
Mean (SD)	-3.9 (9.25)	-3.4 (9.73)
Imputed Cases		
Adjusted change from Baseline		
N*	195	203
Mean (SE)	-4.1 (0.57)	-3.1 (0.56)
95% 2-sided CI	-5.2, -2.9	-4.2, -2.0
Difference in adjusted change from Baseline vs active surveillance		
Mean (SE)	-1.0 (0.80)	
95% 2-sided CI	-2.5, 0.6	
P value vs active surveillance	0.233	

CI: confidence interval; SD: standard deviation; SE: standard error; VTP: vascular-targeted photodynamic therapy.

* Number of subjects with non-missing baseline and Month 24 (imputed) values in the safety population

Source: CLIN1001 PCM301 Clinical Study Report[41]

Figure 12 International Index of Erectile Function - Erectile Function Domain - mean change from baseline* (and standard deviation) over time (observed cases) (safety population)



SD: standard deviation; VTP: vascular-targeted photodynamic therapy.
* Potential range of change in scores: from -29 (worst) to +29 (best).
Source: CLIN1001 PCM301 Clinical Study Report[41]

EuroQol 5D (EQ-5D)

Change in EQ-5D VAS scores from baseline to Month 24 in the indication population is detailed in **Table 34** and **Figure 13**. Subjects in the VTP group reported higher health status scores than subjects in the active surveillance group at Month 24. Although the difference in adjusted change from baseline vs active surveillance favoured VTP, the difference was not statistically significant (P=0.315).

Table 34 EQ-5D scores and change from baseline at Month 24 (indication population)

Statistic	VTP N = 80	Active surveillance N = 78
Observed Cases		

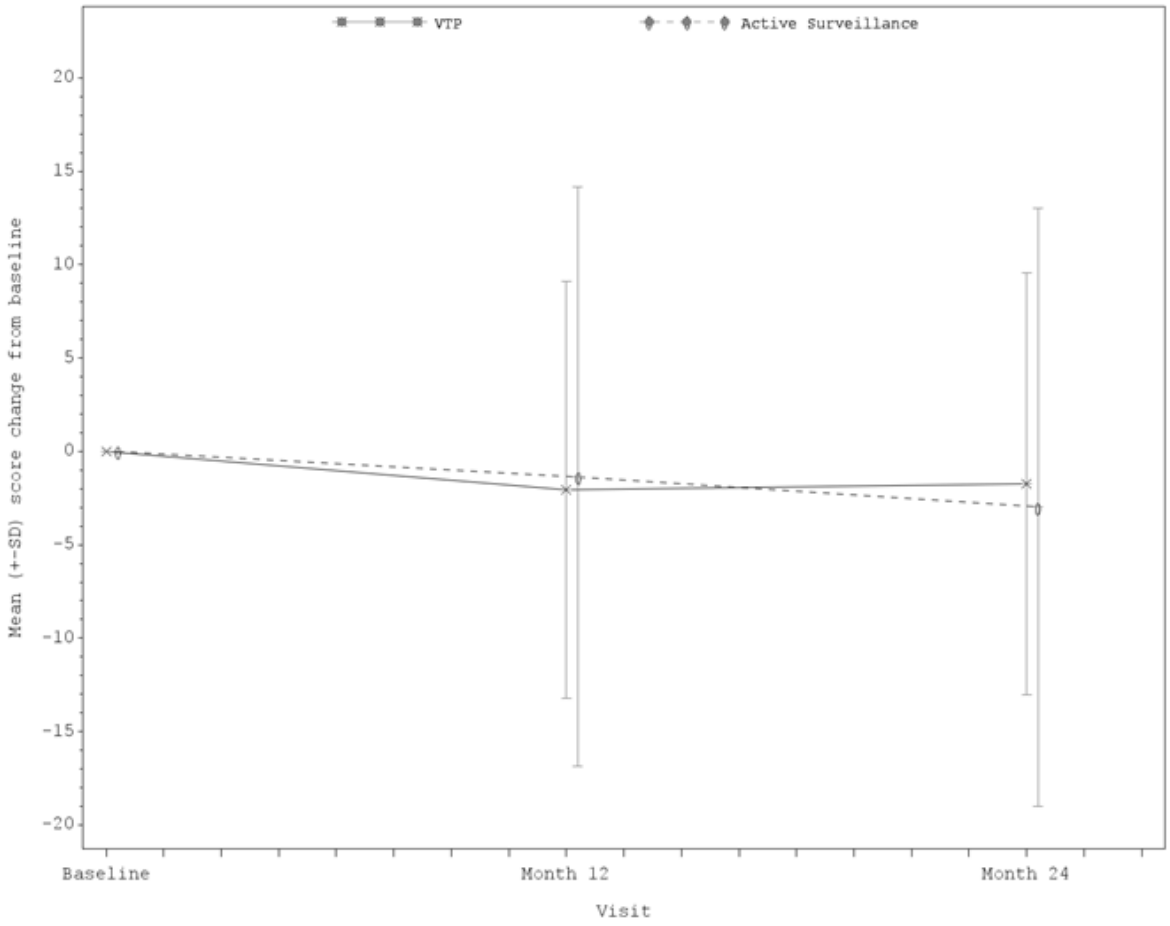
Statistic	VTP N = 80	Active surveillance N = 78
Baseline mean (SD)	83.2 (12.04)	80.2 (12.71)
Month 24 mean (SD)	81.5 (14.09)	77.2 (14.88)
Mean change from baseline (SD)	-1.8 (11.3)	-3.0 (16.02)
Imputed Cases		
Adjusted change from Baseline		
N*	60	47
Mean (SE)	-1.2 (1.63)	-3.7 (1.85)
95% 2-sided CI	-4.4, 2.0	-7.3, -0.0
Difference in adjusted change from baseline vs active surveillance		
Mean (SE)	2.5 (2.47)	
95% 2-sided CI	-2.4, 7.4	
P value vs active surveillance	0.315	

CI: confidence interval; SD: standard deviation; SE: standard error; VTP: vascular-targeted photodynamic therapy.

* Number of subjects with non-missing Baseline and Month 24 (imputed) values in the safety population. Missing scores are imputed using the Markov Chain Monte Carlo method.

Source: [Data on file]. Additional analysis of PCM301 trial data.

Figure 13 EQ-5D score mean change from baseline* (and standard deviation) over time (observed cases) (indication population)



SD: standard deviation; VTP: vascular-targeted photodynamic therapy.
Source: [Data on file]. Additional analysis of PCM301 trial data.

Table 35 and **Figure 14** summarise change in EQ-5D scores from baseline to Month 24 by treatment group for the safety population. The mean scores at Month 24 are similar in the 2 groups and are very slightly decreased from Baseline, indicating no decrease in quality of life associated with VTP at Month 24.

Table 35 EQ-5D scores and change from baseline at Month 24 (safety population)

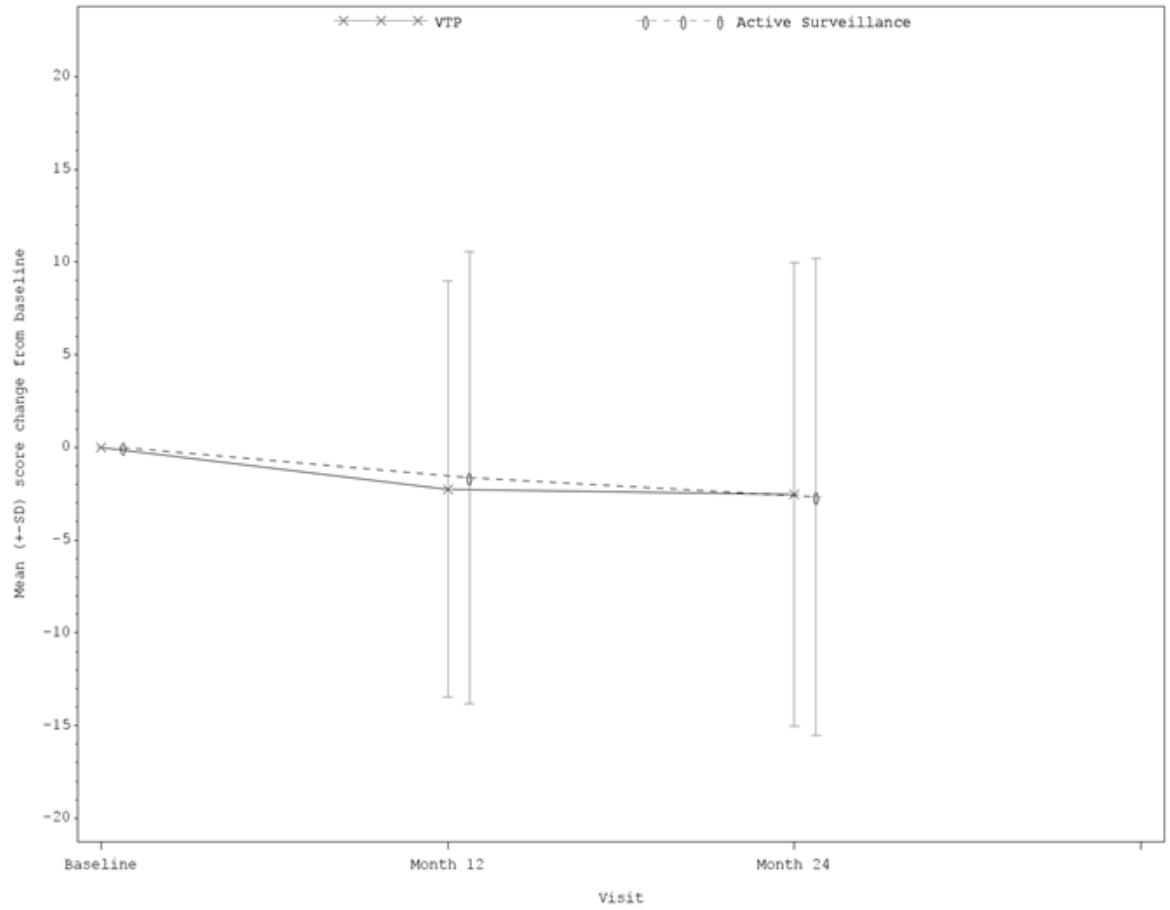
Statistic	VTP N = 197	Active surveillance N = 207
Baseline		
Number of observations	179	184
Mean (SD)	82.5 (12.31)	81.8 (12.09)

Statistic	VTP N = 197	Active surveillance N = 207
Month 24		
Number of observations	166	150
Mean (SD)	80.9 (14.28)	79.2 (13.25)
Change from Baseline		
Number of observations	151	136
Mean (SD)	-2.5 (12.50)	-2.7 (12.87)
Adjusted change from baseline		
Mean SE	-2.3 (0.96)	-3.0 (1.02)
95% 2-sided CI	-4.2, -0.4	-5.0, -1.0
Difference in adjusted change from baseline vs active surveillance		
Mean SE	0.7 (1.40)	
95% 2-sided CI	-2.1, 3.4	
p-value vs active surveillance	0.641	

CI: confidence interval; SD: standard deviation; SE: standard error; VTP: vascular-targeted photodynamic therapy.

Source: CLIN1001 PCM301 Clinical Study Report[41]

Figure 14 EQ-5D score mean change from baseline* (and standard deviation) over time (observed cases) (safety population)



SD: standard deviation; VTP: vascular-targeted photodynamic therapy.
Source: [Data on file]. Additional analysis of PCM301 trial data.

B.2.11 Ongoing studies

Preliminary data from the ongoing PCM301-FU5 follow-up study are presented in **Section B.2.6 Clinical effectiveness results of the relevant trials** (p **40**) and additional data will be available in the coming years. However, as there has been too much loss to follow up for the extension of the randomised study (CLIN1001 PCM301FU5) to provide information on overall and prostate cancer specific survival, an 'In-Depth Biopsy Study' in the post-study follow-up of PCM301 (PCM301 FU5), is planned for localised prostate cancer compared to active surveillance.[44] Further, a phase IV study PCM401 titled: "A long-term observational cohort study of patients with unilateral low risk localised prostate cancer treated with TOOKAD® vascular targeted photodynamic therapy in current clinical practice" - Post-Authorization Safety Study (PASS) & Post Authorisation Efficacy Study (PAES) will be launched in

the coming weeks.[45] Only baseline information should be available within the next 12 months because the first data collection for the PCM401 study is planned at Month 12 after VTP treatment. It is a 7-year follow-up study with stringent methods and techniques with the objective of ensuring real-world validation of the assumptions behind the marketing authorization of TOOKAD®. It will evaluate the importance of tumour location both in relation to toxicity and to oncological outcome. There is also the PCM402 study, which is "An international registry to assess the use of TOOKAD® for localised prostate cancer", which will be initiated shortly, but it is only designed to collect pre-treatment data.[46]

B.2.12 Innovation

Padeliporfin VTP is the first focal therapy with RCT data to support its use. It brings a unique solution to low-risk prostate cancer patients by addressing the limitations of the two current main approaches (active surveillance and radical therapies). It will be the only treatment option with robust clinical data that can robustly control disease progression and preserve quality of life at the same time by directing the treatment only to the area of cancer and preserving surrounding normal tissue.

Padeliporfin VTP has the potential to provide substantial health-related benefits to low-risk patients and ultimately to help further reduce over-treatment in this population. The latter remains a significant issue among newly diagnosed prostate cancer patients, knowing that:

- ~17% are low-risk[47]
- ~49% elect a radical therapy[7;13;14]
- Among the 51% that elect active surveillance,[7;13;14] 25% to 60% switch to a radical therapy within 5-10 years, with a significant portion of them discontinuing active surveillance even in absence of risk upstaging.[15-17]

The main quality of life benefits of padeliporfin VTP relate to urinary and erectile functions.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Padeliporfin VTP is the first focal therapy with RCT data to support its use for the treatment of unilateral low-risk localised prostate cancer. It is a minimally invasive therapy that provides the simultaneous benefits of robust control of disease progression and preservation of quality of life. The clinical evidence consists mainly of a Phase 3, international, multicentre, randomised controlled study, the CLIN1001 PCM301 study,[41] which compared VTP with active surveillance in patients with low-risk localised prostate cancer. In addition, there were three Phase 2 clinical trials (PCM201, PCM202 and PCM203) as well as the Phase 3 PCM304 study, which were all single-arm studies.[48-50]

The study achieved its co-primary efficacy endpoints of absence of definitive cancer and progression of cancer at 24 months. The percentage of subjects with a negative biopsy result at Month 24 was significantly higher in the VTP group than in the active surveillance group (adjusted risk ratio 3.67, 95% CI 2.53–5.33; *P* value <.0001). The percentage of participants who had disease progression at Month 24 was significantly lower in the VTP group than in the active surveillance group (adjusted hazard ratio 0.34, 95% CI 0.24–0.46; *P* value <.0001).

Further, substantially fewer subjects in the VTP group than in the active surveillance group underwent radical therapy (13 [7%] vs 62 [33%]) by Month 24 in the ITT population. There is a lasting reduction in risk as the effect was maintained until Month 48, at which point a smaller proportion of subjects in the VTP group continued to initiate radical therapy compared to those in the active surveillance group (11 [8.6%] vs. 10 [13.2%]). Based on the results of the Kaplan-Meier analysis, the cumulative risks of radical therapy in the ITT population were consistently decreased in the VTP group compared to the active surveillance group at each time point; 7% vs. 33% at Month 24, 14% vs. 44% at Month 36 and 24% vs. 53% at Month 48, further highlighting the benefit of VTP. The absolute risk difference between the two arms was stable over time (26% at Month 24, 30% at Month 36 and 29% at Month 48). The stable absolute reduction of risk of initiation of radical therapy of ~30%, stable absolute risk difference over time and lower cumulative risks at each time point were similarly demonstrated in the indication population.

Quality of life

The mean IPSS score at Month 24 in the VTP group was slightly lower than both the mean score at Month 24 in the active surveillance group and the mean score at baseline in the VTP group, indicating no increase in urinary symptoms associated with VTP at Month 24. Although the change in IIEF scores from baseline to Month 24 in the VTP group indicates a slight deterioration of erectile function in both treatment groups over time, there is no indication of lower erectile function in the VTP group compared to the active surveillance group.

Side effect profile

As expected, incidence and severity of AEs was higher in the VTP group than in the active surveillance group. Subjects in the VTP group experienced greater frequency and severity of TEAEs compared to those in the active surveillance group. AEs related to the drug, device, or procedure were common but generally not severe. Most of these AEs occurred during the procedure or in the days after the procedure and resolved without sequelae. AEs of grade 3 or 4 were reported in 21.8% of subjects in the VTP arm, compared to 9.7% of subjects in the active surveillance arm. Further, SAEs occurred three times more frequently in VTP-treated subjects than in subjects receiving active surveillance. Although the safety profile appears to favour active surveillance, it is important to take into account that AEs occurring after radical therapy have not been reported consistently across all patients because radical therapy was considered a failure in the PCM301 trial, which led to discontinuation of follow-up in some cases.

Strengths and limitations of the clinical evidence

Padeliporfin VTP offers a unique solution to low-risk prostate cancer patients by addressing the limitations of the two current main approaches (active surveillance and radical therapies). It is the only treatment option with robust clinical data that can effectively control disease progression and preserve quality of life, while directing the treatment only to the area of cancer and preserving surrounding normal tissue resulting in the preservation of erectile and urinary functions.

Active surveillance has now become a standard of care for patients with low-risk prostate cancer and is being used by a very high proportion of patients in Europe and North America, highlighting this relevance of the design of this trial. Further, about 49% of men in the United Kingdom are estimated to receive radical treatment for low-risk prostate cancer,[7;13] therefore it is a reasonable patient population in which to explore the potential of a new treatment modality. This trial recruited quickly suggesting that the interventions were both acceptable and valued by both patients and their physicians. Another strength of the study was the use of progression as a primary endpoint because transition to a higher burden or higher grade of disease is what prompts crossover to radical therapy, which is the very thing that patients and their clinicians are trying to avoid by adopting a policy of surveillance. This study was also sufficiently powered to address the issue of the inherent imprecision of using the current practice standard (TRUS-guided biopsy) to assess prostate cancer status. The follow-up period of 2 years minimized the potentially high rate of voluntary withdrawal in the active surveillance group as a result of a longer follow-up period, which would have compromised the integrity of the study. However, data on long-term outcomes will be collected in the ongoing additional 5-year follow-up study.

VTP has demonstrated therapeutic efficacy with high statistical significance along the two co-primary endpoints, which had been validated for their relevance with the EMA Scientific Advice Working Group prior to initiation of the PCM301 pivotal study. There is significant reduction in the risk of undergoing radical therapy within the 24 months of the clinical study. Further, there is practically a neutral impact on time with genitourinary toxicities up to 24 months and seems to result in significant reduction of these over a 48-months period, based on preliminary follow-up data.

The disease status subgroups included subjects who, at selection, had unilateral disease or bilateral disease. These analyses showed similar results to those in the ITT population at Month 24. The consistency of the results across both subgroups demonstrates the robustness of these findings. In particular, the results were directionally better in the target indication sub-population (unilateral low-risk / not very low-risk disease), where the benefit is maximized and which represents only ~40% of the overall population, for virtually all of the key endpoints used for the comparison of VTP versus active surveillance in the efficacy and benefit

assessment, bringing ‘statistically significant’ benefits along each endpoint. The limitation to a single procedure enables to maximize the positive benefits of the treatment, while minimizing the risk of compromising the opportunity to later undertake salvage radical therapy.

However, some uncertainties remain regarding the benefit assessment pertaining mostly to the refined definition of the benefit around reduction of time with toxicity and the willingness to get a longer-term perspective on the benefits. Genitourinary toxicities nor were consistently reported following radical therapy in the PCM301 trial, as initiation of radical therapy was considered a failure event in the trial. A large PASS study has been planned to provide relevant data on time with genitourinary toxicities to alleviate this uncertainty.

Although subjects and investigational site staff were not blinded to study treatment, the study results are robust and the risk of bias is low because the co-primary efficacy endpoints were determined by the ORP, who were blinded to treatment assignment, in order to minimise the potential bias associated with an open-label study. This study has no placebo control and including a third group of subjects for whom padeliporfin VTP would have been replaced by a placebo was considered unethical in this context as subjects would have undergone anaesthesia and other risks associated with surgery. However, to minimise observation bias, various objective methods were used for the determination of efficacy and safety endpoints, which are discussed in **Section B.2.5 Quality assessment of the relevant clinical effectiveness evidence** (p **38**).

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

The methods and results of any published cost-effectiveness analyses (relevant to the technology appraisal) are described in appendix G.

No published cost-effectiveness analysis for padeliporfin VTP was identified in the systematic literature search that was considered relevant to this technology appraisal. However, in the process of conducting the systematic search, a few studies were identified with relevant economic analyses for the UK context with regard to the anticipated introduction of padeliporfin VTP in the treatment landscape (**Section B.3.2 Economic analysis** [p **83**]).

B.3.2 Economic analysis

"Focal therapy offers harm reduction. It is a strategy that attempts to redress the balance of harms and benefits by offering men who place high utility on genitourinary function an alternative to standard care. In fact, the concept is not new — tissue-preserving strategies have been used successfully in all other solid organ cancers, such as breast cancer by offering women a lumpectomy rather than mastectomy," said Mark Emberton, MD, program director at UCL and UCLH, in a British Medical Research Council (MRC) news release.[51]

Prostate cancer has an unusual position in the NHS and global cancer treatment landscapes because it is the only cancer for which tissue-preserving strategies have not been successfully incorporated into routine clinical practice. Most patients opting for active treatment thus have the entire organ excised, a procedure that still comes with a high risk of severe side effects. Focal treatments have received growing attention in the field as possible solutions to the difficult choices patients are facing. Because of the similarities with local breast cancer treatments, which were also initially met with considerable hesitation, the highly anticipated focal treatments have been termed “male lobectomy” by clinicians who support their careful and considerate introduction into clinical practice.[51]

Lobectomy for the breast and focal treatments for the prostate have in common that they can reduce hospital visit duration and side effects. The underlying cancers further have in common that survival in untreated patients is long, causing a considerable amount of uncertainty about long-term outcomes until very long-term follow-up data are available.

At least two important differences exist between the two approaches:

- Patients with prostate cancer are usually, on average, about a decade older at onset/diagnosis than breast cancer patients, and thus many patients with slow-growing cancers of the prostate have a low likelihood of progressing to metastatic disease. Given current life expectancy numbers, many patients with low-risk prostate cancers do not initiate treatment with radical therapy.
- In contrast to lobectomy procedures for breast cancer, new focal treatments for prostate cancer are often comparatively more complex due to the peculiar location, anatomy and function of the prostate gland, and the resulting need for highly specialized equipment and know-how.

The combination of long baseline survival and increased focus on quality of life especially during the introduction phase requires a careful economic evaluation of all therapies in the landscape. The goal is not to prove superiority of a one-size-fits-all approach for all patients, but to evaluate a landscape in which clinicians have “the right tool for the right tumour in the right patient.”[51] We conducted an systematic literature review (SLR) to identify possible prior work regarding relevant cost-effectiveness studies for padeliporfin VTP in the UK context.

Given the recent EMA approval of padeliporfin (TOOKAD®) VTP, it was not surprising to not find any ICER calculations of the new technology that would be of direct relevance for our work. Thus, we did not extract any ICERs from the literature but decided to provide de novo calculations and calculate the costs of an improved treatment landscape that would include padeliporfin VTP.

For this modelling work, we identified three highly relevant economic analyses in our SLR for the UK context with regard to the anticipated introduction of padeliporfin VTP in the treatment landscape.

- A horizon scanning report by the National Institute for Health Research (NIHR) from January 2015 anticipated the future introduction of padeliporfin VTP in the UK market.[47] At the time of the writing of the report, the RCTs had not been completed, and no cost data were available. The current application provides detailed results from the PCM301 RCT and anticipated costs for the NHS.
- A poster by Olaye et al., presented in 2010,[52] presented an analysis of costs of currently available treatments to better understand the current landscape and cost levels that the new technology would be compared to. It mentioned VTP as a possible focal alternative but did not yet contain concrete information about VTP efficacy, side effect rates, or costs.
- An economic analysis by Ramsay et al. from 2015[37] included a very thorough review of the state of the evidence of various focal therapies before the RCTs for padeliporfin VTP were published. It contained a section specifically on VTP with padeliporfin, but because of the timing (ahead of publication of the randomized trials), the authors concluded: “Data were restricted to short-term outcomes only and there was a lack of good-quality prospective comparative studies. The comparative effectiveness of the newer ablative therapies, such as laser ablation and PDT, compared with established therapies remains uncertain.”

The current application provides additional evidence from prospective studies and is now ideally suited to build on the Ramsey et al 2015 report, which is comprehensive and included expert review of all variables in the model. We chose to build upon this work because it provided the best data for a comprehensive, payer-perspective view of the entire treatment landscape, allowing us to demonstrate in our model that padeliporfin VTP is a new tool for the right patient at the right time.

Patient population

The patient population in the cost-effectiveness analysis reflects the population defined in the scope and decision problem for the NICE technology appraisal and marketing authorisation. This patient population is defined as adult patients with

previously untreated, unilateral low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and:

- Clinical stage T1c or T2a,
- Gleason score ≤ 6 based on high-resolution biopsy strategies,
- PSA ≤ 10 ng/mL,
- 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1-2 positive cancer cores with ≥ 50% cancer involvement in any one core or a PSA density ≥ 0.15/mL/cm^3.[43]

The key clinical data source is the PCM301 trial, a phase 3, multicentre, randomized, clinical trial of the efficacy and safety of padeliporfin VTP for treatment of low-risk, localised prostate cancer. In the trial, a total of 413 men (padeliporfin VTP, N=206; active surveillance, N=207) diagnosed with low-risk prostate cancer by transrectal ultrasound (TRUS)-guided biopsy with no prior treatment for prostate cancer were screened and, if eligible, randomized in a 1:1 ratio to receive padeliporfin VTP or to be followed by standard active surveillance.[41] Reflecting the patient population in the PCM301 trial, the initially claimed indication submitted to EMA was for treatment of low-risk localised prostate cancer in adult males. However, the approved indication (described above) is a subgroup, which included 158 patients (padeliporfin VTP, N=80; active surveillance, N=78), of the overall PCM301 trial patient population.

Based on recommendations of the Committee for Medicinal Products for Human Use (CHMP), this indication population aims to target low-risk localised prostate cancer patients who are likely to get the greatest benefit/risk balance from padeliporfin VTP; hence the following restrictions to the PCM301 trial population were made:

- Patients with bilateral disease are excluded, as they would require two padeliporfin VTP procedures. Due to the same reason, 2nd VTP treatment is not recommended after detection of residual cancer, neither in the ipsilateral nor in the contralateral lobe, even in absence of progression. There are insufficient patients who have underwent retreatment of the ipsilateral lobe or sequential treatment of the contralateral lobe to determine the efficacy and safety of a second VTP procedure

- Very low risk patients with 1 or 2 positive cores and a PSA density ≤0.15 ng/mL/cm^3, as they have a lower likelihood of upstaging or progression, especially with modern biopsy techniques[53]

Model structure

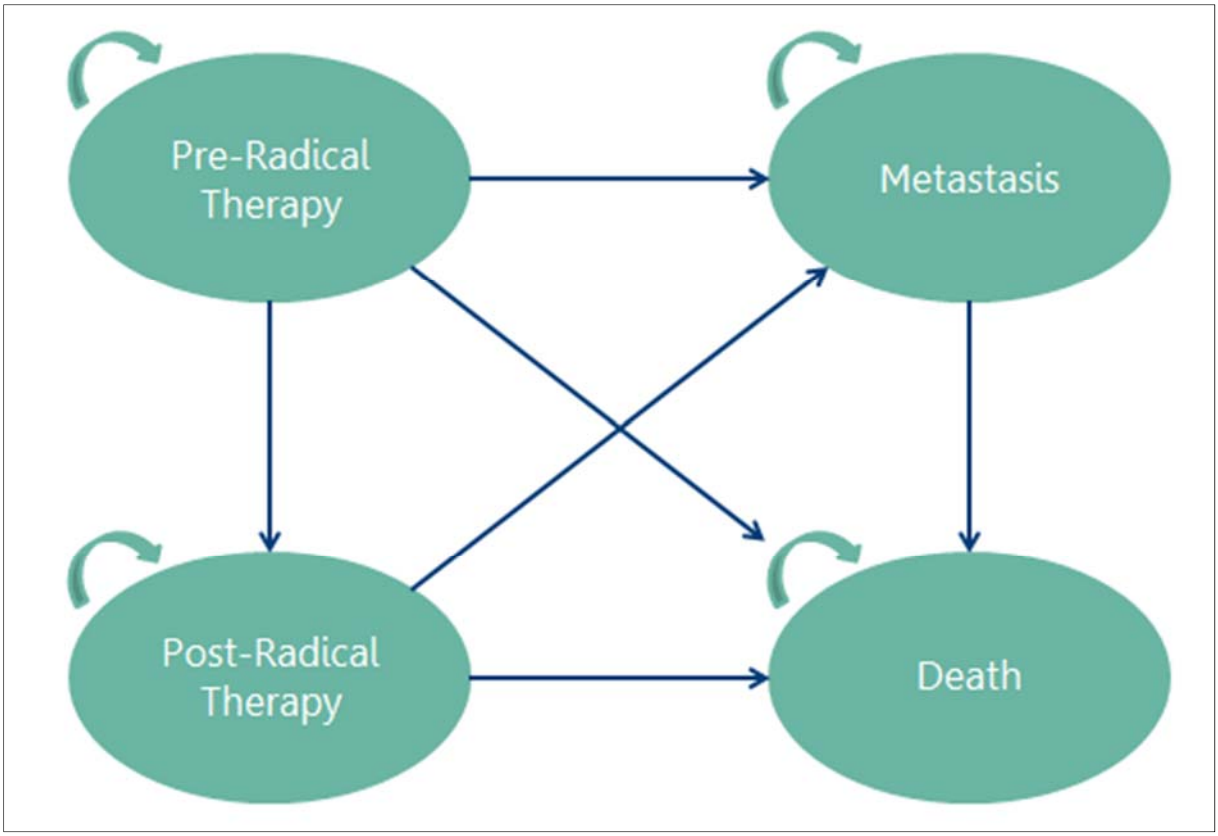
The cost-effectiveness model, developed in Microsoft Excel®, is a partitioned survival analysis. Both the deterministic and probabilistic (Monte Carlo simulation) analyses are based upon this same basic structure. The partitioned survival approach estimates the proportions of patients in each health state based on parametric survival curves fitted to clinical trial data over time. To capture the key difference between padeliporfin VTP and active surveillance, time to radical therapy, the cost-effectiveness model includes the following four mutually exclusive health states (see **Figure 15**):

- Pre-radical therapy: Patients in this health state have elected to undergo either active surveillance or primary active treatment with padeliporfin VTP. For patients under active surveillance, they incur monitoring and testing costs that are part of the active surveillance protocol. Additional costs are due to managing adverse events. For patients who receive padeliporfin VTP, they incur similar costs with the addition of treatment-related acquisition and administration costs. It is assumed that patients in both treatment arms have the same health-related quality of life (HRQoL) when not experiencing any adverse events. Therefore, any differences are due to adverse events, in particular, genitourinary- and bowel-associated toxicities, and their associated impact on HRQoL, which is captured with disutility values.
- Post-radical therapy: Patients who immediately elect for primary active treatment with radical therapy begin in this health state. For patients who initially elected to undergo active surveillance or padeliporfin VTP, they move into this health state when they initiate radical therapy. Patients in this health state incur the cost of radical therapy, adjuvant therapy, salvage therapy, follow-up surveillance and managing adverse events. It is assumed that all patients entering this health state, either entering the model in this health state or moving into this health state, have the same baseline HRQoL as

those beginning in the pre-radical therapy health state. Again, any differences in HRQoL are due to adverse events.

- Metastatic disease: When patients transition into this health state, they all incur a lump-sum cost associated with the treatment of metastatic disease in the first cycle. For each cycle spent in this health state, patients receive the utility value associated with metastatic disease.
- Death: This is an absorbing health state.

Figure 15 Model structure



As stated in **Proportion of subjects with a severe prostate cancer-related event** (p **47**), metastasis only occurred in one patient at Month 36 in each arm in the PCM301 trial. Additionally, there were no prostate-cancer related deaths in either arm. Since there is no evidence to suggest a difference in metastasis or death between padeliporfin VTP versus active surveillance, we assumed that padeliporfin VTP and active surveillance had the same efficacy benefit on these two endpoints. Instead, the most important endpoints collected in PCM301 for the cost-effectiveness

analysis were rate of additional prostate cancer radical therapy, along with rates of urinary incontinence, erectile dysfunction, and bowel-associated toxicities.

As it is well-documented that genitourinary- and bowel-associated toxicities have the most impact on HRQoL following radical treatment, the impact on HRQoL between padeliporfin VTP and active surveillance was based on the differences in the rate of radical therapy between these two treatment arms. Typically, economic evaluations in oncology focus on progression events in metastatic disease, which usually has a significant impact on HRQoL, but this has limited importance in low-risk prostate cancer, as the incidence of metastatic disease is very low and almost the same whether patients initially elect to active surveillance or active treatment. Hence, while metastatic progression is included in the economic analysis, it is not expected to be a major driver of cost effectiveness. In the PCM301 trial, progression from low- to intermediate- or higher-risk localised prostate cancer was a primary objective of the study, but there is evidence to suggest that progression from low- to intermediate-risk does not have a meaningful impact on HRQoL at this early stage in the disease pathway (**Table 46**). Thus, rather than defining a health state on progression from low- to intermediate-risk localised prostate cancer, the cost-effectiveness model included pre- vs post-radical therapy as model health states, which acts as a better inflection point in regards to costs (due to cost of radical treatment and managing the associated toxicities) and QALYs (due to genitourinary- and bowel-associated toxicities associated with radical treatment).

To model these health states, the cost-effectiveness model employs a six month cycle. A scenario analysis with a three month cycle has been explored to estimate the results of having implemented a half-cycle correction (**Scenario analysis** [p **156**]).

Table 36 summarises the primary features of the cost-effectiveness model in the current appraisal as there have been no previous NICE technology appraisals in low-risk, localised prostate cancer in adult males.

Table 36 Features of the economic analysis in the current appraisal

Factor	Chosen values	Justification
Time horizon	Lifetime (40 years)	Long enough to reflect all important differences in costs or outcomes between the technologies being compared per NICE reference case[54]
Treatment waning effect?	No	The treatment effect of padeliporfin VTP is predicated on the chosen distributions used to fit parametric survival curves to the KM data from the PCM 301 trial[14] and digitized KM data from the ProtecT trial[16] (**Figure 21**). In addition, as patients are no longer eligible for radical treatment when life expectancy is <10 years, the treatment effect between padeliporfin VTP and AS reaches a steady state when the average patient in the model reaches 75 years of age, when life expectancy is assumed to be 10 years, which aligns with what was used in the EMA analysis to define the indication population.
Source of utilities	Ramsay et al 2015[37]	The Ramsay et al 2015 analysis includes a systematic review and economic evaluation of ablative therapy for people with localised prostate cancer. It was funded by the HTA programme, part of the National Institute for Health Research (NIHR), as project number 10/136/01. In addition, one of its stated objectives was to determine which therapies are most likely to be cost-effective for implementation in the UK NHS.[37] As this analysis closely aligns with the current appraisal's decision problem, with the exception of having not included padeliporfin VTP in the analysis, the utility and disutility values from this analysis have been incorporated into the current cost-effectiveness model under the assumption that this analysis presents robust and validated data.
Source of costs	Padeliporfin VTP acquisition: Steba Biotech Padeliporfin VTP administration: Steba Biotech, NHS/PPS Other costs: NHS/PPS based on Ramsay et al 2015[37]	The cost of the intervention has been taken from the manufacturer, who is responsible for pricing the product in the UK. Administration costs are from the perspective of NHS/PPS, per the NICE reference case.[54] For all other costs, the cost-effectiveness model incorporates the costs, adjusted for inflation, from the Ramsay et al 2015 analysis[37] under the same rationale provided for utility data.
NICE, National Institute for Health and Care Excellence; VTP, vascular targeted photodynamic therapy; KM, Kaplan-Meier; AS, active surveillance; UK, United Kingdom; HTA, Health Technology Assessment; NIHR, National Institute for Health Research; NHS, National Health Service; PSS, personal social services.		

Table 37 Comparison against the reference case

Element of health technology assessment	Chosen values	Justification
Defining the decision problem	Scope developed by NICE	NICE reference case[54]
Comparator(s)	As listed in the scope developed by NICE	
Perspective on outcomes	All direct health effects	
Perspective on costs	NHS/PSS	
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	
Time horizon	Lifetime (40 years)	
Synthesis of evidence on health effects	Health effects were based on utility values from Ramsay et al 2015.[37]	Systematic review was conducted to identify relevant utility values (**Health-related quality-of-life studies** [p **115**]). Upon review of the utility values identified via systematic review, it was decided that utility values should be taken from Ramsay et al 2015 when selecting utility values for the base case to remain aligned with the Ramsay et al 2015 analysis and because utility values identified in the systematic review were not sufficiently compelling to choose over the utility values in the Ramsay et al 2015 analysis.
Measuring and valuing health effects	QALYs	NICE reference case
Source of data for measurement of health-related quality of life	QALYs were calculated from utility values, to reflect patients' preferences for HRQoL, based on Ramsay et al 2015.[37]	Per Ramsay et al 2015: "Sources of utility data for patient states and events in the model related to diagnosing and treating prostate cancer were identified from systematic searches of several databases, including MEDLINE,EMBASE, NHS Economic Evaluation Database (NHS EED), Health Economic Evaluations Database (HEED)and the Cost-effectiveness Analysis (CEA) Registry." [37] "A total of 306 references were identified. Of these, 56 were

		selected for potential inclusion in terms of reporting utility values by any method. An iterative method of study selection was planned to identify the best evidence regarding utility values… utility values used in the model were calibrated in the model to the EQ-5D by using the value measured using the EQ-5D at initial diagnosis of prostate cancer." [37]
Source of preference data for valuation of changes in health-related quality of life	QALYs were calculated from utility values, to reflect patients' preferences for HRQoL, based on Ramsay et al 2015.[37]	Ramsay et al 2015 assessed the "relative clinical effectiveness and cost-effectiveness" of treatment options in localised prostate cancer "from the perspective of the UK NHS"[37]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	NICE reference case
Evidence on resource use and costs	Costs relate to NHS and PSS resources and are valued using the prices relevant to the NHS and PSS	NICE reference case
Discounting	3.5%	NICE reference case
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; HRQoL, health-related quality of life; NHS EED, NHS Economic Evaluation Database; HEED, Health Economic Evaluations Database; CEA, Cost-effectiveness Analysis; EQ-5D, standardised instrument developed by the EuroQol Group for use as a measure of health outcome.		

Intervention technology and comparators

Padeliporfin VTP is implemented in the cost-effectiveness model per its marketing authorisation. As stated in the decision problem (**Section B.1.1 Decision problem** [p **10**]), the comparators include active surveillance, and among people who choose radical treatment, radical surgery, EBRT and brachytherapy. Active surveillance is a management strategy rather than an active treatment for low-risk, localised prostate cancer. Hence, marketing authorisation is not available. Similarly, radical surgery, EBRT and brachytherapy are broadly defined procedures. For instance, the decision

problem does not indicate specific devices, such as the da Vinci® Surgical System for robotic-assisted radical prostatectomy (RP). Moreover, although there may be several options for radical prostatectomy (e.g. open, laparoscopic, robotic, nerve-sparing), the economic model assesses radical prostatectomy as a blend of practices rather than a single method, as a specific type of radical prostatectomy was not defined in the decision problem. The same approach is taken in consideration of the various approaches to EBRT (e.g. 3D conformal radiation therapy [3-D CRT], intensity-modulated radiation therapy [IMRT], image-guided radiation therapy [IGRT], stereotactic radiation therapy, intraoperative radiation therapy) and brachytherapy. This approach should provide a better assessment of real-life effectiveness of radical surgery, EBRT and brachytherapy in the NHS.

There is insufficient information on retreatment of the ipsilateral lobe or sequential treatment of the contralateral lobe to determine the efficacy and safety of a second padeliporfin VTP procedure. Thus, retreatment is not recommended. As patients are meant to undergo padeliporfin VTP only once, no treatment continuation has been assumed.

B.3.3 Clinical parameters and variables

The partitioned survival model includes four mutually exclusive health states: pre-radical therapy, post-radical therapy, metastasis and death. To determine the time spent in each health state and the accrued costs and QALYs, the proportion of patients in each health state over time is derived from the survival curves of time to radical therapy (TTRT), time to metastasis (TTM) and time to prostate cancer-related death (OS) using the area-under-the-curve (AUC) approach.

TTRT in padeliporfin VTP and AS arms were based on patient-level data from the PCM301 study. TTM and OS were reconstructed by digitally extracting the Kaplan-Meier curves from the ProtecT trial[16] (**Figure 21**) following the algorithm from Guyot 2012[55].

When fitting survival models for TTRT, TTM and OS to the patient-level data, the recommendations of NICE DSU technical support document 14[56] were considered (described below):

- First, the assumption of proportional hazards (PH) was assessed by producing log-cumulative hazard plots to determine whether it was appropriate to apply proportional hazard modelling approach with treatment group included as a covariate, or to fit parametric curves individually to each treatment group
- Second, multiple parametric models were fitted, including exponential, Weibull, log-logistic, log-normal, generalized gamma and Gompertz
- Third, the most plausible model was selected based on internal validity, assessed by Akaike information Criteria (AIC) and Bayesian Information Criteria (BIC) fit statistics and visual inspection, and external validity, assessed by clinical plausibility of the long-term extrapolation

Using the AUC approach, selected parametric curves for TTRT, TTM and OS were used to estimate the proportion of patients in each health state (pre-radical therapy, post-radical therapy, metastasis and death) over time. The proportion of patients in the post-radical therapy and metastasis health state were calculated as the difference between TTM and TTRT and the difference between OS and TTM, respectively.

All the survival analyses were performed using SAS except for fitting the Gompertz distribution, which was performed in R, as the Gompertz distribution is not supported by SAS.

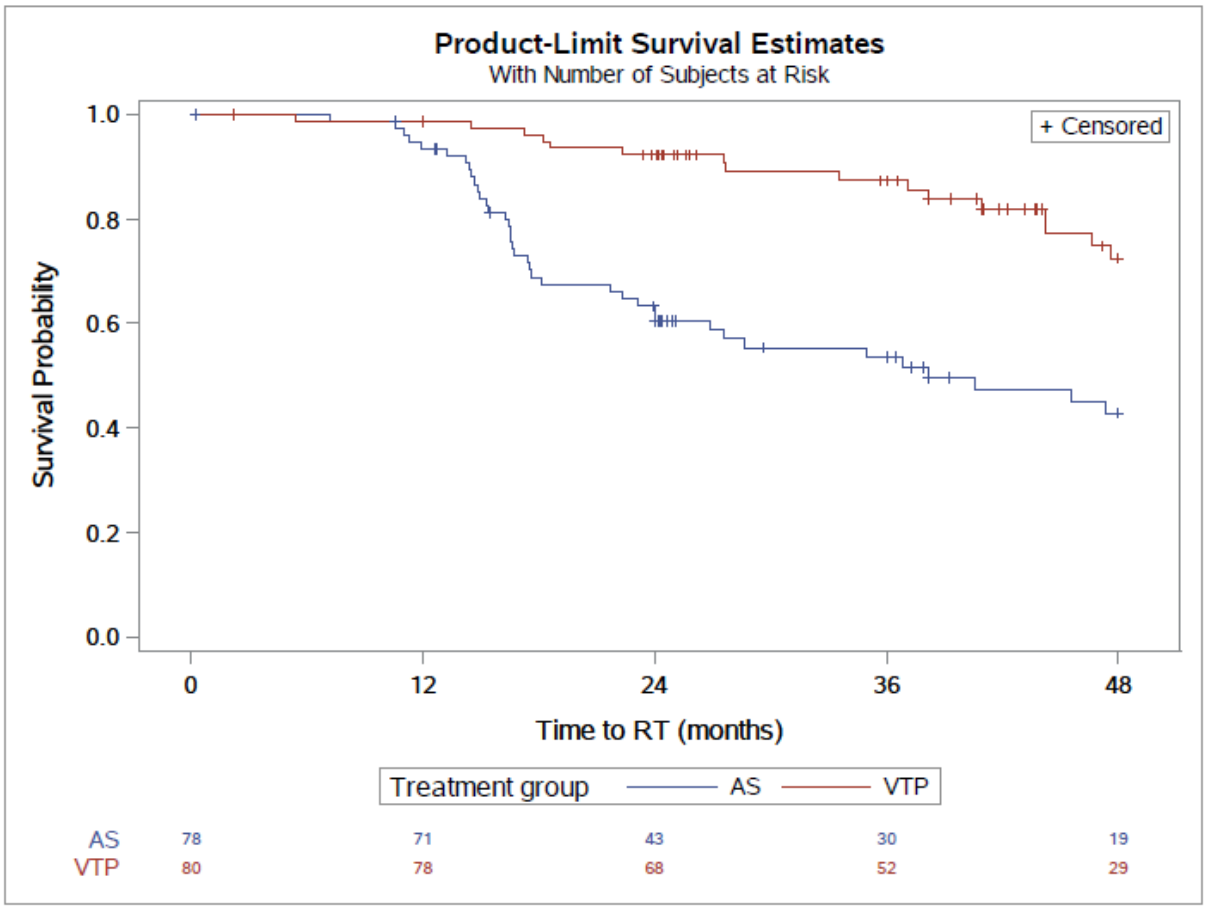
Time to radical therapy

To determine the proportion of patients initiating radical therapies over time, TTRT parametric curves were fitted to the PCM301 study follow-up data to Month 48 for the padeliporfin VTP and AS arms. Because patients in the radical therapy groups (i.e. RP, EBRT and brachytherapy) were assumed to receive radical therapy at baseline thereby entering the post-radical therapy health state directly upon entry into the model, TTRT is irrelevant for these treatment arms.

Figure 16 shows the Kaplan-Meier curve of TTRT for padeliporfin VTP and AS. The proportional hazards (PH) assumption assessment was performed through visual inspection of the log-cumulative hazard plots. Because the plots are not parallel

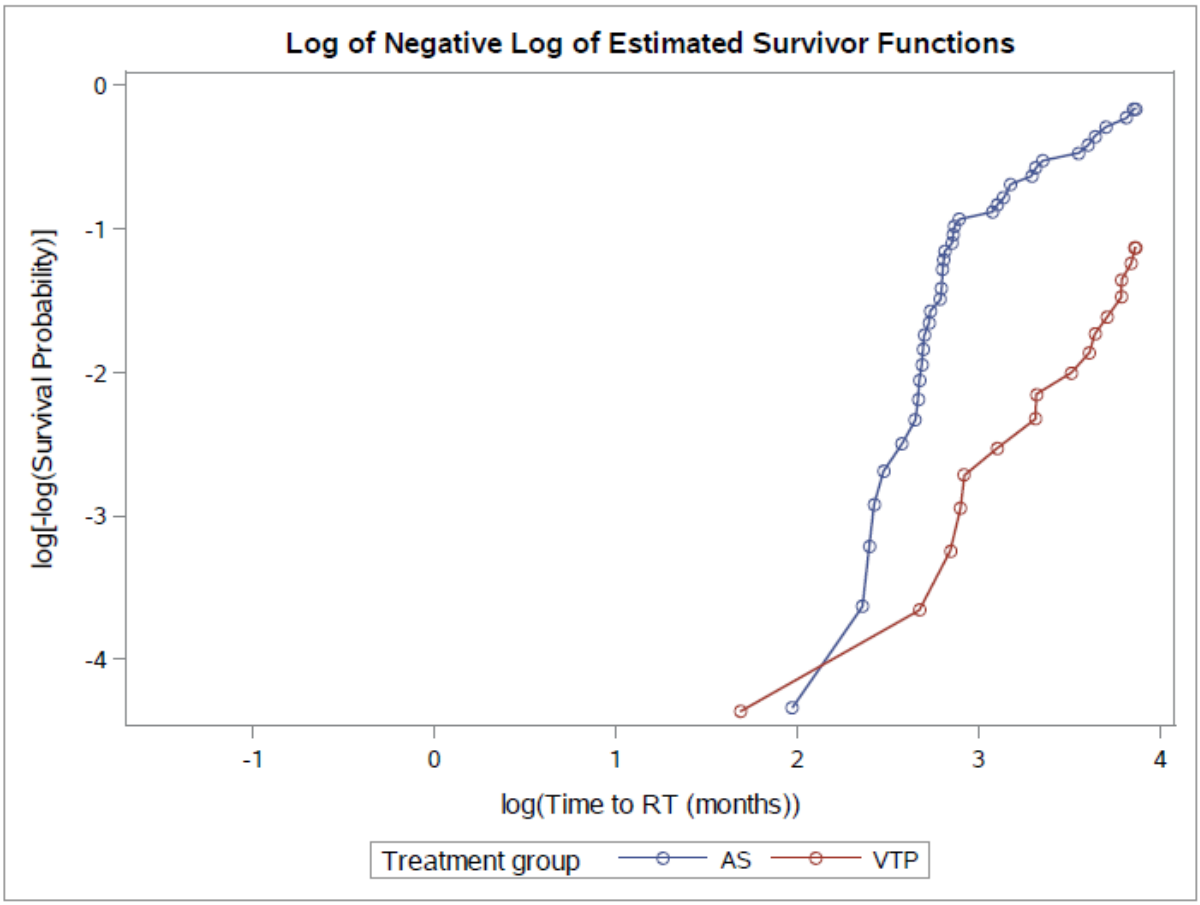
(**Figure 17**), indicating a potential violation of the PH assumption, parametric curves were fitted to each treatment arm, independently. Six parametric distributions were individually fitted to the padeliporfin VTP and AS arms, including the exponential, Weibull, log-logistic, lognormal, generalized gamma and Gompertz distributions.

Figure 16 Kaplan-Meier curve of time to radical therapy



Source: Patient-level data of PCM301 study

Figure 17 Log-cumulative hazard plot of time to radical therapy



Source: Patient-level data of PCM301 study

Goodness-of-fit was assessed with AIC and BIC statistics and visual comparison of the Kaplan-Meier curves against the parametric curves. In the padeliporfin VTP arm, there were minor differences in the fit statistics across distributions with the exception of the exponential distribution, which had the largest values (**Table 40**). The sum of the fit statistics across treatment arms indicate that the generalized gamma has the lowest AIC and BIC statistics. Visual comparisons of the Kaplan-Meier curves against the parametric curves also indicate that the generalized gamma is a good fit (**Figure 18** and **Figure 19**). However, the validity of the parameter estimates is questionable due to the large standard error that is approximately a hundred times greater than the mean. Moreover, the generalized gamma and Gompertz distributions are excluded because the extrapolated TTRT curves for padeliporfin VTP and AS cross at around Year 7 in both instances (**Figure 20**), which is not consistent with the data in the PCM301 trial, which indicates that this is clinically unlikely due to the significant benefit (HR=0.293; 95% CI: 0.163,

0.527) seen in the padeliporfin VTP arm compared to AS, which is maintained up to Month 48 (**Table 17**).

Therefore, the second best-fitting distribution, the lognormal distribution, was selected for the base case analysis. The log-logistic, Weibull and exponential distributions were included in scenario analyses (**Scenario analysis** [p **156**]).

Results of the systematic literature review for padeliporfin VTP efficacy and safety data (**Section B.2.2 List of relevant clinical effectiveness evidence** [p **26**]) did not yield any data on time to radical therapy that likely provides a reasonable comparison to assess 5- or 10-year rates of initiating radical therapy. Various studies had different rates to radical therapy compared to the AS group in the PCM301 trial. However, these differences are likely due to less frequent monitoring for progression (**Table 38**) and more restrictive criteria to inform initiation of active treatment (**Table 39**) compared to the PCM301 trial, which likely delayed initiation of active treatment. Other reasons that may explain the difference in rates to radical therapy include the inclusion of patients with very low risk disease[57], exclusion of patients that progressed early[58] and low compliance on biopsy[58].

Table 38 Monitoring schedules in studies with an active surveillance group

Study	PSA	DRE	Confirmatory biopsy	Repeat biopsy
PCM301	Every 3 months	Every 3 months	Month 12	Month 24
Godtman et al 2016	Every 3 – 6 months	NA	If core < 2mm	Every 2 – 3 years
Hamdy et al 2016	Every 3 – 12 months	NA	NA	NA
Hefermehl et al 2016	Every 6 months	Every 6 months	Month 3 – 6	Every 2 years
Preston et al 2015	Every 4 – 6 months for first two year and every year after	Every 4 – 6 months for first two year and every year after	Month 12 – 18	NA
Klotz et al 2014	Every 3 months for first two years and every 6 months after	NA	Month 0 – 12	Every 3 – 4 years
Bokhorst et al 2016	Every 3 months for first two	Every 6 months for first 2 years	NA	Year 1, 4, 7 and 10, and every 5

	years and every 6 months after	and then every year after		years after

PSA, prostate-specific antigen; DRE, digital rectal exam; NA, not applicable
Sources: PCM301 trial, Godtman 2016[15], Hamdy 2016[16], Hefermehl 2016[59], Preston 2015[58], Klotz 2014[17], Bokourst 2016[57]

Table 39 Criteria to inform initiation of active treatment

Study	Gleason score	PSA	Clinical stage	# of positive core	Core involvement
PCM301	≥7	10ng/mL for 3 consecutive measures	Progression	>3	At least one >5mm
Godtman et al 2016*	≥7	Progression	Progression	NA	Progression
Hamdy et al 2016	NA	Increase >50%	NA	NA	NA
Hefermehl et al 2016	≥7	NA	NA	NA	Bilateral, or at least three unilateral >5mm
Preston et al 2015	≥7	Increase	NA	NA	≥33%
Klotz et al 2014	≥7	Adverse kinetics; DT of <3 years†	Unequivocal palpable nodule	NA	NA
Bokhorst et al 2016	≥7	NA	Progression	NA	NA

PSA, prostate-specific antigen; NA, not applicable; DT, doubling time
* There was lack of predefined protocol detailing the criteria for triggers for intervention.
† For the first 4 years of the study, a PSA doubling time of 2 years was used as a trigger. However, this proved to be overly stringent, insofar as it identified only 10% of patients as high risk. In 1999, the trigger was increased to 3 years. Approximately 20% of patients in the cohort were offered intervention for a PSA DT less than 3 years.
Sources: PCM301 trial, Godtman 2016[15], Hamdy 2016[16], Hefermehl 2016[59], Preston 2015[58], Klotz 2014[17], Bokourst 2016[57]

Table 40 AIC and BIC statistics for time to radical therapy

Treatment	Distribution	AIC	BIC
VTP	Gompertz	194.76	199.52
	Weibull	194.94	199.70
	Log-logistic	195.27	200.03
	Lognormal	196.35	201.11

	Gamma	196.64	203.78
	Exponential	201.28	203.66
AS	Gamma	363.91	370.98
	Lognormal	372.06	376.77
	Log-logistic	375.94	380.65
	Weibull	380.96	385.68
	Gompertz	387.39	392.10
	Exponential	387.56	389.92
(Sum)	Gamma	560.55	574.76
	Lognormal	568.41	577.89
	Log-logistic	571.20	580.68
	Weibull	575.90	585.38
	Gompertz	582.14	591.62
	Exponential	588.84	593.58

VTP, vascular targeted photodynamic therapy; AS, active surveillance; AIC, Akaike information criterion; BIC, Bayesian information criterion

Source: Patient-level data of PCM301 study

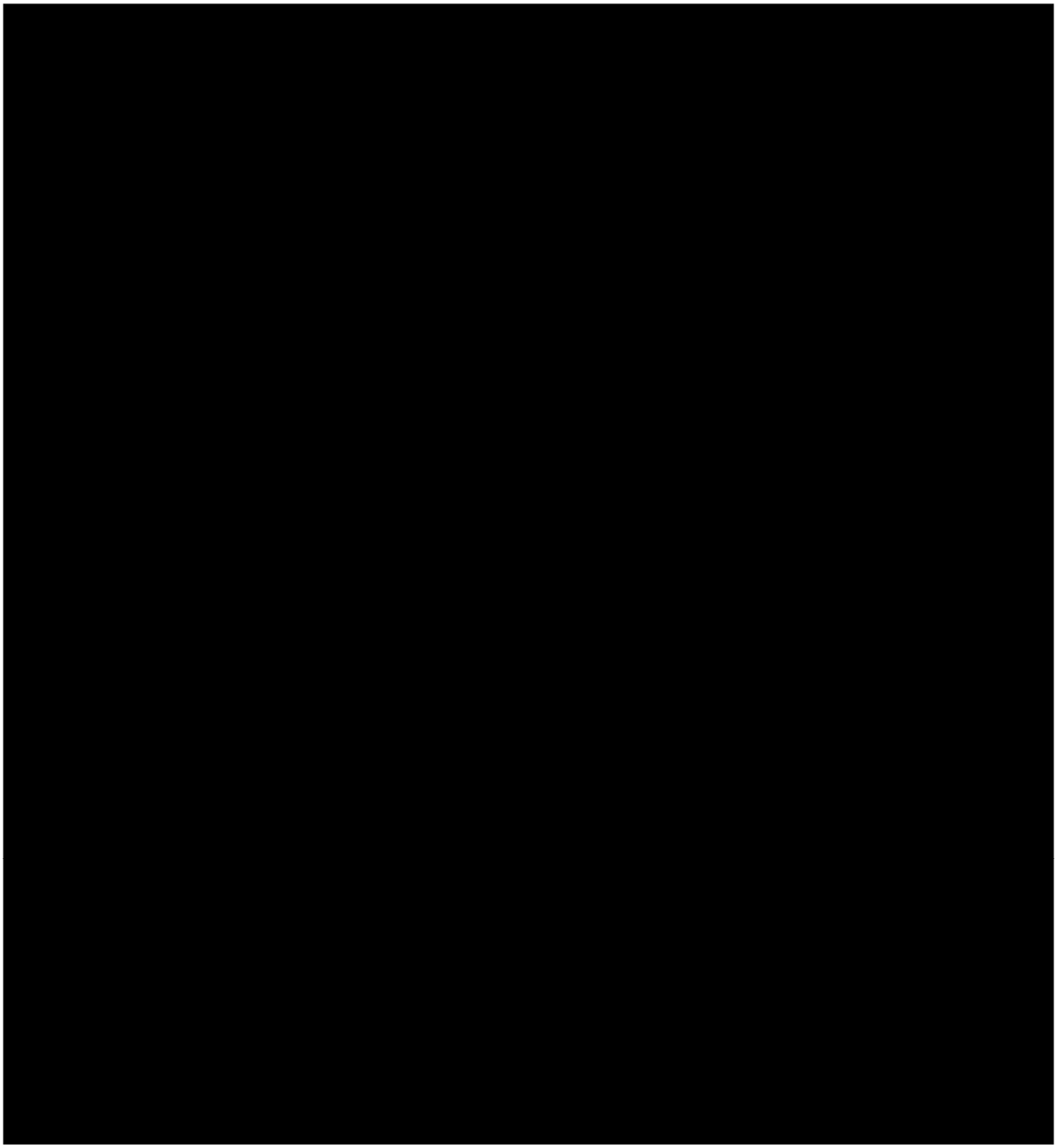
Figure 18 Visual inspection of goodness-of-fit for time to radical therapy for padeliporfin VTP

VTP, vascular targeted photodynamic therapy
Source: Patient-level data of PCM301 study

Figure 19 Visual inspection of goodness-of-fit for time to radical therapy for active surveillance

Source: Patient-level data of PCM301 study

Figure 20 Extrapolation of time to radical therapy for padeliporfin VTP and active surveillance



VTP, vascular targeted photodynamic therapy; AS, active surveillance
Source: Patient-level data of PCM301 study

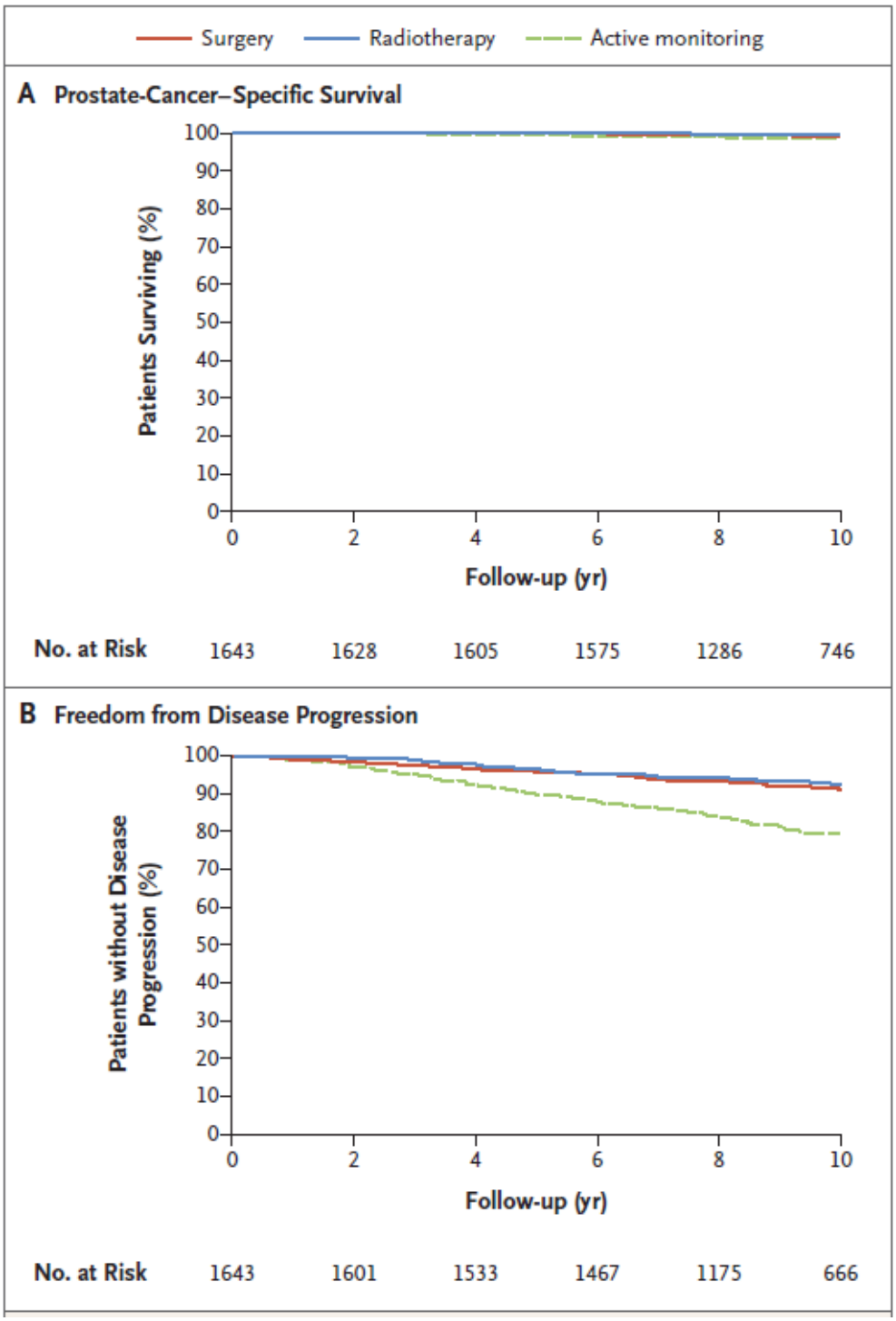
In the cost-effectiveness analysis, it is assumed that TTRT reaches steady state (i.e. no one receives radical therapy anymore) once the average patient in the cost-effectiveness model is 75 years of age, which is at about Year 11.9 based on an average baseline patient age of 63.1 years of age[43]. This assumption is based on the premise that patients are typically not eligible for radical therapy when their life

expectancy is less than 10 years,[6;60] and at 75 years of age life expectancy is assumed to be 10 years, which aligns with what was used in the EMA analysis to define the indication population.

Time to metastasis

Because of the relatively short follow-up time in the PCM301 trial (i.e. 48 months thus far in the PCM301 5-year follow-up study) and the disease nature of localised prostate cancer, metastasis only occurred in one patient by Month 36 in the padeliporfin VTP arm and in one patient by Month 48 in the AS arm (**Proportion of subjects with a severe prostate cancer-related event** [p **47**]). To estimate time to metastasis for the cost-effectiveness model, Kaplan-Meier curves of disease progression from the ProtecT study[16] were digitally extracted using DigitizeIt software (**Figure 21**). Patient-level data from the ProtecT study were regenerated based on the digitized Kaplan-Meier curves following methods from Guyot et al[55] and were subsequently used to fit the parametric curves for extrapolation purposes.

Figure 21 Kaplan-Meier curves of freedom from disease progression and prostate cancer-specific survival from the ProtecT trial



Note: Panel A shows the rate of deaths due to prostate cancer, defined as deaths that were definitely or probably due to prostate cancer or its treatment, as determined by the independent cause-of-death evaluation committee. Panel B shows the rate of clinical progression, defined as death due to prostate cancer or its treatment; evidence of metastatic disease; long-term androgen-deprivation therapy; clinical T3 or T4 disease; and ureteric obstruction, rectal fistula, or the need for a permanent catheter when these are not considered to be a complication of treatment.
Source: ProtecT study (Hamdy et al 2016)[16]

Although the ProtecT trial wasn't restricted to low-risk, localised prostate cancer, this population made up a majority of the ProtecT trial patient population, in which patients had median PSA level at the prostate-check clinic of 4.6 ng/ml, 77% had a Gleason score of 6, and 76% had stage T1c disease (**Table 41**).[16] In addition, the ProtecT trial represented the first time that active monitoring, surgery and radiotherapy have been directly compared in a large randomized trial with a long follow-up period (median of 10 years) and is particular relevant as all patients were recruited from the United Kingdom. [16]

For the cost-effectiveness model, TTM was based on disease progression (**Figure 21**), defined as death due to prostate cancer or its treatment; evidence of metastatic disease; long-term androgen-deprivation therapy; clinical T3 or T4 disease; and ureteric obstruction, rectal fistula, or the need for a permanent catheter when those are not considered to be a complication of treatment in the ProtecT trial. [16] Although this definition includes disease classification beyond just metastasis, there is no evidence from the PCM301 trial to suggest that metastasis between padeliporfin VTP and AS are different (**Proportion of subjects with a severe prostate cancer-related event** [p **47**]) so padeliporfin VTP and AS were assumed to have similar TTM to mitigate any potential bias against AS when compared to padeliporfin VTP.

Table 41 Baseline demographic and clinical characteristics by allocated treatment group in the ProtecT trial

	Active monitoring (n=545)	**Surgery (n=553)**	**Radiotherapy (n=545)**
Mean age, years (SD)	62 (5)	62 (5)	62 (5)
Median PSA, ng/ml (IQR)	4.7 (3.7, 6.7)	4.9 (3.7, 6.7)	4.8 (3.7, 6.7)
PSA 10+ ng/ml (%)	57 (10)	57 (10)	58 (11)
Gleason score			
6	421 (77)	422 (76)	423 (78)
7	111 (20)	120 (22)	108 (20)
8-10	13 (2)	10 (2)	14 (3)
Missing	0	1	0
Clinical stage			
T1c	410 (75)	410 (74)	429 (79)
T2	135 (25)	143 (26)	116 (21)
For the large majority of men with PSA measures from the prostate check clinic to biopsy,			

the mean of these two has been taken
SD, standard deviation; IQR, inter-quartile range; PSA, prostate-specific antigen

Because the Kaplan-Meier curves of the surgery and radiotherapy groups overlap in the ProtecT trial (**Figure 21**), only data in the radiotherapy arm was regenerated and it was assumed this reflected TTM for radical prostatectomy, EBRT and brachytherapy in the cost-effectiveness analysis.

As discussed above, there is no evidence to suggest a difference in TTM between padeliporfin VTP and AS arms in the PCM301 trial. As a result, the regenerated data of the active monitoring arm in the ProtecT trial was applied to both padeliporfin VTP and AS in the cost-effectiveness model.

As with TTRT, six parametric distributions were fitted individually to the regenerated patient-level data of disease progression for each treatment arm, including the exponential, Weibull, log-logistic, lognormal, generalized gamma and Gompertz distributions. Goodness-of-fit was assessed through AIC and BIC statistics (**Table 42**) and visual inspection (**Figure 22** and **Figure 23**).

The lognormal distribution provides the lowest AIC and BIC for each treatment arm and is thereby the statistically best-fitting distribution (**Table 42**). The second and third best fitting distributions are the log-logistic and Weibull distributions, respectively.

Table 42 AIC and BIC statistics for time to metastasis

Treatment	Distribution	AIC	BIC
AS, VTP	Lognormal	986.48	995.08
	Log-logistic	990.52	999.12
	Weibull	991.63	1000.23
	Gamma*	-	-
	Gompertz	996.64	1005.24
	Exponential	997.87	1002.17
Prostatectomy, EBRT, brachytherapy	Lognormal	418.13	426.73
	Log-logistic	420.64	429.25
	Weibull	420.91	429.51
	Gamma*	-	-
	Exponential	423.53	427.83

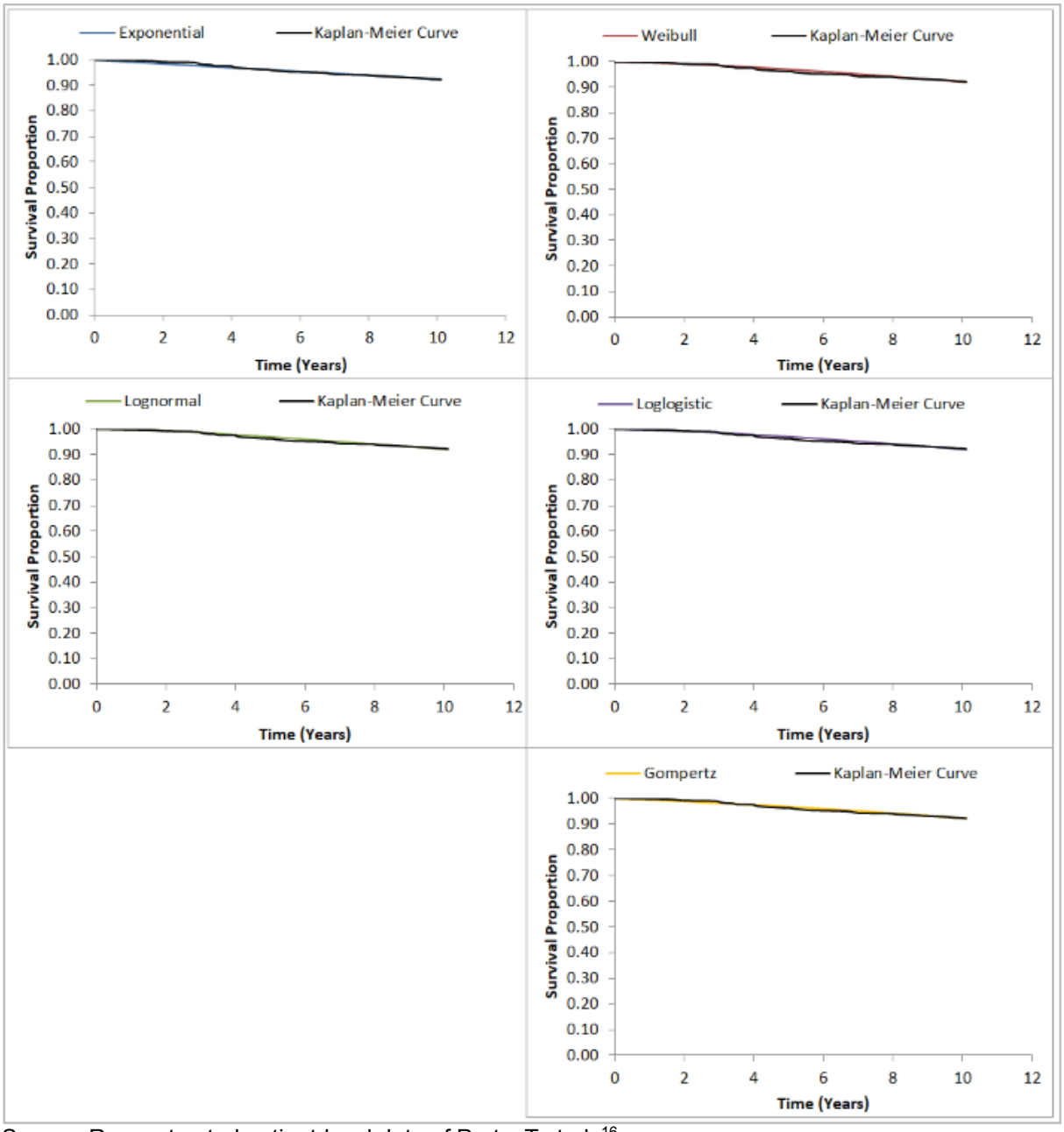
	Gompertz	424.11	432.71
(Sum)	Lognormal	1404.61	1421.81
	Log-logistic	1411.16	1428.36
	Weibull	1412.54	1429.74
	Gamma*	-	-
	Gompertz	1420.75	1437.95
	Exponential	1421.40	1430.00

AS, active surveillance; VTP, vascular targeted photodynamic therapy; EBRT, external beam radiation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion

* Questionable convergence

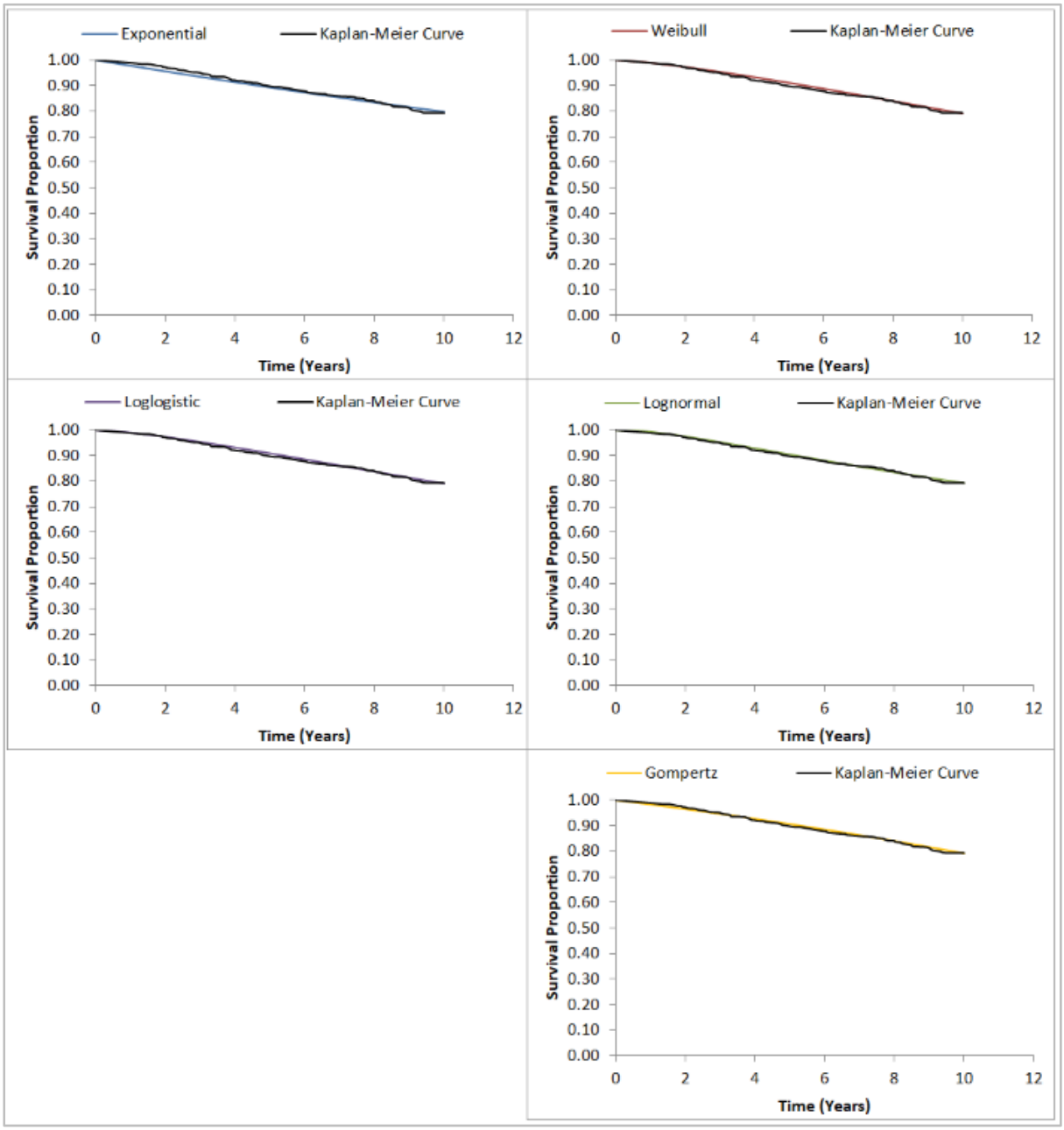
Source: Reconstructed patient-level data of ProtecT study[16]

Figure 22 Visual inspection of goodness-of-fit for time to metastasis for radical therapies



Source: Reconstructed patient-level data of ProtecT study[16]

Figure 23 Visual inspection of goodness-of-fit for time to metastasis (padeliporfin VTP and active surveillance)



VTP, vascular targeted photodynamic therapy
Source: Reconstructed patient-level data of ProtecT study[16]

Time to death

Similar to time to metastasis, no prostate cancer-related deaths were observed by Month 48 in PCM301 due to its relatively short follow-up time and the disease nature of localised prostate cancer. To obtain the time-dependent probabilities of death among localised prostate cancer, Kaplan-Meier curves of prostate cancer-related

death from the ProtecT study[16] were digitally extracted to regenerate the corresponding patient-level data (**Figure 21**).

As discussed above, there is no evidence to suggest a difference in prostate cancer-related death between padeliporfin VTP and AS arms based on the PCM301 trial. Also in the ProtecT study, the KM curves of surgery, radiotherapy and active monitoring overlapped (**Figure 21**), and no statistically significant difference was shown in prostate cancer-related mortality rate (p=0.48) across all three groups, indicating little difference in survival across surgery, radiotherapy and active monitoring. Therefore, only data in the radiotherapy arm, as it was the most visually clear given the overlapping colours, was regenerated and it was assumed this reflected all the treatment arms (radical therapies, padeliporfin VTP and AS) in the cost-effectiveness analysis

Six parametric distributions were fitted to the regenerated patient-level data of prostate cancer-related death, including the exponential, Weibull, log-logistic, lognormal, generalized gamma and Gompertz distributions. Goodness-of-fit was assessed through AIC and BIC statistics (**Table 43**) and visual inspection (**Figure 24**).

The lognormal distribution had the lowest AIC statistics and the exponential distribution had the lowest BIC statistics, which penalized distributions more than the AIC statistics based on the number of parameters (**Table 43**). Because the KM curve of prostate cancer-related death is nearly a horizontal line due to the disease nature of localised prostate cancer (**Figure 21**), the exponential distribution was selected for base case analysis to avoid overfitting. The other distributions contain more parameters than can be justified by the linear nature of the KM curve for prostate cancer-related death and may therefore fail to reliably generate an accurate extrapolation. Based on fit statistics and visual inspection though, the next best fitting distributions are the lognormal and log-logistic distributions.

Table 43 AIC and BIC statistics for time to prostate cancer-related death

Treatment	Distribution	AIC	BIC
Prostatectomy, EBRT,	Lognormal	36.43	45.03
	Log-logistic	36.64	45.25

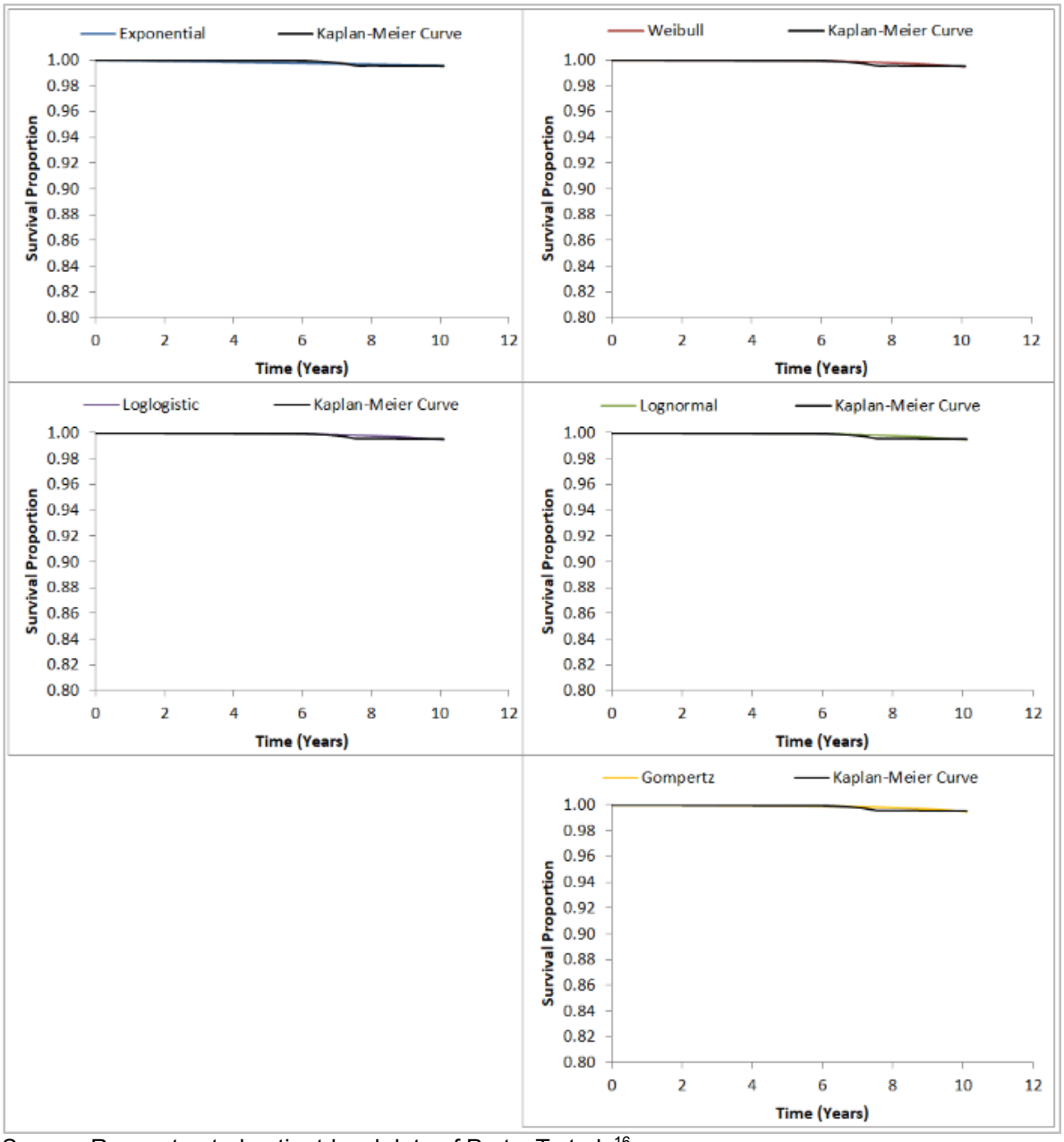
brachytherapy, AS, VTP	Weibull	36.65	45.25
	Gamma*	-	-
	Exponential	37.18	41.48
	Gompertz	37.19	45.80

AS, active surveillance; VTP, vascular targeted photodynamic therapy; EBRT, external beam radiation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion

* Questionable convergence

Source: Reconstructed patient-level data of ProtecT study[16]

Figure 24 Visual inspection of goodness-of-fit for time to prostate cancer-related death



Source: Reconstructed patient-level data of ProtecT study[16]

General mortality

In addition to prostate cancer-related mortality, general mortality was also included to account for deaths due to reasons other than prostate cancer. Depending on the mean age of patients at baseline, age-specific mortality for males from the UK life table[61] were used to estimate probabilities of general death over time as patients aged.

Per cycle probability of general mortality was estimated by converting annual mortality probabilities into per-cycle mortality probabilities for each age to align with the cycle length in the model (six months). The following formulas illustrate the conversion from annual mortality probabilities into per-cycle mortality probabilities.

Annual mortality rate = - LN (1 - Annual mortality probability)

Per-cycle mortality rate = Annual mortality rate / 2

Per-cycle mortality probability = 1 - EXP (-Per cycle mortality rate)

When adjusting the OS curve by general mortality, the OS probabilities at each cycle were calculated as:

Probability of OS state occupancy adjusted by general mortality = P_{os}* (1 - r)

Where,

P_{os} = probability of OS state occupancy at specific cycle, unadjusted by general mortality

r = cumulative general mortality, calculated as $\prod_{\mathrm{i=baseline\ age}}^{\mathrm{age}} \mathrm{age\ specific\ per-cycle\ survival\ probability}$

Transition probabilities

As a pure Markov approach was not implemented in the cost-effectiveness model, an estimation of transition probabilities is not applicable in this case. Instead, the proportion of patients in each health state was determined by the probability of initiating radical therapy, metastasis and death using survival curves following an AUC approach.

Base case

The lognormal distribution was applied in the base-case analysis for TTRT and TTM, while the exponential distribution was applied for prostate cancer-related death. As most patients diagnosed with low-risk, localised prostate cancer are more likely to die due to non-prostate cancer-related reasons, general mortality was incorporated to capture overall survival.

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

For descriptive purposes in PCM301, HRQoL was measured using the EQ-5D questionnaire, which was administered at baseline, Month 12 and Month 24. The EQ-5D is a 6-item questionnaire measuring HRQoL. Five questions relate to the following areas:

- Mobility
- Self-care
- Usual activities
- Pain/discomfort
- Anxiety/depression

The subject had to choose from among 3 responses for each of the questions. A final question asked the subject to mark on a visual analogue scale (VAS) from 0 to 100 to indicate how good or bad his health was on the day. A score for the EQ-5D was calculated in accordance with standard scoring instructions. Scores were calculated for each treatment group regardless of failure and of additional treatment.[41]

As illustrated in **Table 34**, the change in EQ-5D VAS scores from baseline (83.2 and 80.2) to Month 24 (81.5 and 77.2) in the indication population for padeliporfin VTP and AS, respectively, shows a slight decrease though both changes were insignificant.

In the cost-effectiveness analysis, the EQ-5D data was only used to confirm that baseline quality of life was identical across the padeliporfin VTP and active surveillance groups. The remainder of the data was not used to inform the cost-effectiveness model, as:

i. the M12 and M24 data points did not provide sufficiently granular data to assess variations of quality of life in particular shortly after radical therapy,
ii. there is very limited reporting beyond M24, and

iii. EQ-5D is not very sensitive to well-documented adverse events following treatment in localised prostate cancer such as urinary incontinence, erectile dysfunction and bowel dysfunction.

In a study that collected three validated QoL questionnaires (i.e. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer 25 [EORTC QLQ-PR25]; EORTC Quality of Life Questionnaire—Cancer 30 [EORTC QLQ-C30]; and EuroQoL-5D [EQ-5D]) among patients with low- to intermediate- risk prostate cancer, changes in QLQ-PR25 and C30 questionnaires were not strongly correlated with health status (as assessed by EQ-5D scores), which did not significantly change from baseline. The authors hypothesized that the EQ-5D might not be sensitive enough to capture changes in HRQoL following treatment.[62] In the ProtecT trial, while there was well-documented deterioration of HRQoL due to urinary, erectile and bowel dysfunction, general health status as assessed with the Medical Outcomes Study 12-Iterm Short-Form General Health Survey (SF-12) remained unaffected.[63]

Mapping

IIEF and IPSS were also collected in the PCM301 trial. However, a targeted literature review yielded no published mapping algorithms from IIEF or IPSS to EQ-5D. Thus, no mapping techniques were used to estimate HRQoL data in the cost-effectiveness model.

Health-related quality-of-life studies

Description systematic searches for relevant health-related quality-of-life data are provided in appendix H.

As indicated in **Section B.3.2 Economic analysis** (p **83**), the cost-effectiveness analysis relies heavily on the prior work by Ramsay et al. 2015, which calculated utilities, risks of side effects, and other model inputs for focal prostate cancer treatment models based on several large-scale SLRs.[37] In the cost-effectiveness analysis, the frequencies of side effects for brachytherapy, EBRT, and radical

surgery are based on the prior work by Ramsay et al. 2015. As is usually the case in this field, Ramsay et al. synthesized these values from a broad range of studies and instruments.[37] The rates of each side effect were presented as transient (≤ 6 months) or permanent, as described below:

> "For each of the three adverse events [UI, ED and BD] it was assumed that within the first 6 months the rate would differ from any longer-term trend. Prevalence A [transient] was calculated as the median for all sources reporting the prevalence of the adverse event at a follow-up time of ≤ 6 months. It was assumed that after 6 months, the prevalence would settle to a constant rate. All data on each adverse event that were reported for a follow-up time of beyond 6 months were converted to a yearly rate and then the average was taken to calculate prevalence B [permanent]."[37]

These values are matched by counting grade 2 or higher adverse events for UI, ED, and BD in the PCM301 trial based on the fact that Ramsay et al. include UI, ED, BD toxicities that have a meaningful impact on cost or quality of life/utilities over time. The prospective PCM301 trial is the most reliable source for these events, and in the PCM301 study, we consider grade 2 and above AEs as the closest proxy for these toxicities (**Adverse reactions** [p **116**]).

Utility and disutility values are also based on Ramsay et al. without any numerical changes. One practical difference of our model being that we calculate disutility values (i.e., -0.05, -0.04, -0.16), while Ramsay et al. used adjusted utility values for the periods during side effects.[37]

Given the known uncertainties implied in QoL measurements, integrating the PCM301 trial data into the comprehensive prior work by Ramsay et al. described herein is likely the best way forward to obtain a realistic estimate of the cost effectiveness of an updated treatment landscape that includes padeliporfin VTP.

Adverse reactions

As indicated in the ProtecT trial publication,[63] "systematic reviews[64-67] and studies involving large, prospective cohorts[68;69] have shown particular effects on urinary,

bowel, and sexual function and little effect on general quality of life after radical treatments." Thus, as it is well-accepted that urinary, bowel, and sexual dysfunction are adverse events of particular importance in localised prostate cancer, the cost-effectiveness model predicates a patient's HRQoL across treatment arms based on the rate and duration of experiencing urinary incontinence, erectile dysfunction and bowel dysfunction.

Since radical therapies are associated with genitourinary- and bowel-associated toxicities that interfere with HRQoL, minimally invasive and focal treatment such as padeliporfin-VTP has the potential to decrease treatment with radical therapies and thereby improve HRQoL.

In the cost-effectiveness analysis, it is assumed that all patients begin with the same baseline utility value across treatment arms (i.e. VTP, AS, RP, EBRT and BT). In the first six months following treatment, the proportions of patients who experience short-term grade 2 or higher UI, ED or BD incur the disutility value associated with the respective toxicity. For patients who experience these toxicities long-term, the respective disutility values are applied in each subsequent cycle among the proportion of patients that experience long-term toxicities. As a result, any decrease in HRQoL is a result of toxicities experienced while in the relevant health state (i.e. pre-RT for VTP and AS, post-RT for all treatment arms). The probabilities of patients experiencing short- and long-term genitourinary- and bowel-associated toxicities are presented in **Table 44**.

Table 44 Short- vs long-term adverse event probabilities

Treatment	Duration	Urinary incontinence	Erectile dysfunction	Bowel dysfunction
VTP	Short-term	0.013	0.175	0.050
	Long-term	0.000	0.100	0.013
Active surveillance	Short-term	0.013	0.013	0.000
	Long-term	0.000	0.013	0.000
Radical prostatectomy	Short-term	0.248	0.645	0.040
	Long-term	0.278	0.706	0128
EBRT	Short-term	0.092	0.486	0.152
	Long-term	0.111	0.406	0.181
Brachytherapy	Short-term	0.332	0.268	0.055
	Long-term	0.363	0.262	0.116

VTP, vascular targeted photodynamic therapy; EBRT, external beam radiation therapy
Sources: PCM301 trial; Ramsay et al 2015[37]

As described earlier, short- and long-term adverse event probabilities for radical therapies are based on the Ramsay et al 2015 analysis.[37] Short- and long-term adverse event probabilities for padeliporfin VTP and active surveillance in the pre-radical therapy health state are based on the PCM301 study. This includes urinary incontinence, erectile dysfunction or bowel dysfunction grade 2 or above among patients who did not undergo radical therapy by end of follow-up. Grade 1 adverse events were excluded as they do not require intervention based on the Common Terminology Criteria for Adverse Events (CTCAE) definitions (**Table 45**) thereby having no impact on cost. In addition, given the lack of severity as interpreted from the CTCAE definitions for grade 1 adverse events, it is unlikely to have any meaningful impact on HRQoL. In Ramsay et al 2015, the short- and long-term adverse event probabilities used in the analysis do not indicate that severity of adverse events were defined using CTCAE definitions, i.e. there is no explicit mention of what AEs were included by CTCAE grade. However, short- and long-term UI, ED and BD were associated with the costs of managing the AEs and disutility values, which indicates that the Ramsay et al 2015 analysis likely included UI, ED and BD toxicities that would have a meaningful impact on cost or HRQoL over time. Given this interpretation, grade 2 and above adverse events from PCM301, as defined by CTCAE, would be the closest approximation to the AEs included in the Ramsay et al 2015 analysis as grade 1 adverse events are mild and require no intervention.

Table 45 Common Terminology Criteria for Adverse Events (CTCAE) definitions for urinary incontinence, erectile dysfunction and bowel dysfunction

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention	-	-

			indicated; limiting self-care ADL		
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	-	-
Anal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Anal haemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Source: CTCAE v4.3[70]					

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

As stated in **Model structure** (p **87**), the cost-effectiveness model includes pre- and post-radical therapy health states rather than pre- and post-progression health states. From the systematic literature review, two studies were identified that presented utility values for low- and intermediate-risk, localised prostate cancer

(**Table 46**), both suggesting no difference in HRQoL between low- and intermediate-risk disease. On the other hand, it is well-established that radical treatment is associated with deterioration in HRQoL due to genitourinary- and bowel-associated toxicities. Thus, the pre- and post-radical therapy health states were used in the cost-effectiveness model as radical treatment has an important impact on HRQoL.

Table 46 Utility values in low- and intermediate-risk, localised prostate cancer

Author Year	Type of study	Population description	Method	Health State or AE	No. of pts	Value
Avila 2014*	Observational, prospective cohort study	Low or intermediate risk localized prostate cancer (newly diagnosed)	Time trade-off	Low risk group	369	0.97
			Time trade-off	Intermediate risk group	184	0.96
			Standard gamble	Low risk group	396	0.98
			Standard gamble	Intermediate risk group	184	0.98
Naik 2015	Questionnaire study	Prostate cancer (all stages - from 1 to 4)	HUI (from EQ-5D)	Stage 1†	26	0.92
			HUI (from EQ-5D)	Stage 2‡	60	0.92

AE, adverse event; HUI, Health Utilities Index; EQ-5D, standardised instrument developed by the EuroQol Group for use as a measure of health outcome

*The aim of our study was to assess the preferences and willingness to pay of patients with localized prostate cancer who had been treated with radical prostatectomy, external radiation therapy, or brachytherapy, and their related urinary, sexual, and bowel side effects. Of the 580 patients reporting preferences, 165 were treated with radical prostatectomy, 152 with external radiation therapy, and 263 with brachytherapy.

†Stage 1 usually means that a cancer is relatively small and contained within the organ it started in.

‡Stage 2 usually means the cancer has not started to spread into surrounding tissue but the tumour is larger than in stage 1. Sometimes stage 2 means that cancer cells have spread into lymph nodes close to the tumour. This depends on the particular type of cancer.

Sources: Avila 2014[71]; Naik 2015[72]

In the cost-effectiveness model, it is assumed that HRQoL is constant over time unless a patient experiences UI, ED or BD. Once a patient enters metastasis, it is assumed there is a substantial decrease in HRQoL that is constant throughout the time spent in the metastatic disease health state. Similar to the disutility values, the utility values at baseline and metastasis are based on the values in Ramsay et al 2015 (**Table 47**).[37]

Table 47 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission	Justification
Localised PCa				
Localised PCa without AEs	0.88 (0.088)	0.708, 1.052	Adverse reactions (p 116)	Based on PCM301 data (i.e. similar utility in VTP and AS groups) and Ramsay et al 2015[37] analysis (i.e. similar utility in focal therapy, brachytherapy, EBRT and surveillance)
Metastasis				
Metastasis	0.58 (0.058)	0.708, 1.052	Health-related quality-of-life data used in the cost-effectiveness analysis (p 119)	HRQoL once patients have metastatic disease unlikely to differ based on prior treatment
Adverse effects				
Urinary incontinence	-0.05 (0.005)	-0.060, -0.040	Adverse reactions (p 116)	Well-documented that active treatment of prostate gland leads to urinary, erectile and bowel dysfunction in many patients, which leads to deterioration in HRQoL
Erectile dysfunction	-0.04 (0.004)	-0.048, -0.032		
Bowel dysfunction	-0.16 (0.016)	-0.191, -0.129		

SE, standard error; CI, confidence interval; PCa, prostate cancer; AEs, adverse events; VTP, vascular targeted photodynamic therapy; AS, active surveillance; EBRT, external beam radiation therapy; HRQoL, health-related quality of life

Source: Ramsay et al 2015[37]

As described in **Health-related quality-of-life data from clinical trials** (p **114**), several limitations prevented the use of EQ-5D data collected in the PCM301 trial. Instead, disutility values from the Ramsay et al 2015 analysis[37] were applied to a common baseline utility value to capture the different HRQoL experiences by patients following treatment (**Table 47**). Thus, HRQoL was dictated by the incidence and duration of genitourinary- and bowel-associated toxicities and it was assumed that the procedures themselves, except for subsequent UI, ED or BD, did not itself lead to a meaningful deterioration of HRQoL. HRQoL is captured using this approach in both the pre- and post-radical therapy health states to ensure associated costs and QALYs are estimated consistently across treatment arms. In addition, using the

utility values from Ramsay et al 2015 is consistent with the rest of the analysis, in which other inputs such as costs are based on the Ramsay et al 2015 analysis.[37]

As mentioned above, treatment with padeliporfin VTP, radical prostatectomy, EBRT or brachytherapy in and of itself has no inherent effect on a patient's HRQoL unless the patient was to experience UI, ED or BD. In that case, the patient would experience a deterioration of HRQoL until the resolution of the adverse event. Following radical therapy for prostate cancer, UI, ED and BD can be either transient, typically resolving in the short-term, or permanent. To reflect this reality, each treatment, including active surveillance, is associated with unique short-term and long-term probabilities of experiencing each adverse event of interest, i.e. urinary incontinence, erectile dysfunction and bowel dysfunction (**Table 44)**.

In the initial cycle that a patient receives active treatment or active surveillance, the disutility values associated with UI, ED and BD, respectively, are subtracted from the baseline utility values (**Table 47**) to calculate the utility value for the proportion of patients who are experiencing UI, ED and BD, respectively. In subsequent cycles, the proportion of patients expected to experience permanent UI, ED or BD accrue the corresponding disutility for the remainder of the time spent in the health state.

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

Description of relevant cost and healthcare resource data provided in appendix I.

Intervention and comparators' costs and resource use

The acquisition cost of padeliporfin VTP includes the padeliporfin drug, optical fibres, catheters and rectal probe (**Table 48**). The recommended dosage of padeliporfin is 3.66 mg/kg.[1] As a vial of padeliporfin contains 183 mg, each vial is suitable for 50 kg. For patients weighing >50 kg and ≤100 kg, two vials of padeliporfin are required. For patients weighing >100 kg and ≤150 kg, three vials of padeliporfin are required. In addition, each vial is for single use only. In PCM301, of the 158 patients in the indication population, 152 patients weighed >50 kg and ≤100 kg and the remaining

six patients weighted >100 kg and ≤150 kg.[14] Based on this distribution, each VTP procedure requires approximately 2.04 vials of padeliporfin. Based on data from the overall PCM301 trial population, about 12.9 fibres were required per VTP procedure.[41]

Table 48 Acquisition cost of padeliporfin VTP

Material description	Cost/procedure (£)	# units/procedure	Cost/unit (£)
Padeliporfin (183 mg vial)	7,672.95	2.04	3,761.25
Optical fibres	3,282.24	12.9	254.44
Catheters	713.53	12.9	55.31
Rectal probe	331.88	1	331.88
Catheters	110.63	2	55.31
Total	**12,111.23**		
VTP, vascular targeted photodynamic therapy			

Padeliporfin administration costs per VTP procedure include the cost of a laser generator, physical exams, electrocardiograms, operating room session and hospital staff. Steba is offering to lease the laser generator for £619.50 per VTP procedure to alleviate the burden of initial capital expenditures for purchasing a laser generator. The cost of a physical exam is based on the cost of a general practitioner surgery consultation lasting 9.22 minutes.[73] Aside from the cost of leasing the laser generator, all administration costs are based on NHS/PSS list prices (**Table 49**).

Table 49 Unit costs associated with intervention and comparators in the economic model

Items	Cost (SE), £	Reference in submission
Padeliporfin VTP treatment costs		
Acquisition cost	12,111.23 (1,211,1)	Table 48
Administration cost	2,293.53 (229.4)	Intervention and comparators' costs and resource use (p 122)
Laser generator	619.50	
Physical exams	96.09	
Operating room	1,010.05	
Anaesthesiologist	119.94	
Uro-oncologist surgeon	166.50	
Nurse	5.72	
Electrocardiogram	275.74	
Active surveillance and padeliporfin VTP post-treatment monitoring costs		
First year	510.95 (85.8)	Table 50
Second year	425.31 (78.3)	
Third year	195.39 (32.6)	
Fourth year	425.31 (78.3)	
Fifth year	195.39 (32.6)	
Annually thereafter	22.89 (2.9)	
Radical prostatectomy	4,446.71 (444.7)	Intervention and comparators' costs and resource use (p 122)
EBRT	2,898.32 (369.7)	
Brachytherapy	7806.32 (1207.5)	
SD, standard deviation; VTP, vascular targeted photodynamic therapy; EBRT, external beam radiation therapy		

Active surveillance, radical prostatectomy, EBRT and brachytherapy costs are based on the Ramsay et al 2015 analysis,[37] adjusted for inflation to 2017-18 price levels.[74] In Ramsay et al 2015,[37] active surveillance costs were estimated using a micro-costing approach based on the resource inputs (**Table 50**) being identified by clinical experts. In the first five years, costs of active surveillance varied based on the different resource use each year, but incurred the same fixed annual cost annually thereafter as the AS protocol requires the same annual resource use following the fifth year on AS. Of note, padeliporfin VTP has a monitoring schedule similar to active surveillance. As a result, the same post-treatment costs were applied to padeliporfin VTP.

Table 50 Annual active surveillance resource inputs

Year	Resource inputs
1	• 4 nurse-led outpatient appointments • 4 PSA tests • 1 digital rectal exam (DRE) • 1 multidisciplinary team (MDT) meeting
2	• 1 transrectal ultrasound (TRUS)-guided biopsy • 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE
3	• 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE
4	• 1 TRUS-guided biopsy • 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE
5	• 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE
Annually thereafter	• 1 practice nurse appointment • 1 PSA test • 1 DRE
PSA, prostate-specific antigen; DRE, digital rectal exam; MDT, multidisciplinary team; TRUS, transrectal ultrasound guided Source: Ramsay et al 2015[37]	

Cost of radical prostatectomy was based on the assumption that the providing unit would carry out 200 procedures annually. Cost of EBRT was based on the assumption that IMRT procedure was performed and on the basis of 37 sessions within seven weeks. Cost of brachytherapy was based on the assumption that a two-stage procedure with a one night length of stay was performed.[37]

Health-state unit costs and resource use

Patients either enter the cost-effectiveness model in the pre-radical therapy health state (padeliporfin VTP or AS) or post-radical therapy health (RP, EBRT, brachytherapy). Patients in the padeliporfin VTP arm incur the cost of padeliporfin

VTP acquisition and administration cost in the initial cycle. For patients in both the padeliporfin VTP and AS arms, patients incur similar monitoring costs as padeliporfin VTP has a monitoring schedule similar to active surveillance (**Table 50** and **Table 54**). Patients continue to incur these monitoring costs until they leave the pre-RT health state. Following five years in the pre-RT health state, these patients incur £22.89 annually in subsequent years until progressing to the post-RT, metastatic or death health states. Additionally, patients incur the cost of managing adverse events (**Table 56**) in the pre-RT health state based on the respective short- and long-term probabilities (**Table 44**) of UI, ED and BD for patients who received padeliporfin VTP and those who are on active surveillance. Upon leaving the pre-RT health state, patients in the padeliporfin VTP and AS arms that move into the post-RT health state can receive RP, EBRT or brachytherapy. The distribution of radical therapies following padeliporfin VTP and AS was assumed to be similar across treatment arms as there is no real world data to suggest otherwise. In the PCM301 trial, the distribution was similar. To estimate the distribution, current market share values (**Current market share** [p **141**]) were readjusted assuming no patient would receive AS (i.e., relative proportions to sum to 100% after removing AS market share). As current market share values for AS, RP, EBRT and brachytherapy were estimated to be 51%, 25%, 12% and 12%, respectively, the distribution of radical therapy following padeliporfin VTP or AS was estimated to be 51.3%, 24.4% and 24.4% for RP, EBRT and brachytherapy, respectively.

On the other hand, patients in the RP, EBRT or brachytherapy treatment arms enter the model in the post-RT health state. Patients initially randomized to the padeliporfin VTP and AS arms also enter this health state at varying times following the initial cycle based on time to radical therapy based on the PCM301 trial. Upon entry into the post-RT health state (initial cycle for RP, EBRT and brachytherapy arms), patients incur the cost of radical therapy, adjuvant treatment and salvage therapy. Although patients usually do not receive adjuvant therapy and salvage therapy immediately following initial radical therapy, the cost was incurred in the upon entry into post-RT as the model approach, partitioned survival analysis, limits the ability to ascertain when individual patients enter and leave the post-RT health state among patients in the padeliporfin VTP and AS arms who do not enter post-RT in the initial

cycle. To calculate cost of adjuvant therapy, the unit cost of adjuvant hormone therapy and adjuvant EBRT, both based on the Ramsay et al 2015 analysis,[37] are multiplied by the proportion of patients who receive adjuvant hormone therapy and adjuvant EBRT, respectively, following each type of radical therapy (**Table 51**).

Table 51 Adjuvant therapy costs per primary radical treatment procedure

Primary treatment	Adjuvant HT			Adjuvant EBRT		
	Unit cost, £	Frequency	Total cost, £	Unit cost, £	Frequency	Total cost, £
RP	522.56	0.22	115.87	2,722.56	0.36	982.67
EBRT		0.84	438.95		0.00	0.00
Brachytherapy		0.46	240.38		0.00	0.00

HT, hormone therapy; EBRT, external beam radiation therapy; RP, radical prostatectomy; EBRT, external beam radiation therapy

Source: Ramsay et al 2015[37]

The cost of salvage therapy following radical therapy was based on the Ramsay et al 2015 analysis.[37] To calculate the cost of salvage therapy, the aggregate cost associated with salvage therapy and diagnosing local recurrence per patient was multiplied by the probability of recurrence, the probability that identified recurrence was localised disease, and the probability that local recurrence led to salvage therapy (**Table 52**).[37] As the probability that identified recurrence was localised disease varies depending on the number of years since initial radical therapy, the annual costs varied as well. These costs were adjusted by the proportion of patients receiving each radical therapy in each cycle. Since the cost of salvage therapy was incurred upon entry into post-RT, each patient cohort, i.e. the proportion of patients who enter post-RT during the same cycle, accrue the cost of salvage therapy each cycle throughout their time spent in post-RT, which are then aggregated and incurred in the cycle at which the patient cohort entered post-RT.

Table 52 Salvage therapy costs

Initial radical therapy	Year	Cost of salvage therapy (SD), £	Cost of diagnosing local recurrence (SD), £	Probability of recurrence	Annual probability that recurrence, if identified, was localised	Probability local recurrence lead to salvage therapy	Annual cost, £

					disease		
RP	≤ 1	5,560.33 (556.0)	657.40	0.02	0.07	0.96	8.34
	1-2				0.10		11.91
	> 2				0.61		72.67
	> 3				0.74		88.16
EBRT	≤ 1	5,597.52 (559.8)		0.01	0.07	0.96	3.36
	1-2				0.10		4.79
	> 2				0.61		29.24
	> 3				0.74		35.47
BT	≤ 1	6,172.92 (617.3)		0.02	0.07	0.96	7.33
	1-2				0.10		10.47
	> 2				0.61		63.86
	> 3				0.74		77.47
SD, standard deviation; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy Source: Ramsay et al 2015[37]							

Similar to pre-RT, patients in post-RT incur costs of follow-up surveillance and managing adverse events. However, annual surveillance costs (**Table 53** and **Table 54**) following radical therapy, based on Ramsay et al 2015,[37] are less resource-intensive and costly than active surveillance and annual surveillance costs following padeliporfin VTP.

Table 53 Annual surveillance resource inputs

Year	Resource inputs
1	• 4 nurse-led outpatient appointments • 4 PSA tests • 1 DRE
2-5	• 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE
Annually thereafter	• 1 practice nurse appointment • 1 PSA test
PSA, prostate-specific antigen; DRE, digital rectal exam Source: Ramsay et al 2015[37]	

Table 54 Monitoring / follow-up costs after active treatment

Items	Year	Cost (SD), £	Reference in

			submission
Padeliporfin with VTP follow-up costs	First year	510.95 (85.8)	Table 50
	Second year	425.31 (78.3)	Table 50
	Third year	195.39 (32.6)	Table 50
	Fourth year	425.31 (78.3)	Table 50
	Fifth year	195.39 (32.6)	Table 50
	Annually thereafter	22.89 (2.9)	Table 50
Radical treatment follow-up costs	First year	393.28 (50.2)	Table 53
	Second year to fifth year	196.64 (25.1)	Table 53
	Annually thereafter	22.89 (2.9)	Table 53
SD, standard deviation; VTP, vascular targeted photodynamic therapy			

To calculate the cost of metastatic disease, based on Ramsay et al 2015, it was assumed on the basis of expert opinion that the only difference between diagnosing local and metastatic recurrence would be that patients with suspected metastasis would also have to undergo a bone scan (£755).[37] It was also assumed that 50% of patients would undergo a first-line docetaxel-based chemotherapy regimen (£10,450) and that 70% of these patients would go on to receive a second-line abiraterone-based regimen (£24,670) prior to death.[37] Lastly, it was assumed that patients with metastatic disease would be treated with 3 weeks of cypoterone acetate (Androcur®, Bayer) (100 mg) and two courses, each of 3 months, of the LHRH agonist goserelin (Zoladex® LA, AstraZeneca) (10.8-mg 3-month injection). It was assumed that goserelin would be administered by a practice nurse in a primary care setting.[37] The cost of cypoterone acetate and goserelin were based on current NHS list prices[75] and all other costs were adjusted for inflation to 2017-18 price levels[74]. The cost of metastatic disease was only incurred upon entry into the metastatic health state.

End-of-life care cost was based on Ramsay et al 2015[37] and adjusted for inflation to 2017-18 price levels[74]. This cost was also only incurred upon entry in the death health state.

Table 55 List of health states and associated costs in the economic model

Health states	Items	Value (SD), £	Reference in submission
Pre-radical therapy	Treatment (VTP)	14,404.76*	Table 48
	Monitoring / follow-up	-	Table 50 and Table 54
	Adverse events	-	Table 56
Post-radical therapy	Radical treatment	-	Table 50
	Adjuvant therapy	-	Table 51
	Adjuvant EBRT	2,722.56† (347.3)	Table 51
	Adjuvant HT	522.56† (52.3)	Table 51
	Salvage therapy	-	Table 52
	Post-RP	5,560.33† (556.0)	Table 52
	Post-EBRT	5,597.52† (559.8)	Table 52
	Post-BT	6,172.92† (617.3)	Table 52
	Monitoring / follow-up	-	Table 54
	Adverse events	-	Table 56
Metastatic disease	Metastatic disease	17,488.76	Health-state unit costs and resource use (p 125)
Death	Palliative treatment	5,145.98	Health-state unit costs and resource use (p 125)

SD, standard deviation; VTP, vascular targeted photodynamic therapy; EBRT, external beam radiation therapy; HT, hormone therapy; RP, radical prostatectomy; BT, brachytherapy

*Includes acquisition and administration costs

†Unit costs

Adverse reaction unit costs and resource use

The costs of managing adverse events were based on the Ramsay et al 2015 analysis.[37] Recurring costs, in the short-term, are incurred for six months. On the other hand, recurring costs, in the long-term, are incurred throughout the time spent in the pre-RT or post-RT health state for the respective proportion of patients experience long-term adverse events, which varies by adverse event, treatment and health state (**Table 44**).

Table 56 summarizes the cost of managing adverse events. For non-recurring treatment costs such as penile prosthesis, the cost-effectiveness analysis assumes only patients who have permanent (i.e. long-term) adverse event would incur the cost of treatment as transient adverse events resolve in the near term. Of the proportion of patients who experience long-term urinary incontinence, 5.2% incur the one-time cost of AUS device. Of the proportion of patients who experience either short- or long-term urinary incontinence, 94.8% incur recurring self-management costs. Of the proportion of patients who experience long-term erectile dysfunction, 57% are treated. Of those treated, 2.4% incur the one-time cost of penile prosthesis. Of the proportion of patients who experience short- or long-term erectile dysfunction, 57% are treated. Of those treated, 82.2% and 15.4% incur the recurring cost of sildenafil and alprostadil, respectively. Of the proportion of patients who experience long-term bowel dysfunction, it was assumed all these patients incur the mean treatment cost on a recurring, annual basis. Of the proportion of patients who experience short- and long-term bowel dysfunction it was assumed that all these patients incurred annual monitoring costs.

Table 56 List of adverse reactions and summary of costs in the economic model

Adverse events	Management / treatment strategy	Cost (SD), £	Short-term frequency	Long-term frequency	Reference in submission
Urinary incontinence	Self-management	304.54 (30.5) per year	0.948	0.948	Adverse reaction unit costs and resource use (p 130)
	AUS device*	10,220.32 (1022.0)	0.000	0.052	
	Implantation	4,538.26	-	-	
	Device	5,682.07	-	-	
Erectile dysfunction	No treatment	-	0.430	0.430	
	Treatment	-	0.570	0.570	
	Sildenafil, 100 mg	5.88 (0.6) per week	0.822 of treated	0.822 of treated	
	Alprostadil, 20 µg	11.94 (1.2) per week	0.154 of treated	0.154 of treated	
	Penile prosthesis*	8,416.81 (841.7)	0.000	0.024	
	Implantation	2,613.43	-	-	
	Device	5,803.38	-	-	

Bowel dysfunction	Annual monitoring cost	425.75 (42.6) per year	1.000	1.000
	Mean treatment cost	2,718.45 (271.8)	0.000	1.000

SD, standard deviation; AUS, artificial urinary sphincter

*Non-recurring cost

Source: Ramsay et al 2015[37]

Miscellaneous unit costs and resource use

All costs and healthcare resource use have been covered elsewhere.

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

Summary of base-case analysis inputs

Table 57 provides a summary of variables used in the economic model.

Table 57 Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Patient characteristics			
Age, years	63.1 (6.3)	Normal	General mortality (p 112)
Age when life expectancy is 10 years	75.0 (7.5)	Normal	General mortality (p 112)
Efficacy			
Time to radical therapy, lognormal distribution - padeliporfin VTP	Intercept: [redacted] Scale: [redacted]	Cholesky decomposition	Time to radical therapy (p 94)
Time to radical therapy, lognormal distribution - active surveillance	Intercept: [redacted] Scale: [redacted]	Cholesky decomposition	Time to radical therapy (p 94)
Time to metastasis, lognormal - active surveillance	Intercept: 3.452 (0.151) Scale:	Cholesky decomposition	Time to metastasis (p 103)

	1.410 (0.116)		
Time to metastasis, lognormal - radical therapy	Intercept: 4.451 (0.373) Scale: 1.519 (0.220)	Cholesky decomposition	Time to metastasis (p 103)
Time to prostate cancer-related death, exponential - radical therapy	Intercept: 7.795 (0.707) Scale: 1.000	Cholesky decomposition	Time to death (p 109)
Utilities			
Localised PCa without AEs	0.88 (0.088)	Beta	Health-related quality-of-life data used in the cost-effectiveness analysis (p 119)
Metastasis	0.58 (0.058)	Beta	
Urinary incontinence	-0.05 (0.005)	Beta	
Erectile dysfunction	-0.04 (0.004)	Beta	
Bowel dysfunction	-0.16 (0.016)	Beta	
Probability of short- vs long-term UI, ED and BD by treatment arm			
Probability of adverse event, padeliporfin VTP	Short-term UI: 0.013 ED: 0.175 BD: 0.050 Long-term UI: 0.000 ED: 0.100 BD: 0.013	Beta	Health-related quality-of-life studies (p 115) and Table 44
Probability of adverse event, active surveillance	Short-term UI: 0.013 ED: 0.013 BD: 0.000 Long-term UI: 0.000 ED: 0.013 BD: 0.000	Beta	
Probability of adverse event, radical prostatectomy	Short-term UI:0.248 ED:0.645 BD:0.040 Long-term UI:0.278 ED:0.706 BD:0.128	Beta	
Probability of adverse event, EBRT	Short-term UI:0.092	Beta	

	ED:0.486 BD:0.152 Long-term UI:0.111 ED:0.406 BD:0.181		
Probability of adverse event, brachytherapy	Short-term UI:0.332 ED:0.268 BD:0.055 Long-term UI:0.363 ED:0.262 BD:0.116	Beta	
Short-term AE duration			
Urinary incontinence, months	6 (0.6)	Normal	Adverse reactions (p 116)
Erectile dysfunction, months	6 (0.6)	Normal	
Bowel dysfunction, months	6 (0.6)	Normal	
Distribution of radical therapies after padeliporfin VTP or AS			
Radical surgery	0.51 (0.051)	Beta	Health-state unit costs and resource use (p 125)
EBRT	0.24 (0.024)	Beta	
Brachytherapy	0.24 (0.024)	Beta	
Costs			
Padeliporfin acquisition	12,111.23 (1,211.1)	Gamma	Table 48
VTP administration, laser generator	619.50	Gamma	Intervention and comparators' costs and resource use (p 122) and Table 49
VTP administration, physical exams	96.09	Gamma	
VTP administration, operating room	1,010.05	Gamma	
VTP administration, Anaesthesiologist	119.94	Gamma	
VTP administration, uro-oncologist surgeon	166.50	Gamma	
VTP administration, nurse	5.72	Gamma	
VTP administration, electrocardiograms	275.74	Gamma	
VTP surveillance, year 1	510.95 (85.8)	Gamma	Table 54

VTP surveillance, year 2	425.31 (78.3)	Gamma	
VTP surveillance, year 3	195.39 (32.6)	Gamma	
VTP surveillance, year 4	425.31 (78.3)	Gamma	
VTP surveillance, year 5	195.39 (32.6)	Gamma	
VTP surveillance, annually thereafter	22.89 (2.9)	Gamma	
Active surveillance, year 1	510.95 (85.8)	Gamma	Table 49 and Table 50
Active surveillance, year 2	425.31 (78.3)	Gamma	
Active surveillance, year 3	195.39 (32.6)	Gamma	
Active surveillance, year 4	425.31 (78.3)	Gamma	
Active surveillance, year 5	195.39 (32.6)	Gamma	
Active surveillance, annually thereafter	22.89 (2.9)	Gamma	
Radical therapy surveillance, year 1	393.28 (50.2)	Gamma	Table 54
Radical therapy surveillance, year 2-5	196.64 (25.1)	Gamma	
Radical therapy surveillance, annually thereafter	22.89 (2.9)	Gamma	
Radical prostatectomy	4,446.71 (444.7)	Gamma	Intervention and comparators' costs and resource use (p 122)
EBRT	2,898.32 (369.7)	Gamma	
Brachytherapy	7,806.32 (1,207.5)	Gamma	
Diagnosis of local recurrence	657.40 (73.4)	Gamma	Table 52
Salvage therapy, post-RP	5,560.33 (556.0)	Gamma	
Salvage therapy, post-EBRT	5,597.52 (559.8)	Gamma	
Salvage therapy, post-brachytherapy	6,172.92 (617.3)	Gamma	
Adjuvant EBRT	2,722.56 (347.3)	Gamma	Table 51
Adjuvant hormone therapy	522.56 (52.3)	Gamma	
UI, self-management (per year)	304.54 (30.5)	Gamma	Table 56
UI, AUS device	4,538.26	Gamma	

(implantation)			
UI, AUS device (device)	5,682.07	Gamma	
ED, sildenafil (per week)	5.88 (0.6)	Gamma	
ED, alprostadil (per week)	11.94 (1.2)	Gamma	
ED, penile prosthesis (implantation)	2,613.43	Gamma	
ED, penile prosthesis (device)	5,803.38	Gamma	
BD, monitoring (per year)	425.75 (42.6)	Gamma	
BD, treatment	2,718.45 (271.8)	Gamma	
Metastatic disease	17,488.76 (1,748.9)	Gamma	Health-state unit costs and resource use (p 125)
End-of-life care	5,145.98 (514.6)	Gamma	Health-state unit costs and resource use (p 125)
Probability of receiving short- vs long-term treatment by type of AE			
UI, self-management, short-term	0.948	Beta	Table 56
UI, self-management, long-term	0.948	Beta	
UI, AUS device, short-term*	0.000	Beta	
UI, AUS device, long-term*	0.052	Beta	
ED, treated, short-term	0.570	Beta	
ED, treated, long-term	0.570	Beta	
ED, sildenafil, short-term	0.822	Beta	
ED, sildenafil, long-term	0.822	Beta	
ED, alprostadil, short-term	0.154	Beta	
ED, alprostadil, long-term	0.154	Beta	
ED, penile prosthesis, short-term*	0.000	Beta	
ED, penile	0.024	Beta	

prosthesis, long-term*			
BD, monitoring, short-term	1.000	No distribution	
BD, monitoring, long-term	1.000	No distribution	
BD, treatment, short-term*	1.000	No distribution	
BD, treatment, long-term*	1.000	No distribution	
Probability of salvage therapy			
Yearly probability of recurrence, RP	0.020 (0.0020)	Beta	Table 52
Yearly probability of recurrence, EBRT	0.008 (0.0008)	Beta	
Yearly probability of recurrence, brachytherapy	0.016 (0.0016)	Beta	
Annual probability that identified recurrence was localised, ≤ 1 year	0.07 (0.007)	Beta	
Annual probability that identified recurrence was localised, 1-2 years	0.10 (0.010)	Beta	
Annual probability that identified recurrence was localised, > 2 years	0.61 (0.061)	Beta	
Annual probability that identified recurrence was localised, > 3 years	0.74 (0.074)	Beta	
Probability of salvage therapy after local recurrence	0.958 (0.0958)	Beta	
Probability of adjuvant therapy			
Adjuvant hormone therapy, RP	0.222 (0.0222)	Beta	Table 51
Adjuvant hormone therapy, EBRT	0.840 (0.0840)	Beta	
Adjuvant hormone therapy, brachytherapy	0.460 (0.0460)	Beta	
Adjuvant EBRT, RP	0.361 (0.0361)	Beta	
Adjuvant EBRT, EBRT	0.000 (0.0000)	Beta	

Adjuvant EBRT, brachytherapy	0.000 (0.0000)	Beta	
Market share			
Current market share, %	VTP: 0% AS: 51% RP: 25% EBRT: 12% BT: 12%	N/A	Table 61
Future market share, %	VTP: [redacted] AS: [redacted] RP: [redacted] EBRT: [redacted] BT: [redacted]	N/A	Table 61
CI, confidence interval; VTP, vascular targeted photodynamic therapy; PCa, prostate cancer; AEs, adverse events; EBRT, external beam radiation therapy; AS, active surveillance; RP, radical prostatectomy; UI, urinary incontinence; AUS, artificial urinary sphincter; ED, erectile dysfunction; BD, bowel dysfunction; BT, brachytherapy *Non-recurring			

Assumptions

Key assumptions in the base-case analysis are described in **Table 58**.

Table 58 Assumptions in the cost-effectiveness model

Assumption	Justification
Pre- and post-radical therapy model the clinical pathway more effectively than pre- and post-progression in localised prostate cancer in regards to costs and QALYs.	Evidence suggests that HRQoL is similar in low- vs intermediate-risk, localised cancer. In addition, the primary reason for any cost differences in low- vs intermediate-risk localised prostate cancer can be attributed to radical therapy and managing its associated adverse events.
Time to metastasis and time to prostate cancer-related death were based on the ProtecT trial.	The PCM301 trial follow-up period was too short to detect metastasis and death. Thus, the ProtecT trial, a randomized controlled trial in the UK with a 10 year follow-up period that compared active monitoring, radical surgery and radiation therapy, provided the best available evidence.[16]
Padeliporfin VTP and active surveillance are assumed to have equivalent time to metastasis and prostate cancer-related mortality.	There is no evidence from the PCM301 trial to suggest any differences in metastasis or death between padeliporfin VTP and active surveillance.
All treatments are assumed to have equivalent prostate cancer-related mortality.	In the ProtecT trial, there was no significant difference in prostate cancer-related mortality or all-cause mortality between active monitoring, surgery and radiotherapy.

Just prior to Year 12, the absolute risk reduction in radical therapy between padeliporfin VTP and active surveillance remains constant until patients move to metastasis or death.	Patients are no longer eligible for radical therapy when life expectancy is less than 10 years.
Any HRQoL differences between treatment arms are due to genitourinary- and bowel-associated toxicities.	As primary active treatment in the indication population is administered during low- or intermediate-risk disease, the evidence suggests that HRQoL is not substantially affected at this stage so early on in the disease, but rather by the toxicities associated with radical treatments or padeliporfin VTP.
Model inputs for the comparators (active surveillance and radical therapies) are based on the Ramsay et al 2015 analysis.	The Ramsay et al 2015 analysis was a comprehensive study, funded by the HTA programme that included detailed and carefully validated systematic reviews and cost-effectiveness analyses from the NHS perspective in localised prostate cancer.[37]
QALY, quality-adjusted life years; HRQoL, health-related quality of life; UK, United Kingdom; VTP, vascular targeted photodynamic therapy; AS, active surveillance; EBRT, external beam radiation therapy; NHS, National Health Service	

B.3.7 Base-case results

Pairwise comparisons

The base-case results, listed from least to most expensive, are presented in **Table 59**. In **Table 59**, the incremental cost-effectiveness ratios (ICERs) are presented compared to EBRT, which is the baseline being the least expensive comparator, and as an incremental analysis. Pairwise comparisons versus padeliporfin VTP are presented in **Table 60**. When compared to each comparator in the decision problem, padeliporfin is cost-effective at a willingness-to-pay (WTP) threshold of £30,000 per QALY versus radical prostatectomy and brachytherapy, but not active surveillance and EBRT.

Table 59 Base-case results: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Active surveillance	16,609	13.673	11.413	-	-	-	-	-
EBRT	16,999	13.673	11.340	390	0.000	-0.073	Dominated by Active surveillance	Dominated by Active surveillance
Radical prostatectomy	18,752	13.673	11.185	2,143	0.000	-0.227	Dominated by Active surveillance	Dominated by EBRT
Brachytherapy	19,871	13.673	11.393	3,262	0.000	-0.020	Dominated by Active surveillance	5,392
VTP	26,714	13.673	11.643	10,105	0.000	0.230	43,960	27,390
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy; VTP, vascular-targeted photodynamic therapy								

Table 60 Base-case results: pairwise comparisons against padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
VTP	26,714	13.673	11.643	-	-	-	-
Active surveillance	16,609	13.673	11.413	-10,105	0.000	-0.230	43,960
Radical prostatectomy	18,752	13.673	11.185	-7,962	0.000	-0.457	17,408
EBRT	16,999	13.673	11.340	-9,715	0.000	-0.303	32,082
Brachytherapy	19,871	13.673	11.393	-6,843	0.000	-0.250	27,390
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy; VTP, vascular-targeted photodynamic therapy							

Market with and without padeliporfin VTP

Given the multiplicity of treatments in use in the indication population, the results of the cost-effectiveness analysis, as a whole, can be assessed by estimating the ICER of a population where padeliporfin VTP is a treatment option versus the current population without padeliporfin as a treatment option.

Currently, three options are recommended by NICE for men with low-risk localised prostate cancer, including active surveillance, radical prostatectomy and radical radiotherapy (EBRT or brachytherapy). According to Greenberg et al 2015,[13] among patients newly diagnosed with low risk prostate cancer of 60 – 69 years of age, 61.0%, 15.9%, 18.9% and 4.2% of the patients receive conservative management (i.e. either active surveillance or watchful waiting), radical prostatectomy, radical radiotherapy and primary androgen deprivation therapy (PADT), respectively. Among patients newly diagnosed low risk prostate cancer of <60 years of age, 53.4%, 26.1%, 16.1% and 4.3% of the patients receive conservative management, radical prostatectomy, radical radiotherapy and PADT, respectively.[13]

Current market share

To determine the current market share for active surveillance, radical prostatectomy, EBRT and brachytherapy among patients diagnosed with unilateral low risk but not very low risk prostate cancer (indication population), the following steps were taken.

First, it was assumed that patients <69 years of age all have life expectancy greater than 10 years, and therefore 100% of the newly diagnosed patients in conservative management from Greenberg et al[13] received active surveillance and 0% received watchful waiting.

Second, PADT was excluded since it is not recommended by NICE for low-risk, localised prostate cancer and thereby not included as comparator in the analysis.[6] After readjusting the market share values for the other options (so that the relative proportions summed up to 100% total market share), the resultant market share values for active surveillance, radical prostatectomy and radical radiotherapy were 63.7%, 16.6% and 19.7%, respectively, for patients 60 – 69 years of age, and 55.9%, 27.3% and 16.8%, respectively, for patients <60 years of age.

Third, to determine the market share among patients with unilateral low risk but not very low risk prostate cancer (indication population), the proportion of patients receiving each treatment option among patients with unilateral very low risk and bilateral low risk prostate cancer were excluded from the total market share above. According to PCM301 trial data, the distribution of risk profiles among patients with

low risk localised prostate cancer was 37%, 40% and 23% for unilateral very low risk, unilateral low risk but not very low risk (indication population), and bilateral low risk, respectively. Based on the market share among patients with low risk prostate cancer calculated above, it was assumed that the market share values for active surveillance, radical prostatectomy and radical radiotherapy were 80%, 10% and 10%, respectively, among patients with unilateral very low risk prostate cancer and 50%, 25% and 25%, respectively, among patients with bilateral low risk prostate cancer. Combining the distribution of risk profiles in low risk prostate cancer with the distribution of treatments received within each risk strata, the market share value for each treatment option among patients with unilateral low risk but not very low risk prostate cancer (indication population) was calculated as the total market share for the treatment option of interest in low risk prostate cancer minus the share attributable to patients with unilateral very low risk prostate cancer and the share attributable to patients with bilateral low risk prostate cancer. For example, among patients 60 – 69 years of age, the market share for radical prostatectomy among patients with unilateral low risk but not very low risk prostate cancer was calculated as the market share of radical prostatectomy among all patients with low risk prostate cancer (i.e. 16.6%) minus the sum of shares for patients with unilateral very low risk prostate cancer, i.e. proportion of unilateral very low risk among all low risk (37%) multiplied by share of radical prostatectomy among unilateral very low risk (10%), and for patients with bilateral low risk prostate cancer, i.e. proportion of bilateral low risk among all low risk (23%) multiplied by share of radical prostatectomy among bilateral low risk (25%). After removing the share attributable to patients with unilateral very low risk and bilateral low risk prostate cancer for each treatment option, the resulting market share values for active surveillance, radical prostatectomy and radical radiotherapy for patients with unilateral low risk but not very low risk prostate cancer (indication population) were 22.6%, 7.1% and 10.3%, respectively, among patients 60 – 69 years of age, and 14.8%, 17.9% and 7.4%, respectively, among patients <60 years of age.

Fourth, the market share for patients with unilateral low risk but not very low risk prostate cancer (indication population) <69 years of age was estimated by calculating the weighted average of the market share for patients 60 – 69 years of

age and <60 years of age weighted by the number of patients newly diagnosed in 2016 in the 60 – 69 age group (i.e. 13,382) and <60 age group (i.e. 4,888), respectively.[7] It was assumed that EBRT and brachytherapy were evenly split, each accounting for 50% of radical radiotherapy. Thus, the market share values for active surveillance, radical prostatectomy, EBRT and brachytherapy were estimated to be 51%, 25%, 12% and 12%, respectively (**Table 61**).

Future market share

To determine the future market share values following the introduction of padeliporfin VTP among patients diagnosed with unilateral low risk but not very low risk prostate cancer (indication population), the following assumptions and calculations were made.

Based on current market share values for newly diagnosed patients with unilateral low risk but not very low risk prostate cancer (i.e. 51%, 25%, 12% and 12% for active surveillance, radical prostatectomy, EBRT and brachytherapy, respectively), it was assumed that padeliporfin VTP will reach ***** market share in the future, of which ***** and ***** will be taken from radical prostatectomy and brachytherapy, respectively. Given this assumption, the future market share values for active surveillance, padeliporfin VTP, radical prostatectomy, EBRT and brachytherapy were estimated to be *****, *****, *****, ***** and *****, respectively (**Table 61**).

Results

Table 61 presents the market share estimates used to estimate the ICER in the world without vs with padeliporfin VTP (**Table 62**). At a WTP threshold of £30,000 per QALY, a scenario in which padeliporfin VTP is a treatment option is cost-effective compared to the current scenario in which padeliporfin is not a reimbursed, treatment option.

Table 61 Market share: without vs with padeliporfin VTP

Technologies	World without padeliporfin VTP	World with padeliporfin VTP
VTP	0%	*****
Active surveillance	51%	*****
Radical prostatectomy	25%	*****

EBRT	12%	*****
Brachytherapy	12%	*****
VTP, vascular targeted photodynamic therapy; EBRT, external beam radiation therapy		

Table 62 Base-case results: without vs with padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without padeliporfin VTP	17,579	13.673	11.345	-	-	-	-
World with padeliporfin VTP	19,856	13.673	11.461	2,277	0.000	0.116	19,549
VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year							

In appendix J, the following are provided:

- Estimates of clinical outcomes included in the cost-effectiveness analysis compared with the clinical trial results.
- Disaggregated results of the base-case incremental cost effectiveness analysis.

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed using a second-order Monte Carlo simulation. In this analysis, each variable (costs and outcomes) was assigned a probability distribution, and cost-effectiveness results associated with simultaneously selecting random values from those distributions were generated for 1,000 iterations. Whenever there was no information on the variability of some of these variables, the standard error (SE) was assumed to be equal to 10% of the mean.

The mean ICER vs. active surveillance based on the PSA is £46,709/QALY (£43,960/QALY in the base case analysis). The probability of the ICER being lower than £30,000/QALY is 23.2% and it is 5.3% for a £20,000/QALY threshold.

Table 63 PSA results: padeliporfin VTP vs active surveillance

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Padeliporfin VTP	26,824	13.657	11.664	-	-	-	-
Active surveillance	16,573	13.657	11.444	10,251	0.001	0.219	46,709

Figure 25 PSA scatterplot results: padeliporfin VTP vs active surveillance

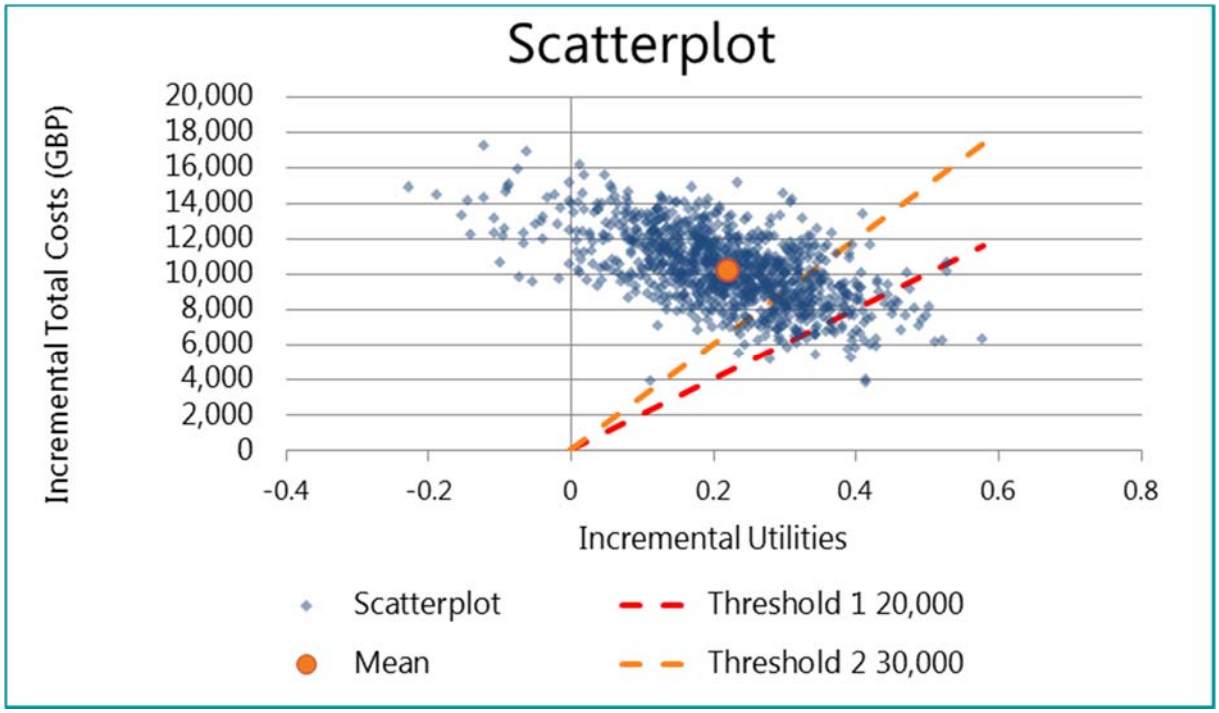
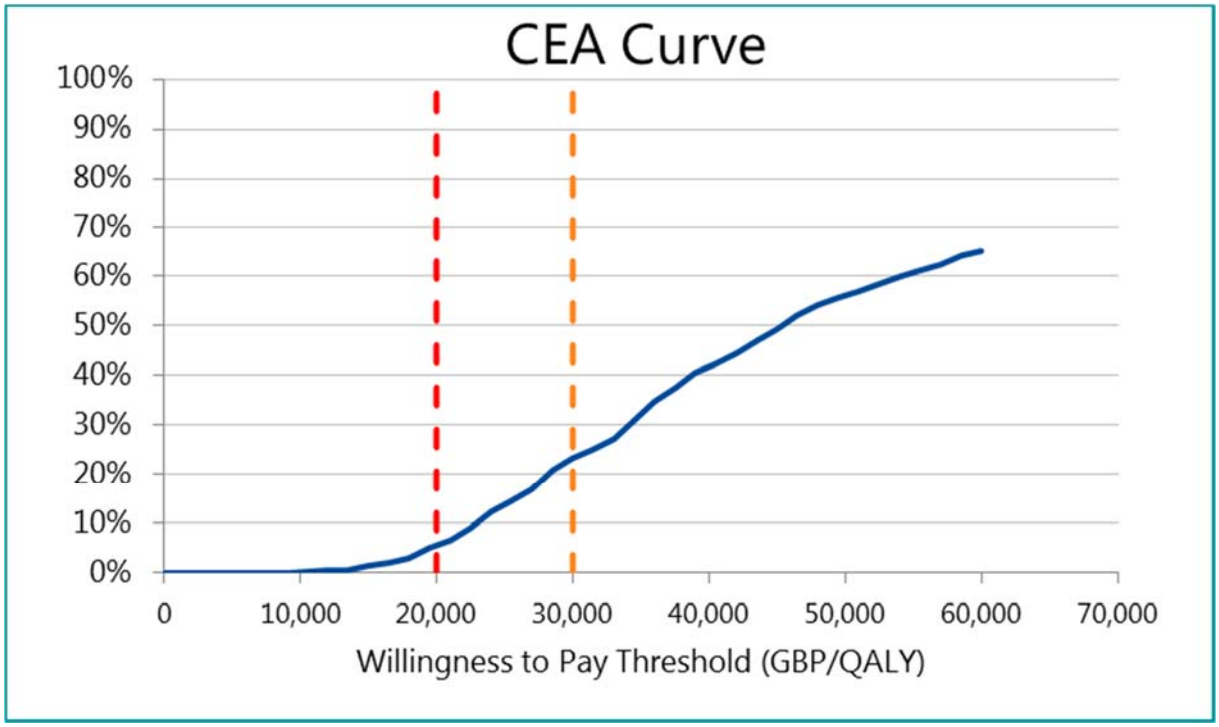


Figure 26 Cost-effectiveness acceptability curve: padeliporfin VTP vs active surveillance



The mean ICER vs. radical prostatectomy based on the PSA is £17,998/QALY (£17,408/QALY in the base case analysis). The probability of the ICER being lower than £30,000/QALY is 86.9% and it is 61.7% for a £20,000/QALY threshold.

Table 64 PSA results: padeliporfin VTP vs radical prostatectomy

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Padeliporfin VTP	26,853	13.658	11.633	-	-	-	-
Radical prostatectomy	18,786	13.658	11.185	8,066	0.001	0.448	17,998

Figure 27 PSA scatterplot results: padeliporfin VTP vs radical prostatectomy

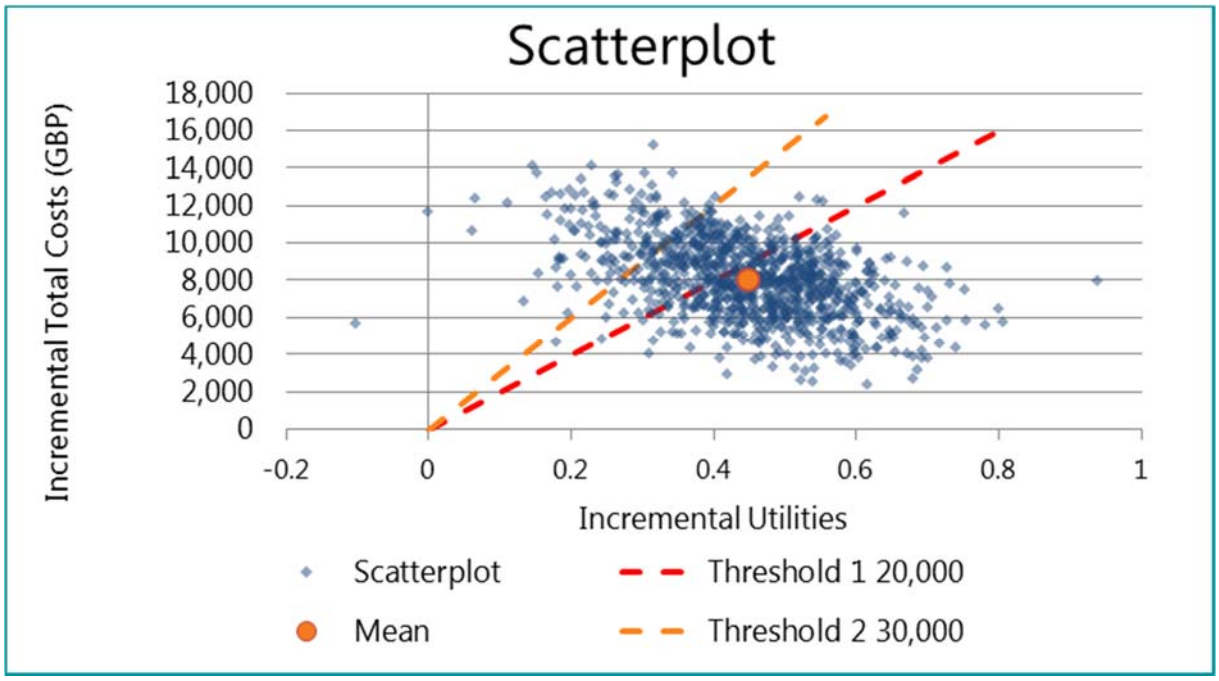
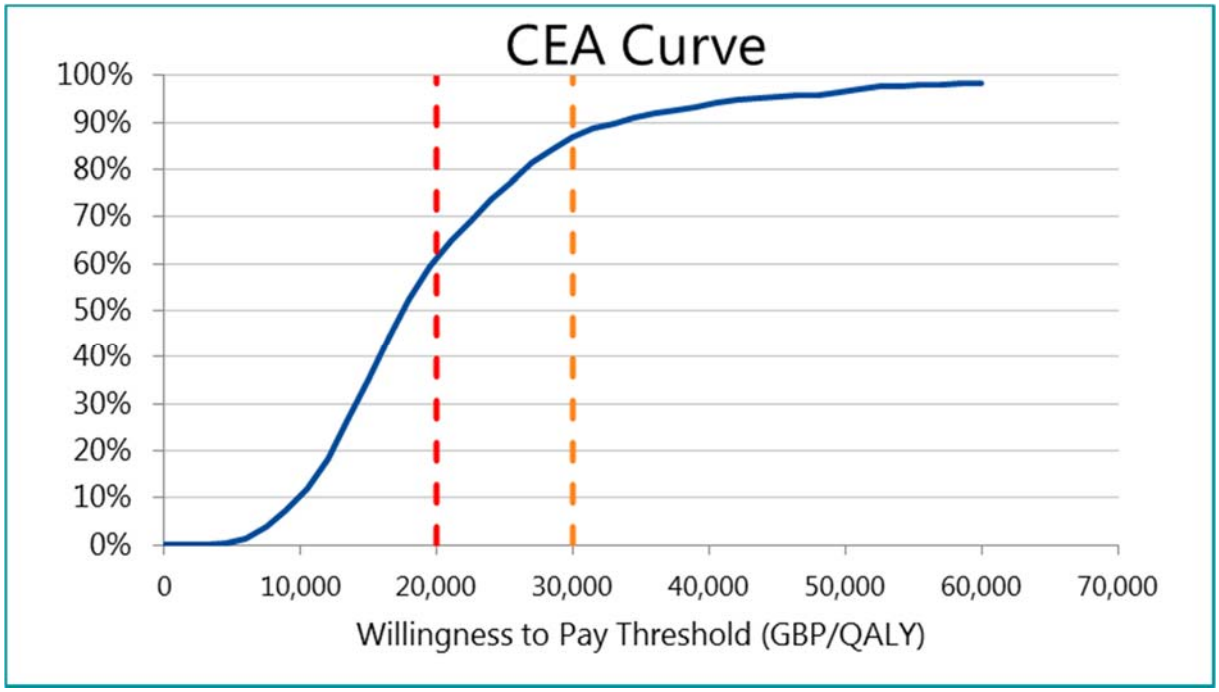


Figure 28 Cost-effectiveness acceptability curve: padeliporfin VTP vs radical prostatectomy



The mean ICER vs. EBRT based on the PSA is £34,178/QALY (£32,082/QALY in the base case analysis). The probability of the ICER being lower than £30,000/QALY is 42.4% and it is 16.2% for a £20,000/QALY threshold.

Table 65 PSA results: padeliporfin VTP vs EBRT

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Padeliporfin VTP	26,834	13.657	11.568	-	-	-	-
EBRT	17,011	13.659	11.281	9,823	-0.002	0.287	34,178

Figure 29 PSA scatterplot results: padeliporfin VTP vs EBRT

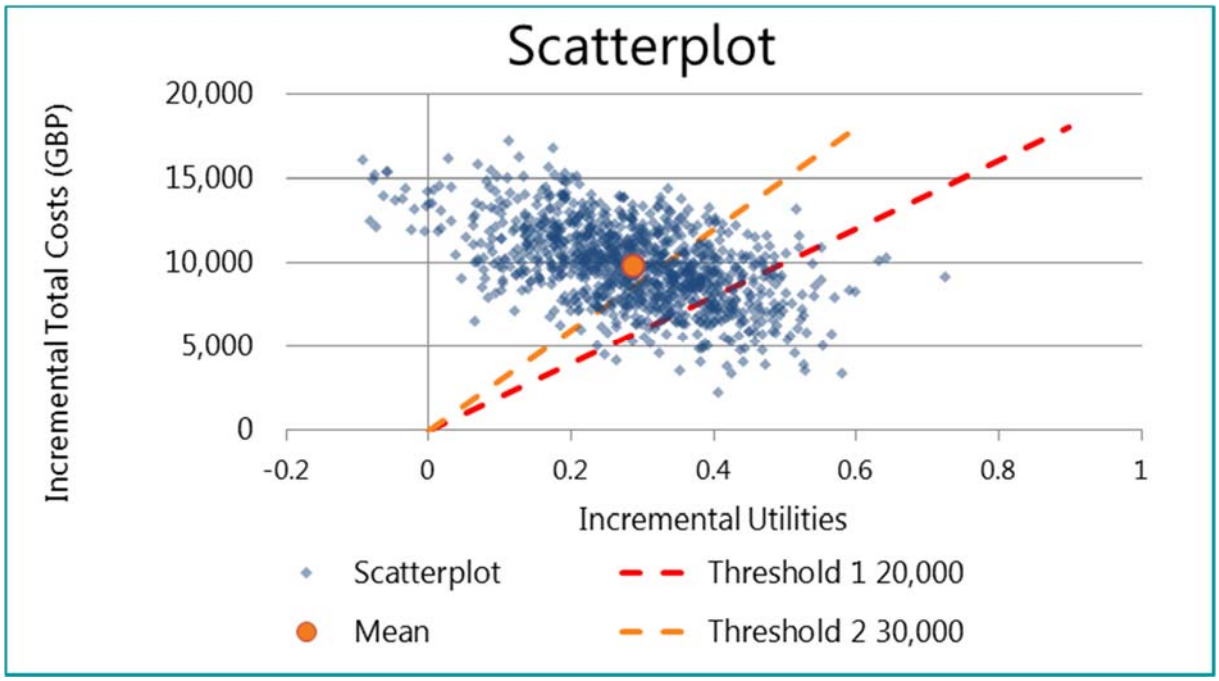
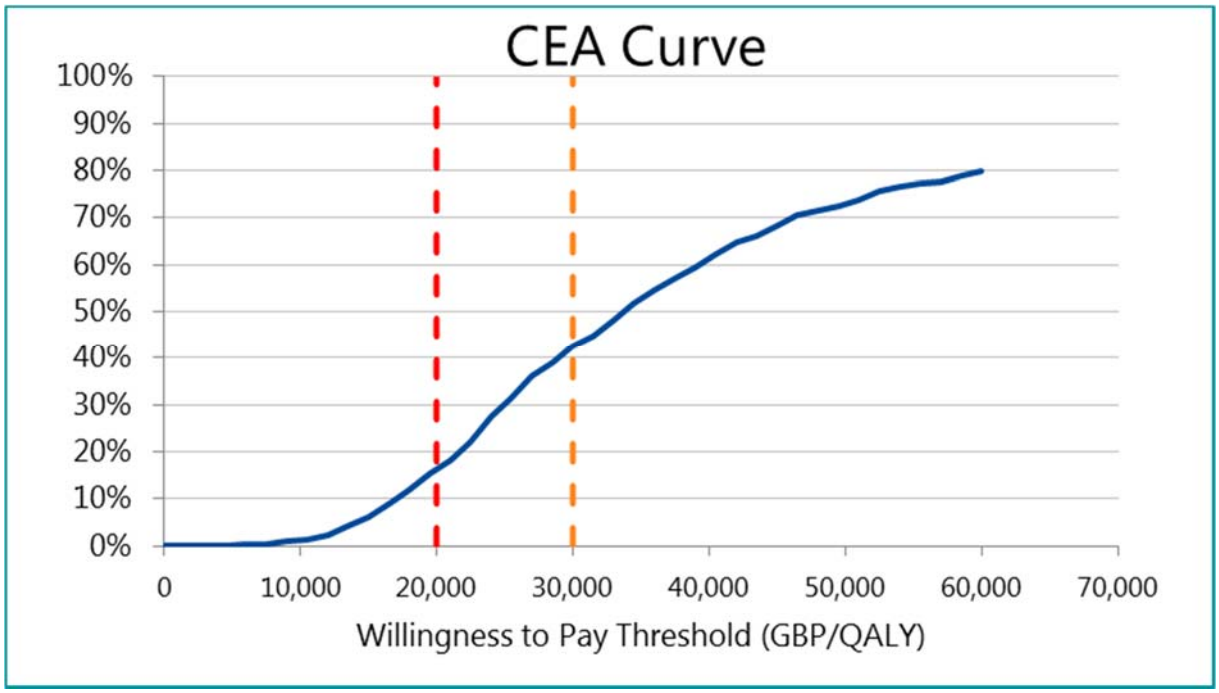


Figure 30 Cost-effectiveness acceptability curve: padeliporfin VTP vs EBRT



The mean ICER vs. brachytherapy based on the PSA is £29,400/QALY (£27,390/QALY in the base case analysis). The probability of the ICER being lower than £30,000/QALY is 51.9% and it is 30.2% for a £20,000/QALY threshold.

Table 66 PSA results: padeliporfin VTP vs brachytherapy

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Padeliporfin VTP	26,911	13.659	11.594	-	-	-	-
Brachytherapy	19,935	13.657	11.357	6,976	0.002	0.237	29,400

Figure 31 PSA scatterplot results: padeliporfin VTP vs brachytherapy

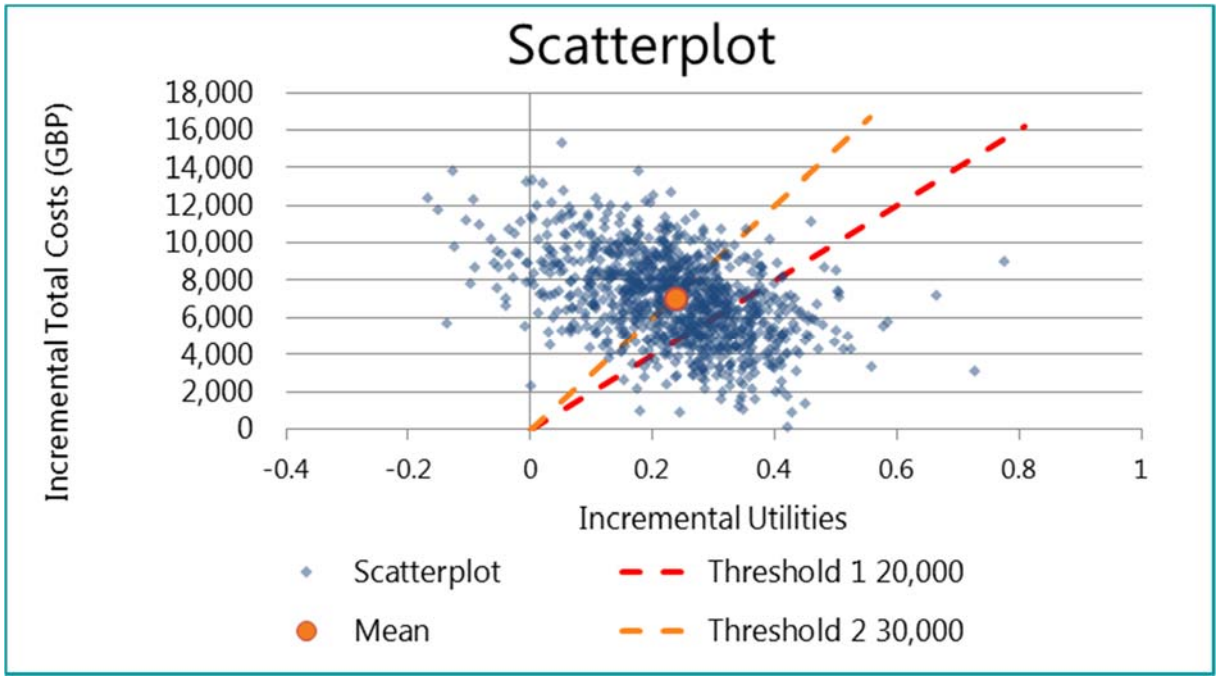
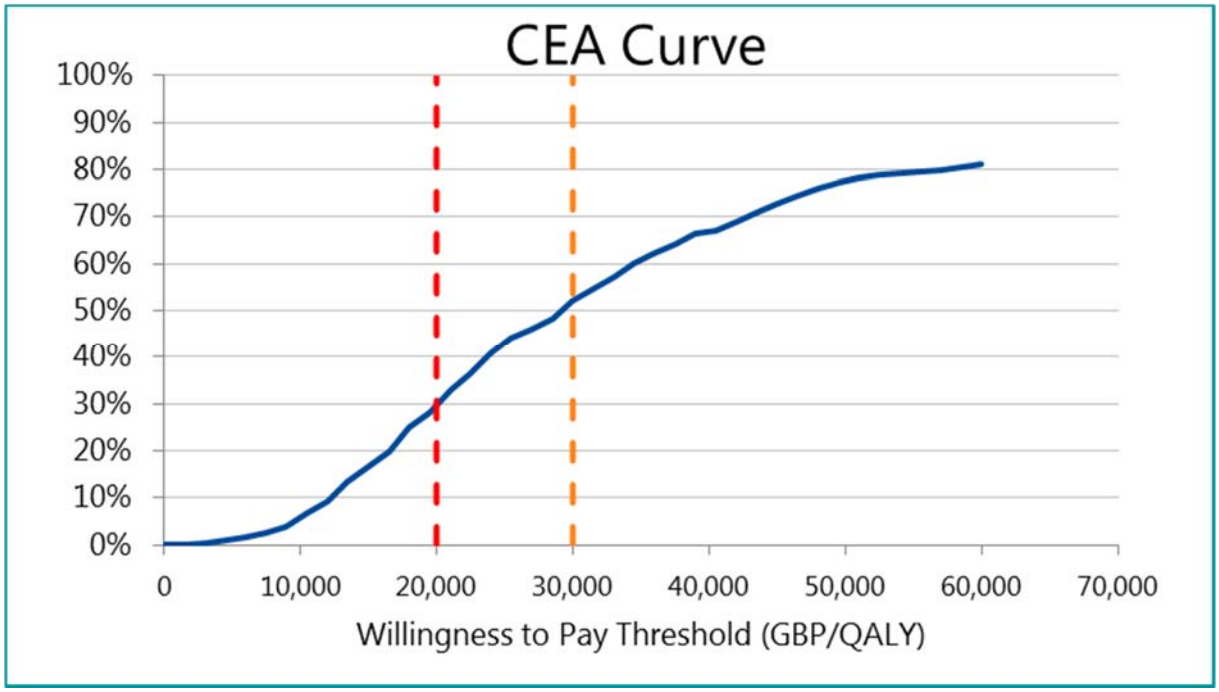


Figure 32 Cost-effectiveness acceptability curve: padeliporfin VTP vs brachytherapy



Deterministic sensitivity analysis

To identify key model variables, one-way deterministic sensitivity (OWSA) analyses were conducted using extreme values for all model variables. Those extreme values corresponded to the respective 95% confidence interval bounds for continuous variables, and each category value for categorical variables or predefined values, such as cost discount and effect discount. Any variables that generated a minimum and maximum ICER with a difference greater than £4,000 per QALY are presented in a tornado diagram for each pairwise comparison (**Figure 33**, **Figure 34**, **Figure 35** and **Figure 36**).

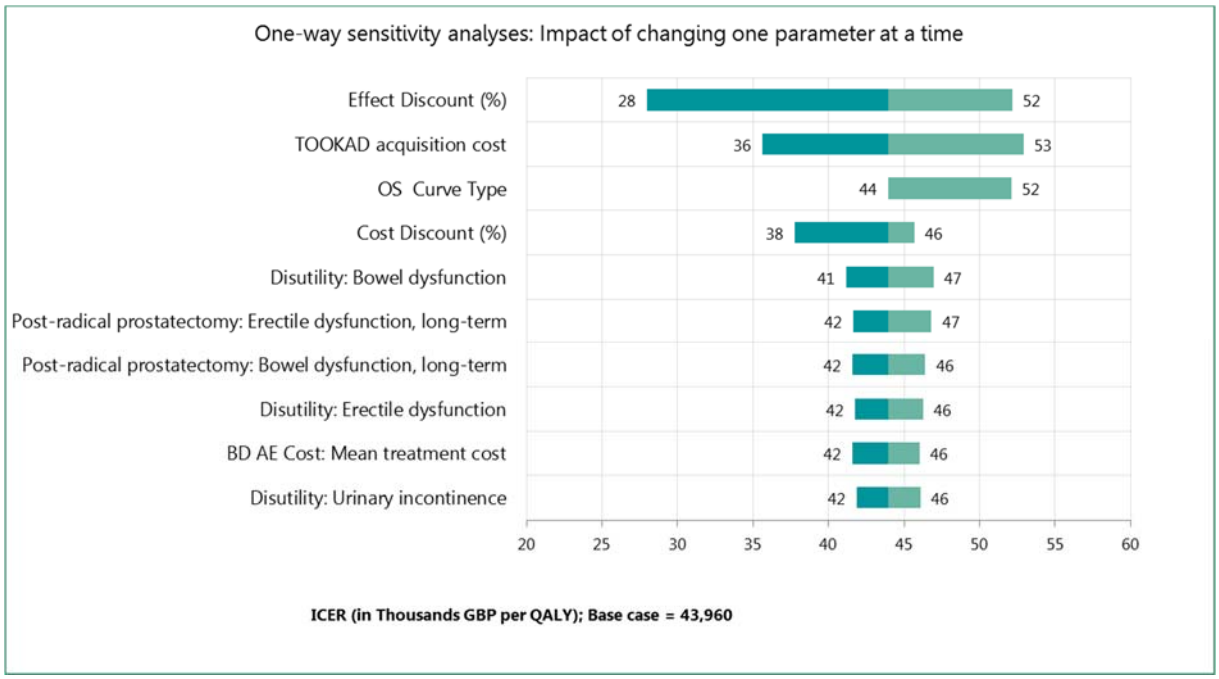
Two primary drivers, TTRT and time horizon were not included in the OWSA. However, these variables were explored in scenario analyses. They were excluded from the OWSA so that the magnitude of impact of the other variables could be more easily assessed in the tornado diagram.

Not accounting for the TTRT and time horizon, the following variables have the greatest effect on the ICER when comparing padeliporfin VTP to AS (in order of importance):

- Effect discount
- Padeliporfin (TOOKAD®) VTP acquisition cost
- OS curve type
- Cost discount
- Disutility: BD
- Post-radical prostatectomy: Long-term probability of ED
- Post-radical prostatectomy: Long-term probability of BD
- Disutility: ED
- Mean treatment cost for BD
- Disutility: UI

The effect and cost discount tested in the OWSA are 0%, 2.5% and 5%. As expected, lowering the discount rate to 0% and 2.5% have a very favourable effect on the ICER as the benefit of padeliporfin VTP is accrued over time as the HRQoL benefit associated with delaying and avoiding radical therapy is extended with time as the benefit accrues gradually. On the other hand, any change in OS, which is equivalent across both treatment groups, results in a less favourable ICER as other distributions predict lower OS, which truncates the benefit of padeliporfin VTP, which as we just discussed, accrues over time.

Figure 33 OWSA results: padeliporfin VTP vs AS

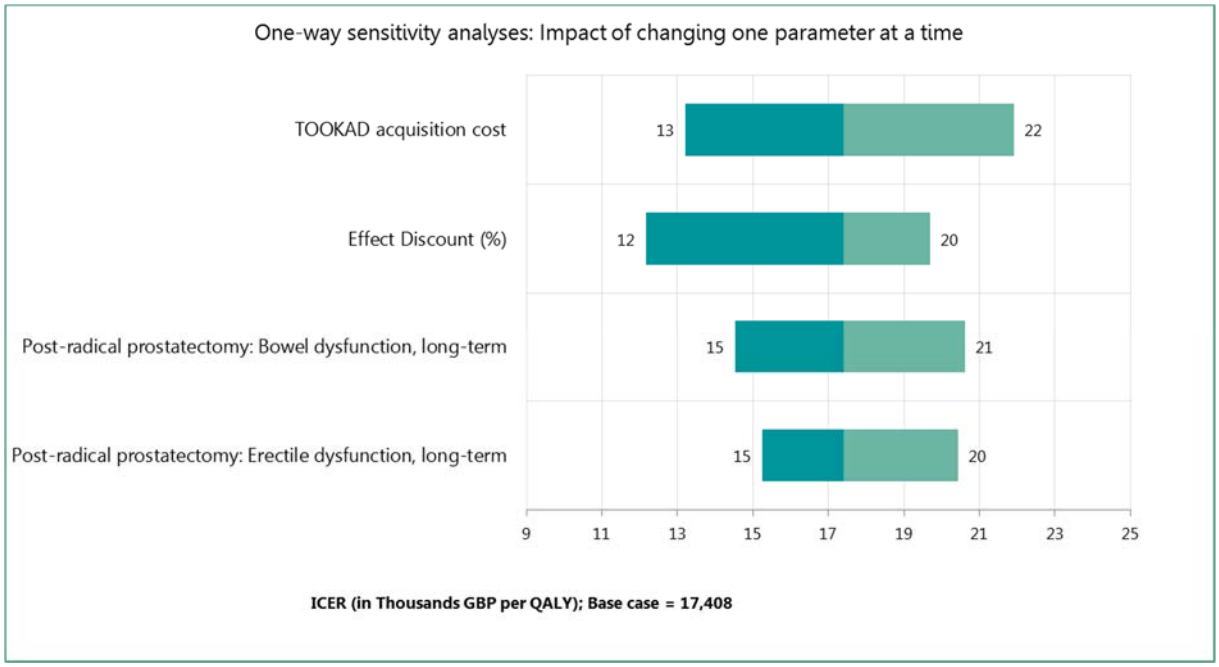


Not accounting for the TTRT and time horizon, the following variables have the greatest effect on the ICER when comparing padeliporfin VTP to RP (in order of importance):

- Padeliporfin (TOOKAD®) VTP acquisition cost
- Effect discount
- Post-radical prostatectomy: Long-term probability of BD
- Post-radical prostatectomy: Long-term probability of ED

Similar to the comparison against AS, the ICER is sensitive to discounting. However, against RP, the acquisition cost of padeliporfin has more influence on the ICER.

Figure 34 OWSA results: padeliporfin VTP vs radical prostatectomy

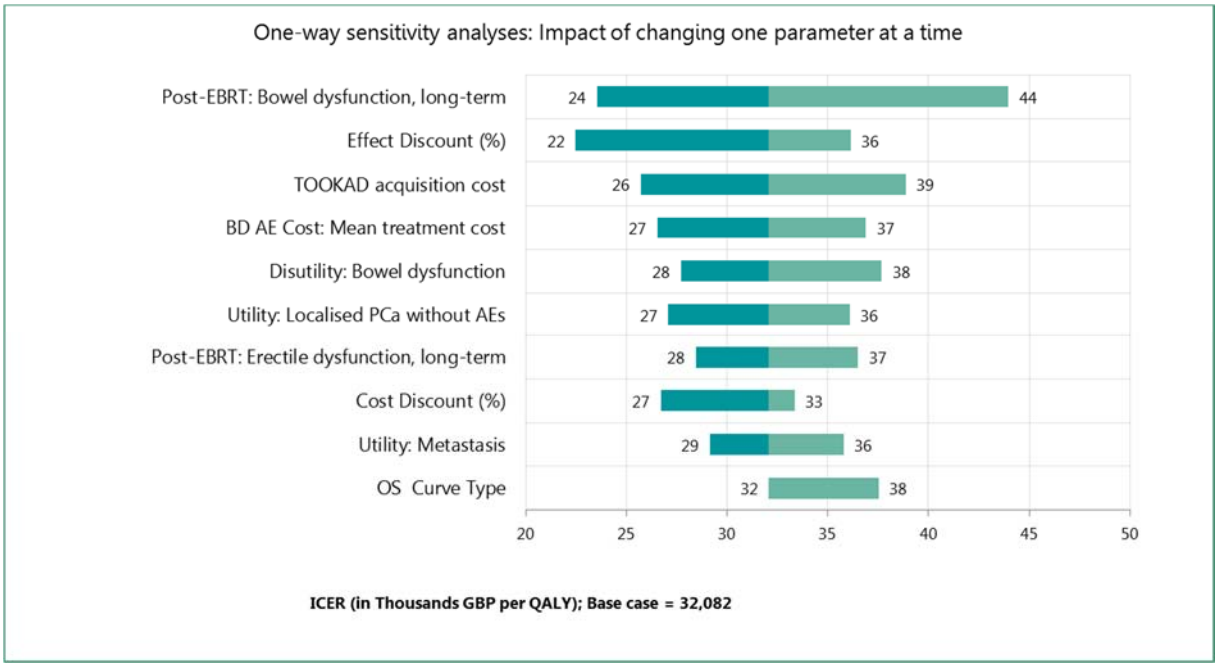


Not accounting for the TTRT and time horizon, the following variables have the greatest effect on the ICER when comparing padeliporfin VTP to EBRT (in order of importance):

- Post-radical EBRT: Long-term probability of BD
- Effect discount
- Padeliporfin (TOOKAD®) VTP acquisition cost
- Mean treatment cost for BD
- Disutility associated with BD
- Utility associated with localised PCa without AEs
- Post-EBRT: Long-term probability of ED
- Cost discount
- Utility associated with metastatic disease
- OS distribution

As BD is a well-documented side effect of EBRT, it's not surprising that the long-term probability of BD is a significant driver of the ICER. In addition, the ICER is also sensitive to the mean treatment cost for BD and disutility associated with BD.

Figure 35 OWSA results: padeliporfin VTP vs EBRT

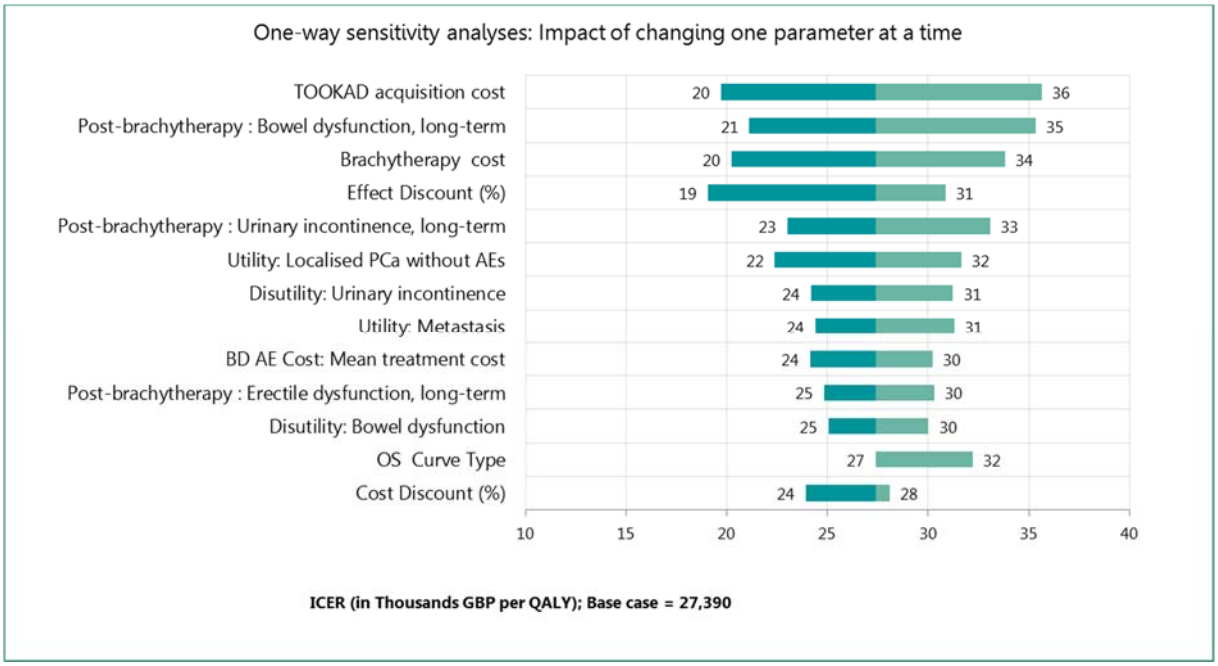


Not accounting for the TTRT and time horizon, the following variables have the greatest effect on the ICER when comparing padeliporfin VTP to brachytherapy (in order of importance):

- Padeliporfin (TOOKAD®) VTP acquisition cost
- Post-brachytherapy: Long-term probability of BD
- Brachytherapy cost
- Effect discount
- Post-brachytherapy: Long-term probability of UI
- Utility associated with localised PCa
- Disutility associated with UI
- Utility associated with metastatic disease
- Mean treatment cost for BD
- Post-brachytherapy: Long-term probability of ED
- Disutility associated with BD
- OS distribution
- Cost discount

Incremental QALYs between padeliporfin VTP and brachytherapy are lower than in any other comparison with padeliporfin VTP. Thus, the ICER is highly sensitive to incremental costs. As presented in the tornado diagram, padeliporfin (TOOKAD®) VTP acquisition cost and brachytherapy costs are significant drivers of the ICER. In addition, the ICER is sensitive to the long-term probability of BD or UI in patients who undergo brachytherapy. Other variables with a substantial impact on the ICER include the usual suspects such as the discount rate, mean treatment cost for BD, and utility/disutility values.

Figure 36 OWSA results: padeliporfin VTP vs brachytherapy



Scenario analysis

Scenario analyses were performed on key parameters that may have substantial effects on the results. **Table 67** describes the scenario analyses that were explored for each pairwise comparison (i.e. padeliporfin VTP vs comparator).

Table 67 Description of scenario analyses

Scenario	Value	Description
Time horizon	20 and 30 years	Explore the differences in costs or outcomes between the technologies being compared at different time horizons
Cycle length	3 months	Simulates the results of having implemented a half-cycle correction in the base case (i.e. using a six month cycle)

TTRT and TTM curves	Log-logistic Weibull Exponential	Test all distributions aside from gamma and Gompertz, which are clinically implausible due to the curves crossing (i.e. AS has TTRT benefit compared to padeliporfin VTP), which doesn't reflect the evidence from the PCM301 trial. As padeliporfin VTP and AS have equivalent TTM in the cost-effectiveness analysis, TTM was not included in the scenario analyses comparing padeliporfin VTP against AS.
OS curve	Lognormal	The lognormal distribution was the second best-fitting distribution for OS based on BIC fit statistics.
Localised PCa without AEs utility	0.96	Baseline utility value among PCM301 patients in indication population
AE disutility	UI: -0.14 ED: -0.10 UI: -0.14 ED: -0.10	Based on differences in Patient Oriented Prostate Utility Scale (PORPUS-U) mean utility scores between Prostate Cancer Index (PCI) score ≤25 and 100 for PCI urine function and PCI sexual function.[76]
Radical therapy distribution after padeliporfin VTP or AS	RP: 83% EBRT: 9% BT: 9%	In Godtman 2016, of the secondary treatment strategies following progress in cancer volume and/or Gleason score, 85 patients received RP and 18 patients received radiation therapy.[15] Assuming radiation therapy was split evenly between EBRT and brachytherapy, it was assumed that of the patients who received radical therapy following padeliporfin VTP or AS, 82.5%, 8.75% and 8.75% received RP, EBRT and brachytherapy, respectively.
Cost	RP: £5,418 RP: £7,362 RP: £13,193	RP cost based on number of procedures (prior to price adjustment for inflation):[77] • 200 procedures: £3467.35 • 150 procedures: £4225.11 • 100 procedures: £5740.61 • 50 procedures: £10,287.10 Adjusted to 2017-18 price levels using UK CPI Health Index (Series ID: D7BZ)
	RP: £6,344	Weighted average cost of HRG codes LB69Z Major Robotic, Prostate or Bladder Neck Procedures (Male); LB22Z Major Laparoscopic, Prostate or Bladder Neck Procedures (Male); LB21A Major Open, Prostate or Bladder Neck Procedures (Male), with CC Score 2+; and LB21B Major Open, Prostate or Bladder Neck Procedures (Male), with CC Score 0-1[78] Adjusted to 2017-18 price levels using UK CPI Health Index (Series ID: D7BZ)[74]
	EBRT: £3,952	The costs of EBRT by a NHS unit carrying out the IMRT procedure were calculated on the basis of 37 sessions within a 7-week time frame.[37] Based on HRG code SC22Z Deliver a Fraction of Treatment on a Megavoltage Machine,[78] the unit cost is £103.37 per session Adjusted to 2017-18 price levels using UK CPI Health Index (Series ID: D7BZ)
	EBRT: £5,292	The costs of EBRT by a NHS unit carrying out the IMRT procedure were calculated on the basis of 37 sessions within a 7-week time frame.[37] Based on HRG code SC23Z Deliver a Fraction of Complex Treatment on a Megavoltage Machine,[78] the unit cost is £138.42 per session Adjusted to 2017-18 price levels using UK CPI Health Index (Series ID: D7BZ)

TTRT, time to radical therapy; TTM, time to metastasis; VTP, vascular targeted photodynamic therapy; AS, active surveillance; OS, overall survival; BIC, Bayesian information criterion; PCa, prostate cancer; AEs, adverse events; UI; urinary incontinence; ED, erectile dysfunction; PORPUS-U (PORPUS-U); PCI, Prostate Cancer Index; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy; UK, United Kingdom; CPI, consumer price index; HRG, healthcare resource group; NHS, National Health Service; IMRT, intensity-modulated radiation therapy

Among the scenarios explored comparing padeliporfin VTP to AS, 17.6% (3/17) of the scenarios resulted in ICERs below the £30,000/QALY gained WTP threshold. The scenario where UI and ED disutility are assumed to be -0.14 and -0.10, respectively, led to the lowest ICER of £22,066/QALY gained (Δ-£21,894/QALY). The scenario where the Weibull distribution was used to model TTRT led to the highest ICER of £117,254/QALY gained (Δ+£73,295/QALY). Using a time horizon of 20 years and the log-logistic distribution to model TTRT also had a substantial negative impact on the ICER whereas using the exponential distribution to model TTRT, a disutility of -0.14 for UI, a disutility of -0.10 for ED and a cost of £13,193 for RP also had a substantial positive impact on the ICER.

Table 68 Scenario analysis: padeliporfin VTP vs active surveillance

Scenario		Total cost		Total QALY		ICER
		Padeliporfin VTP	Active surveillance	Padeliporfin VTP	Active surveillance	
Base case		26,714	16,609	11.64	11.41	43,960
Time horizon	20 years	25,349	14,740	10.42	10.23	57,319
	30 years	26,513	16,400	11.55	11.32	44,111
Cycle length	3 months	26,760	16,610	11.77	11.54	43,729
TTRT curves	Log-logistic	28,092	16,474	11.58	11.42	73,462
	Weibull	30,042	17,349	11.48	11.37	117,254
	Exponential	25,064	15,795	11.72	11.46	35,696
Localised PCa without AEs utility	0.96	26,714	16,609	12.72	12.49	43,960
AE disutility value	UI: -0.14	26,714	16,609	11.55	11.20	28,813
	ED: -0.10	26,714	16,609	11.45	11.11	29,976
	UI: -0.14 ED: -0.10	26,714	16,609	11.36	10.90	22,066
Radical therapy distribution after padeliporfin	RP: 51% EBRT: 24% BT: 24%	26,731	16,664	11.63	11.37	40,015

VTP or AS						
Cost	RP: £5,418	26,992	17,033	11.64	11.41	43,324
	RP: £7,362	27,549	17,882	11.64	11.41	42,054
	RP: £13,193	29,220	20,429	11.64	11.41	38,243
	RP: £6,344	27,258	17,438	11.64	11.41	42,719
	EBRT: £3,952	26,857	16,828	11.64	11.41	43,633
	EBRT: £5,292	27,039	17,105	11.64	11.41	43,217

VTP, vascular targeted photodynamic therapy; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; TTRT, time to radical therapy; AE, adverse event; UI, urinary incontinence; ED, erectile dysfunction; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

Among the scenarios explored comparing padeliporfin VTP to RP, 94.4% (17/18) of the scenarios resulted in ICERs below the £30,000/QALY gained WTP threshold. The scenario where cost of RP was £13,193 led to the lowest ICER of £3,870/QALY gained (Δ-£13,538/QALY). The scenario where the Weibull distribution was used to model TTRT and TTM led to the highest ICER of £40,399/QALY gained (Δ+£22,991/QALY). Using a time horizon of 20 years and the log-logistic distribution to model TTRT and TTM also had a substantial negative impact on the ICER whereas using the exponential distribution to model TTRT, disutility values of -0.14 and -0.10 for UI and ED (individually and concurrently), respectively, and a cost of £6,344 or £7,363 for RP also had a substantial positive impact on the ICER.

Table 69 Scenario analysis: padeliporfin VTP vs radical prostatectomy

Scenario		Total cost		Total QALY		ICER
		Padeliporfin VTP	RP	Padeliporfin VTP	RP	
Base case		26,714	18,752	11.64	11.19	17,408
Time horizon	20 years	25,349	16,658	10.42	10.03	22,499
	30 years	26,513	18,492	11.55	11.10	17,763
Cycle length	3 months	26,760	18,670	11.77	11.30	17,384
TTRT and TTM curves	Log-logistic	28,073	18,752	11.57	11.19	24,294
	Weibull	30,003	18,752	11.46	11.19	40,399
	Exponential	25,037	18,752	11.70	11.19	12,107
OS curve	Lognormal	26,699	18,680	11.53	11.07	17,615
Localised PCa without AEs utility	0.96	26,714	18,752	12.72	12.29	18,462
AE disutility value	UI: -0.14	26,714	18,752	11.55	10.84	11,347
	ED: -0.10	26,714	18,752	11.45	10.61	9,436

	UI: -0.14 ED: -0.10	26,714	18,752	11.36	10.27	7,318
Radical therapy distribution after padeliporfin VTP or AS	RP: 51% EBRT: 24% BT: 24%	26,731	18,752	11.63	11.19	18,121
Cost	RP: £5,418	26,992	19,719	11.64	11.19	15,904
	RP: £7,362	27,549	21,652	11.64	11.19	12,895
	RP: £13,193	29,220	27,450	11.64	11.19	3,870
	RP: £6,344	27,258	20,639	11.64	11.19	14,471
	EBRT: £3,952	26,857	18,752	11.64	11.19	17,722
	EBRT: £5,292	27,039	18,752	11.64	11.19	18,120
VTP, vascular targeted photodynamic therapy; RP, radical prostatectomy; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; TTRT, time to radical therapy; TTM, time to metastasis; OS, overall survival; AE, adverse event; UI, urinary incontinence; ED, erectile dysfunction; AS, active surveillance; EBRT, external beam radiation therapy; BT, brachytherapy						

Among the scenarios explored comparing padeliporfin VTP to EBRT, 33.3% (6/18) of the scenarios resulted in ICERs below the £30,000/QALY gained WTP threshold. The scenario where UI and ED disutility are assumed to be -0.14 and -0.10, respectively, led to the lowest ICER of £19,968/QALY gained (Δ-£12,114/QALY). The scenario where the Weibull distribution was used to model TTRT and TTM led to the highest ICER of £104,901/QALY gained (Δ+£72,818/QALY). Using a time horizon of 20 years, log-logistic distribution to model TTRT and TTM and cost of £13,193 for RP also had a substantial negative impact on the ICER whereas using the exponential distribution to model TTRT, disutility values of -0.14 and -0.10 for UI and ED (individually and concurrently), respectively, and a cost of £5,292 for EBRT also had a substantial positive impact on the ICER.

Table 70 Scenario analysis: padeliporfin VTP vs EBRT

Scenario		Total cost		Total QALY		ICER
		Padeliporfin VTP	EBRT	Padeliporfin VTP	EBRT	
Base case		26,714	16,999	11.64	11.34	32,082
Time horizon	20 years	25,349	14,871	10.42	10.17	42,160
	30 years	26,513	16,736	11.55	11.26	32,782
Cycle length	3 months	26,760	17,023	11.77	11.46	31,825

TTRT and TTM curves	Log-logistic	28,073	16,999	11.57	11.34	48,327
	Weibull	30,003	16,999	11.46	11.34	104,901
	Exponential	25,037	16,999	11.70	11.34	22,047
OS curve	Lognormal	26,699	16,923	11.53	11.22	32,333
Localised PCa without AEs utility	0.96	26,714	16,999	12.72	12.44	35,110
AE disutility value	UI: -0.14	26,714	16,999	11.55	11.20	28,400
	ED: -0.10	26,714	16,999	11.45	11.00	21,721
	UI: -0.14 ED: -0.10	26,714	16,999	11.36	10.87	19,968
Radical therapy distribution after padeliporfin VTP or AS	RP: 51% EBRT: 24% BT: 24%	26,731	16,999	11.63	11.34	34,056
Cost	RP: £5,418	26,992	16,999	11.64	11.34	33,002
	RP: £7,362	27,549	16,999	11.64	11.34	34,841
	RP: £13,193	29,220	16,999	11.64	11.34	40,359
	RP: £6,344	27,258	16,999	11.64	11.34	33,878
	EBRT: £3,952	26,857	18,047	11.64	11.34	29,095
	EBRT: £5,292	27,039	19,379	11.64	11.34	25,297

VTP, vascular targeted photodynamic therapy; EBRT, external beam radiation therapy; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; TTRT, time to radical therapy; TTM, time to metastasis; OS, overall survival; AE, adverse event; UI, urinary incontinence; ED, erectile dysfunction; AS, active surveillance; RP, radical prostatectomy; BT, brachytherapy

Among the scenarios explored comparing padeliporfin VTP to brachytherapy, 66.7% (12/18) of the scenarios resulted in ICERs below the £30,000/QALY gained WTP threshold. The scenario where UI and ED disutility are assumed to be -0.14 and -0.10, respectively, led to the lowest ICER of £10,987/QALY gained (Δ-£16,402/QALY). The scenario where the Weibull distribution was used to model TTRT and TTM led to the highest ICER of £142,749/QALY gained (Δ+£115,359/QALY). Using a time horizon of 20 years, log-logistic distribution to model TTRT and TTM and cost of £13,193 for RP also had a substantial negative impact on the ICER whereas using the exponential distribution to model TTRT and UI disutility of -0.14 also had a substantial positive impact on the ICER.

Table 71 Scenario analysis: padeliporfin VTP vs brachytherapy

Scenario		Total cost		Total QALY		ICER
		Padeliporfin VTP	BT	Padeliporfin VTP	BT	
Base case		26,714	19,871	11.64	11.39	27,390
Time horizon	20 years	25,349	17,930	10.42	10.22	36,987
	30 years	26,513	19,622	11.55	11.31	28,056
Cycle length	3 months	26,760	19,787	11.77	11.52	27,728
TTRT and TTM curves	Log-logistic	28,073	19,871	11.57	11.39	46,559
	Weibull	30,003	19,871	11.46	11.39	142,749
	Exponential	25,037	19,871	11.70	11.39	16,578
OS curve	Lognormal	26,699	19,815	11.53	11.28	27,552
Localised PCa without AEs utility	0.96	26,714	19,871	12.72	12.50	30,587
AE disutility value	UI: -0.14	26,714	19,871	11.55	10.95	11,430
	ED: -0.10	26,714	19,871	11.45	11.18	24,980
	UI: -0.14 ED: -0.10	26,714	19,871	11.36	10.73	10,987
Radical therapy distribution after padeliporfin VTP or AS	RP: 51% EBRT: 24% BT: 24%	26,731	19,871	11.63	11.39	29,469
Cost	RP: £5,418	26,992	19,871	11.64	11.39	28,504
	RP: £7,362	27,549	19,871	11.64	11.39	30,734
	RP: £13,193	29,220	19,871	11.64	11.39	37,422
	RP: £6,344	27,258	19,871	11.64	11.39	29,566
	EBRT: £3,952	26,857	19,871	11.64	11.39	27,963
	EBRT: £5,292	27,039	19,871	11.64	11.39	28,693

VTP, vascular targeted photodynamic therapy; BT, brachytherapy; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; TTRT, time to radical therapy; TTM, time to metastasis; OS, overall survival; AE, adverse event; UI, urinary incontinence; ED, erectile dysfunction; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy

Summary of sensitivity analyses results

The primary drivers of the cost-effectiveness model are:

- Time to radical therapy
- Time horizon
- Discount rate
- Padeliporfin (TOOKAD®) VTP acquisition cost

- Post-radical therapy: Long-term probabilities of ED
- Post-radical therapy: Long-term probabilities of BD
- Mean treatment cost for BD

Regardless of the comparator, these variables had a substantial impact on the ICER. As the benefit of padeliporfin VTP is predicated on either delaying or avoiding treatment with radical therapy, it's not surprising that the ICER would be particularly sensitive to TTRT. In addition, the benefit of padeliporfin VTP is accrued over time as patients spend more and more time accruing the benefit of not actualizing the deterioration in HRQoL associated with radical therapies. Therefore, the time horizon and the discount rate (effects) can have a significant impact on the ICER. Similarly, the post-radical therapy (i.e. RP, EBRT or brachytherapy) long-term probabilities of ED and BD are particular meaningful as these probabilities define the proportion of patients who accrue the costs and disutility values associated with ED and BD throughout a patient's entire time in the post-radical therapy health state. Mean treatment cost for BD is also a primary driver of the model results because all patients who experience BD incur this cost on a recurring basis.

In the scenario analyses, the disutility values associated with UI and ED led to a substantial change in the ICER, but the disutility values tested in this scenario were more than double those in the base case analysis. In the aggregate, i.e. looking at all the pairwise comparisons with padeliporfin VTP, the other variables do not consistently make a significant impact on the ICER.

At a WTP threshold of £30,000/QALY, the PSA results indicate that the probability of padeliporfin VTP being cost-effective is 23.2%, 86.9%, 42.4% and 51.9% against AS, RP, EBRT and brachytherapy, respectively.

B.3.9 Subgroup analysis

Subgroup analyses were not explored in the cost-effectiveness analysis.

B.3.10 Validation

Validation of cost-effectiveness analysis

Model validation was performed by a health economist not involved in the development of the original cost-effectiveness model. The checks involved in the technical validation are listed below:

- Detection of coding errors
- Sheet by sheet testing, including macros
- Check model parameters, testing of dropdown menus, names of cells, and all switches, including all sensitivity analyses
- Check if any elements seem redundant
- Check intended functionality of macros versus actual functionality, and for interpretability
- Run model with extreme values
- Additional checks:
    - Absence of bugs
    - Logical code structure
    - Appropriate transition of the conceptual model
    - Appropriateness of data and model

Model inputs were primarily based on the PCM301 trial and Ramsay et al 2015[37] analysis. In the Ramsay et al 2015 analysis, "all data inputs were scrutinised by the research team and the external advisory group to ensure that the model structure suitably reflected the decision problem addressed and that data inputs and methods to assemble these inputs seemed plausible."[37]

In addition, basing the cost-effectiveness model on the Ramsay et al 2015 analysis[37] inherently provides a level of external validity.

B.3.11 Interpretation and conclusions of economic evidence

In pairwise comparisons, padeliporfin VTP is cost-effective against RP and brachytherapy in the base case analysis using a WTP threshold of £30,000/QALY gained (£17,408/QALY gained and £27,390/QALY gained, respectively). Based on

PSA results and a WTP threshold of £30,000/QALY gained, padeliporfin is 23.2%, 86.9%, 42.4% and 51.9% likely to be cost-effective against AS, RP, EBRT and brachytherapy in unilateral low-risk, localised prostate cancer.

However, padeliporfin VTP shouldn't be compared against each comparator in isolation. Instead, it would be more meaningful to compare the costs and benefits of the currently available treatment options to a future scenario in which padeliporfin VTP is a treatment option. Padeliporfin VTP has the opportunity to be an important alternative to radical therapy for patients who choose active treatment either because of experienced symptoms, clinical indicators, clinician recommendation, or psychological factors (e.g., family history, other negative experiences, risk aversion). For these patients, focal treatment with padeliporfin VTP can reduce overtreatment by radical therapies and provide HRQoL benefits by avoiding the side effects associated with radical therapy. As such, padeliporfin VTP is not a direct comparator to AS. The current market distribution of currently available treatment options for unilateral low risk, localised prostate cancer is estimated to be 51%, 25%, 12% and 12% for AS, RP, EBRT and brachytherapy, respectively. Assuming padeliporfin VTP captures ***** of the market share in the future, mostly displacing RP and brachytherapy (***** and *****, respectively), the ICER of this future scenario with padeliporfin VTP compared to the current reality without padeliporfin is £19,549 per QALY gained assuming future market shares of *****, *****, *****, ***** and ***** for AS, padeliporfin VTP, RP, EBRT and brachytherapy, respectively.

Sensitivity analyses suggest that the ICER of padeliporfin VTP compared to RP is very robust. At a WTP threshold of £30,000/QALY gained, padeliporfin VTP is 86.9% likely to be cost-effective against radical prostatectomy. In addition, no variables that were explored in the OWSA yielded an ICER over £22,000/QALY gained. Moreover, only four variables explored met the £4,000/QALY gained threshold criteria to be included into the tornado diagram suggesting that all other variables have a very minimal impact on the ICER (i.e. the difference between the minimum and maximum ICER is less than £4,000/QALY gained). Scenario analyses corroborate these findings as only two scenarios led to an ICER over £30,000/QALY gained, i.e. time horizon of 10 years and Weibull distribution for TTRT and TTM. Given that padeliporfin VTP is predicted to mostly displace RP, these results suggest that the

ICER comparing the world without padeliporfin VTP to the world with padeliporfin VTP is robust; indicating that padeliporfin VTP is likely a cost-effective alternative to radical therapy for unilateral low risk, localised prostate cancer.

The key strength of this analysis is its reliance primarily on a recent phase 3 RCT (PCM301) and comprehensive NIHR-funded economic evaluation in the UK NHS context, which was thoroughly validated:[37] "With respect to face validity the structure of the model and all data inputs were scrutinised by the research team and the external advisory group to ensure that the model structure suitably reflected the decision problem addressed and that data inputs and methods to assemble these inputs seemed plausible."

The results of this analysis suggest that the introduction of padeliporfin VTP would likely be a cost-effective option to reduce overtreatment with radical therapy, thereby increasing long-term HRQoL in patients diagnosed with unilateral low risk, localised prostate cancer.

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Ref Type: Report

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B.5 Appendices

The SmPC, EPAR and checklist of confidential information are supplied as separate documents. The rest of the appendices (listed below) are supplied in a consolidated document.

- 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: Clinical outcomes and disaggregated results from the model
- Appendix K: Checklist of confidential information

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Single technology appraisal

Padeliporfin for treating localised prostate cancer [ID866]

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The Evidence Review Group, Aberdeen HTA, and the technical team at NICE have looked at the submission received on Tuesday 27th February 2018 from Steba Biotech. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on 4th April**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

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If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sharlene Ting, Technical Lead (Sharlene.Ting@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Technical Adviser – Technology Appraisals
Centre for Health Technology Evaluation
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Section A: Clarification on effectiveness data

PCM301 trial: 'indication population'

A1. Company submission (CS), section B.2.3, tables 9 and 10 (pages 28-35). The company's PCM301 trial's 'indication population' includes 80 participants receiving vascular-targeted photodynamic therapy (VTP) and 78 receiving active surveillance (AS). The company submission describes the exclusion criteria that were used to determine this subgroup: bilateral disease and 'very-low-risk' patients. Table 9 confirms that all participants in this subgroup had unilateral disease. However, table 10 shows higher numbers of participants had unilateral disease in the full trial population; 157 receiving VTP and 163 receiving AS.

- Table 10 does not provide details of the number of participants in the different risk categories, that is 'very-low risk' and 'low-risk'. Please provide this information.
    - If different, please account for the 77 participants receiving VTP and 85 receiving AS who have been excluded from the 'indication population'.

Clinical effectiveness results

Relative risks

A2. PRIORITY QUESTION. CS, section B.2.6, table 13 (page 41). The relative risks of VTP compared with active surveillance are presented for 2 outcomes (negative biopsy in lobe diagnosed at baseline and negative biopsy in both lobes). The calculations of the relative risks rely on the total sample sizes for each group as the denominators. This assumes that people without a negative biopsy all had a positive biopsy. However, from the table, 11 people in the VTP group and 34 people in the active surveillance group did not have a biopsy. As a consequence, the relative risks are skewed in favour of VTP. Please clarify what effect this has on the economic model.

Safety data

A3. CS, section B.2.10, table 22 (pages 54-56). Table 22 provides the treatment-emergent adverse effects by treatment arm for the safety population. Please provide the total number of participants in each broad group of symptoms (for example, blood and lymphatic system disorders, cardiac disorders, endocrine disorders) by treatment arm.

A4. CS, section B.2.10, table 23 (page 57). Table 23 refers to the adverse events in the 'indication population'.

- It states that the number of participants in the active surveillance group is 207. Please clarify.
- Please clarify the difference between the groups 'VTP' and 'VTP drug, device or VTP procedure related'.

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- The number of participants reporting Grade 1 AEs are higher in the 'VTP drug, device or VTP procedure related' group (n=22) than the 'VTP' group (n=18). Please clarify.

Loss to follow up

A5. CS, section B.2.10, 'Limitation' (page 61). The company submission states " … *radical therapy was considered a failure in the PCM301 trial, which led to discontinuation of follow-up in some cases*". Please provide the number of participants whose follow up was discontinued because of having radical therapy.

Appendix D

Search strategy

A6. Appendix D, section D.1.1, Tables 1 and 2 (pages 7-8). Table 1 specifies the time frame of the searches as '2008 or later' while table 2 specifies time frames of '2008 to 2017/18' and for conference abstracts only, '2014-2017'. Please provide the rationale for the time frames specified in the search strategy eligibility criteria.

Flow diagram

A7. Appendix D, section D.1.2, Tables 16-19 (pages 32-45). The flow diagrams (labelled Tables 16 and 17) report that 215 and 270 full-text articles were excluded respectively. However, tables 18 and 19 which provide the 'complete reference list of excluded studies' only include 68 and 53 references respectively. Please clarify and provide the correct versions, if necessary.

Extracted data

A8. Appendix D, section D.1.2, Tables 20-22 (pages 46-134). Tables 20 to 22 provide raw extracted data on the efficacy and safety (table 20) and rate of radical therapy (table 21) for VTP and active surveillance, and radical therapy safety (table 22).

- Please clarify how these tables have been used to inform the main submission.
    - If not provided in the main submission, please provide a summary of the results from these tables.
- The tables are truncated on the right margins. Please provide complete versions of these tables.

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Section B: Clarification on cost-effectiveness data

Economic model

B1. CS, section B.2.10, table 19 (page 51) and B.3.2 (page 86). The company submission did not include a second VTP treatment in its model because it is not recommended and "*There are insufficient patients who have underwent retreatment of the ipsilateral lobe … to determine the efficacy and safety of a second VTP procedure*" (CS, page 86). However, in the 'indication population', 5 people had received retreatment with VTP (Table 19).

- Please provide further rationale for excluding second VTP treatments in the model.
- Please clarify how second VTP treatments were accounted for in the 'time to radical therapy' analysis.
- Please explore the impact of adding the costs of second VTP treatments in the model.

Clinical parameters and variables

PCM301 and ProtecT

B2. PRIORITY QUESTION. CS, section B.3.3 (page 93). The proportion of patients in each health state at each time point in the partitioned survival model is derived using 3 parametric survival curves; time to radical therapy (TTRT), time to metastasis (TTM) and time to prostate cancer-related death (overall survival, OS). PCM301 is used to derive TTRT for the 'indication' subgroup, while the ProtecT trial is used to derive TTM and OS.

- Please further clarify to what extent the populations in PCM301 and ProtecT are comparable. In particular, please consider risk status, stage of disease, prostate specific antigen (PSA) levels and any other observable factors that could influence the risk of disease progression.

Time to metastasis and disease progression

B3. CS, section B.3.3 (page 105). Time to metastasis (TTM) is derived from the outcome 'disease progression' defined as "*death due to prostate cancer or its treatment; evidence of metastatic disease; long-term androgen-deprivation therapy; clinical T3 or T4 disease; and ureteric obstruction, rectal fistula, or the need for a permanent catheter when those are not considered to be a complication of treatment in the ProtecT trial*" (CS, page 105).

- Please clarify to what extent ProtecT's 'disease progression' definition is consistent with the health state costs and utility values applied to people who progress in the model. For example, do progression costs assume that everyone who progresses have distant metastases, although in ProtecT's definition, some people progressing have local progression?

Time to radical therapy

B4. PRIORITY QUESTION. CS, section B.3.3 (pages 93-103). The ProtecT trial shows a substantially lower rate of progression to radical therapy in patients having active

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surveillance recruited from UK centres compared with the observed and extrapolated rate based on data from PCM301. In particular, the base case extrapolation (lognormal) projects that ~90% of patients having active surveillance in PCM301 will undergo radical therapy by 10 years compared with 55% in ProtecT.

- Please provide a scenario analysis using the ProtecT data to model time to radical therapy on active surveillance, and estimate the time to radical therapy in the VTP arm relative to this baseline. This may require the use of time dependent hazard ratios derived from PCM301.

B5. PRIORITY QUESTION. CS, section B.3.3, figures 18-20 (pages 100-102). The tails of the Kaplan Meier curves for time to radical therapy in PCM301 appear to be converging slightly and the 'best fitting' generalised gamma curves appear to be a good visual fit to the observed data.

- Please provide an exploratory scenario analysis using the generalised gamma function for time to radical therapy, and allow the curves for active surveillance and VTP to converge but not cross.

Utility values

B6. CS, section B.3.2, tables 36 and 37 (pages 90-92) and section B.3.4 (pages 114-116). The company's model used baseline utility values from Ramsay (2015), a literature review of studies that derived utility values using different methods (EQ-5D, HUI, SF-6D and direct preference elicitation methods). PCM301 collected EQ-5D data at baseline, 12 and 24 months for the 'indication population' (preferred approach for deriving utilities by NICE).

- Please clarify the rationale for not using the EQ-5D data from PCM301 to derive the baseline utility values in the partitioned survival model.
- Please explore the impact of adverse events on utility and cost-effectiveness estimates using the available EQ-5D data from PCM301.

Adverse events

B7. PRIORITY QUESTION. CS, section B.2.10 (page 59), section B.3.4 (pages 114-122) and section B.3.5 (pages 130-132). The company's model includes costs and utility decrements associated with three specific adverse events; urinary incontinence (UI), bowel dysfunction (BD) and erectile dysfunction (ED). PCM301 provides adverse event rates for the pre-radical therapy health state, while Ramsey (2015) provides these rates for the post-radical therapy health state.

- Please clarify to what extent the original study populations used in Ramsay (2015) are comparable to the 'indication population' from PCM301. In particular, please consider stage of disease, baseline prevalence of UI, BD and ED and any other factors that might influence the prevalence of UI, BD and ED at follow-up.
- Please further justify excluding the costs and utility decrements associated with VTP-specific adverse events listed in Table 25 (CS, page 59).

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Costs

B8. CS, section B.3.5, table 49 (pages 123-124).

- The cost of physical examinations and nurse consultations in the VTP administration costs are based on primary care, not secondary care. Please justify the rationale for using primary care costs.
- The company submission states that a lease will be offered for the use of laser generator at a unit cost per VTP procedure.
    - Please clarify whether the leasing fee includes maintenance.
    - Please provide the full cost of a laser generator.
        - Please explore the impact of using the full cost of a laser generator on the cost-effectiveness estimates.

Excel model

B9. PRIORITY QUESTION. Excel spreadsheet "ID866_Padeliporfin VTP_CE Model_2018Feb27_ACIC - JP 280218 [ACIC]". The company uses ProtecT trial data on 'prostate cancer specific survival' and 'freedom from disease progression' (including prostate cancer specific deaths) to model overall survival and disease progression (time to metastasis). Survival curves from the ProtecT trial on 'prostate cancer specific survival' and 'freedom from disease progression' are used to partition the cohort between pre-progressed, progressed (to metastasis) and dead states. The company adjusts the 'prostate cancer specific survival' curve to include general population all-cause mortality, but it does not adjust the 'freedom from disease progression' curve. As a result, for people starting the model on radical treatment, overall survival is always lower than 'freedom from disease progression'. The apparent consequence is that no one in the radical treatment arms progress to metastasis before they die.

- Please check the calculations and inputs used in cells K4:V164 of the 'CurveOverview' worksheet in the company's model.

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Yours sincerely

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- Table 10 does not provide details of the number of participants in the different risk categories, that is 'very-low risk' and 'low-risk'. Please provide this information.
    - If different, please account for the 77 participants receiving VTP and 85 receiving AS who have been excluded from the 'indication population'.

Response: Please see **Table 1** for the number of participants in the different risk categories and those retained in the analyses of progression to radical therapy (RT).

Of the 157 unilateral patients receiving VTP, 70 were very low risk and 87 were low risk but not very low risk. Of these, 80 patients were retained in the analyses of progression to RT (as per the EMA submission). 7 patients were excluded from the analyses for the following reasons: i) 3 were over 75 years old at randomization and as a result had uncertain eligibility to radical therapy as their life expectancy is potentially less than 10 years; ii) 1 patient had a co-morbidity detected after randomization (myocardial infarction) that would likely result in RT ineligibility; iii) 3 patients had a time from diagnosis to randomization greater than 2 years that could bias the outcome of time to radical therapy.

Of the 163 unilateral patients receiving AS, 83 were very low risk and 80 were low risk but not very low risk. Of these, 78 patients were retained in the analyses of progression to RT (as per the EMA submission). 2 patients were excluded from the analyses for the following reason: they were over 75 years old at randomization and as a result had uncertain eligibility to radical therapy as their life expectancy is potentially less than 10 years. No AS patient in the indication subgroup was detected with significant co-morbidities after randomization that could affect eligibility to RT or had a time from diagnosis to randomization over 2 years.

Table 1 Distribution of patients along the 3 sub-groups of interest

	Overall ITT population			Patients retained in analyses of progression to RT		
Sub groups	VTP N=206 n (%)	AS N=207 n (%)	Total N=413 n (%)	VTP [a] N=189 n (%)	AS [b] N=193 n (%)	Total [c] N=382 n (%)

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Indication population (unilateral, low risk / not very low risk)	87 (42%)	80 (39%)	167 (40%)	80 (42%)	78 (40%)	158 (41%)
Unilateral, very low risk disease	70 (34%)	83 (40%)	153 (37%)	66 (35%)	74 (38%)	140 (37%)
Bilateral disease	49 (24%)	44 (21%)	93 (23%)	43 (23%)	41 (21%)	84 (22%)

[a] 17 subjects excluded from analyses: 6 with age at randomization > 75 years, 3 with co-morbidities detected after randomization, 8 subjects diagnosed for more than 2 years before randomization

[b] 14 subjects excluded from analyses: 6 with age at randomization > 75 years, 1 with co-morbidities detected after randomization, 7 subjects diagnosed for more than 2 years before randomization

[c] 31 subjects excluded from analyses: 12 with age at randomization > 75 years, 4 with co-morbidities detected after randomization, 15 subjects diagnosed for more than 2 years before randomization

Clinical effectiveness results

Relative risks

A2. PRIORITY QUESTION. CS, section B.2.6, table 13 (page 41).

The relative risks of VTP compared with active surveillance are presented for 2 outcomes (negative biopsy in lobe diagnosed at baseline and negative biopsy in both lobes). The calculations of the relative risks rely on the total sample sizes for each group as the denominators. This assumes that people without a negative biopsy all had a positive biopsy. However, from the table, 11 people in the VTP group and 34 people in the active surveillance group did not have a biopsy. As a consequence, the relative risks are skewed in favour of VTP. Please clarify what effect this has on the economic model.

Response: The absence of biopsy at Month 24 does not have an impact on the economic model, as the key clinical trial data used in the model are the rate of progression to RT over time, and the incidence and duration of ED, UI, and BD toxicities of Grade 2 and above.

For the sake of completeness, the Company is providing a censored analysis of the negative biopsy endpoint, which corrects for the disproportional rate of RT and missing biopsies at Month 24 observed in the AS arm (see **Table 2**). As a reminder, Table 13 in the CS is an analysis of biopsy at Month 24 without censoring of patients prior to initiation of radical therapy. Patients who initiate radical therapy prior to Month 24 have missing biopsy data as these patients could not be biopsied at Month 24. Hence, the higher proportion of missing biopsies in the active surveillance group. **Table 2** presents the absence of positive histology results by Month 24, rather than at Month 24, by using the results of Month 12 biopsy whenever biopsy data is missing at Month 24. In doing so, the numbers of patients with missing biopsies are reduced and more comparable, with only 1 patient in the VTP group and 5 patients in the active surveillance group. The relative risks in this censored analysis remain comparable to the ones in the uncensored analysis: respectively 4.63 (95%CI=2.70-7.94) vs. 4.61 (95%CI=2.60-8.16) for negative biopsy in the lobe diagnosed at baseline, and 4.39 (95%CI=2.18-8.83) vs. 4.39 (95%CI=2.18-8.83) for negative biopsy in both lobes.

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Table 2 Absence of positive histology results by Month 24 based on lobe diagnosed at baseline (indication population)*

Number of Subjects with	VTP N = 80	AS N = 78	RR (95%CI) (VTP vs AS)
Negative biopsy in lobe diagnosed at baseline, n (%)	57 (71.3)	12 (15.4)	4.63 (2.70-7.94)
Negative biopsy in both lobes, n (%)	36 (45.0)	8 (10.3)	4.39 (2.18-8.83)
Positive biopsy in lobe diagnosed at baseline, n (%)	22 (27.5)	61 (78.2)	
No biopsy for any reasons†, n (%)	1 (1.3)	5 (6.4)	

VTP: vascular-targeted photodynamic therapy; AS: active surveillance; RR: relative risk; CI: Confidence Interval.

* Month 12 biopsy results used if biopsy data missing for Month 24

† Radical therapy prior to Month 12, study withdrawal, medical reason, subject refusal

Safety data

A3. CS, section B.2.10, table 22 (pages 54-56).

Table 22 provides the treatment-emergent adverse effects by treatment arm for the safety population. Please provide the total number of participants in each broad group of symptoms (for example, blood and lymphatic system disorders, cardiac disorders, endocrine disorders) by treatment arm.

Response: Please see **Table 3**, which provides the total number of participants in each broad group of symptoms by treatment arm.

Table 22 in the CS was based on "Table 3: Treatment-emergent adverse effects" in the PCM301 pivotal trial publication by Azzouzi AR et al. 2017 in *Lancet Oncology*. In turn, this table was derived from Table 14.3.1.3 in Appendix 14 of the PCM301 clinical study report (CSR). Thus, Table 3 in Azzouzi AR et al. 2017, and therefore Table 22 in the CS, were not labelled accurately. Rather than "treatment-emergent" adverse effects, it should have been labelled "randomisation-emergent" adverse effects. Per the CSR:

> *The definition of emergent AEs was modified to start after randomisation. Because subjects in the active surveillance group were given no treatment after randomisation while the TOOKAD® VTP procedure might have taken place several weeks after randomisation, this change provided comparable periods of AE collection between the 2 treatment groups.*

In addition, while reporting the total number of participants in each broad group of symptoms by treatment arm, the Company noticed the following transcription errors, which are updated in **Table 3**.

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- Inguinal hernia, Grade 3, VTP group: 4 (2%) → 2 (1%)
- Rectal haemorrhage, Grade 3, VTP group: 4 (2%) → 1 (<1%)
- Device failure, Grade 1-2, VTP group: 0 → 1 (<1%)
- Osteoarthritis, Grade 3, VTP group: 2 (1%) → 1 (<1%)
- Headache, Grade 1-2, AS group: 2 (<1%) → 1 (<1%)
- Dysuria, Grade 3, VTP group: 0 → 3 (2%)
- Urethral stenosis: Grouped under "Reproductive system and breast disorders" in Table 22 in CS. In **Table 3** below, was moved to "Renal and urinary disorders,"

Table 3 provides details by organ for Grade 1–2 when the event occurred in ≥10% of the patients in at least one group) and all grade 3 and 4 randomisation-emergent adverse events that occurred during the study period.

Table 3 Randomisation-emergent adverse effects by treatment arm (safety population)

	VTP (N=197)*			Active surveillance (N=207)		
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders	**3 (1.5%)**	**1 (<1%)**	**0**	**3 (1.4%)**	**0**	**0**
Thrombocytopenia	0	1 (<1%)	0	0	0	0
Cardiac disorders	**6 (3%)**	**2 (1%)**	**1 (<1%)**	**3 (1.4%)**	**2 (<1%)**	**1 (<1%)**
Angina unstable	0	0	1 (<1%)	0	0	0
Atrial fibrillation	0	1 (<1%)	0	1 (<1%)	0	0
Myocardial infarction	0	1 (<1%)	0	0	2 (<1%)	1 (<1%)
Endocrine disorders	**1 (<1%)**	**1 (<1%)**	**0**	**2 (<1%)**	**0**	**0**
Hyperthyroidism	1 (<1%)	1 (<1%)	0	0	0	0
Eye disorders	**6 (3%)**	**2 (1%)**	**0**	**0**	**0**	**0**
Cataract	0	2 (1%)	0	0	0	0
Gastrointestinal disorders	**65 (33%)**	**4 (2%)**	**0**	**17 (8%)**	**1 (<1%)**	**0**
Abdominal pain	4 (2%)	1 (<1%)	0	1 (<1%)	0	0
Gastrointestinal haemorrhage	0	0	0	0	1 (<1%)	0
Inguinal hernia	4 (2%)	2 (1%)	0	1 (<1%)	0	0
Rectal haemorrhage	4 (2%)	1 (<1%)	0	0	0	0

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General disorders and administration site conditions	**17 (9%)**	**1 (<1%)**	**0**	**11 (5%)**	**1 (<1%)**	**0**
Device failure	1 (<1%)	1 (<1%)	0	0	0	0
Pyrexia	4 (2%)	0	0	2 (<1%)	1 (<1%)	0
Immune system disorders	**2 (1%)**	**2 (1%)**	**1 (<1%)**	**2 (<1%)**	**0**	**0**
Anaphylactic reaction	0	0	1 (<1%)	0	0	0
Drug hypersensitivity	1 (<1%)	2 (1%)	0	0	0	0
Infections and infestations	**55 (28%)**	**4 (2%)**	**0**	**33 (16%)**	**4 (2%)**	**0**
Epididymitis	4 (2%)	1 (<1%)	0	0	0	0
Liver abscess	0	0	0	0	1 (<1%)	0
Otitis externa	0	0	0	0	1 (<1%)	0
Orchitis	6 (3%)	1 (<1%)	0	0	0	0
Staphylococcal infection	1 (<1%)	0	0	0	1 (<1%)	0
Urinary tract infection	19 (10%)	2 (1%)	0	7 (3%)	2 (<1%)	0
Injury, poisoning, and procedural complications	**34 (17%)**	**2 (1%)**	**0**	**4 (2%)**	**4 (2%)**	**1 (<1%)**
Accident	0	1 (<1%)	0	0	0	0
Craniocerebral injury	0	1 (<1%)	0	0	0	0
Procedural pain	2 (1%)	0	0	2 (<1%)	1 (<1%)	0
Investigations	**11 (6%)**	**2 (1%)**	**0**	**3 (1%)**	**0**	**0**
Fibrin D-dimer increased	2 (1%)	2 (1%)	0	0	0	0
Musculoskeletal and connective tissue disorders	**18 (9%)**	**11 (6%)**	**1 (<1%)**	**14 (7%)**	**4 (2%)**	**1 (<1%)**
Arthralgia	3 (2%)	2 (1%)	0	4 (2%)	0	0
Osteoarthritis	2 (1%)	1 (<1%)	0	3 (1%)	1 (<1%)	0
Nervous system disorders†	**19 (10%)**	**3 (2%)**	**0**	**9 (4%)**	**1 (<1%)**	**0**
Headache†	3 (2%)	1 (<1%)	0	1 (<1%)	0	0

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Neoplasms benign, malignant, and unspecified	**4 (2%)**	**3 (2%)**	**0**	**2 (<1%)**	**2 (<1%)**	**0**
Ear neoplasm	0	0	0	0	1 (<1%)	0
Neuroendocrine carcinoma	0	1 (<1%)	0	0	0	0
Tongue cancer recurrent	0	0	0	0	1 (<1%)	0
Tonsillar neoplasm	0	1 (<1%)	0	0	0	0
Ureteric cancer metastatic	0	0	0	0	1 (<1%)	0
Ureteric cancer regional	0	0	0	0	1 (<1%)	0
Nervous system disorders	**16 (8%)**	**3 (2%)**	**3 (2%)**	**4 (2%)**	**6 (3%)**	**1 (<1%)**
Cerebrovascular accident	0	2 (1%)	0	0	0	0
Transient ischaemic attack	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0
Psychiatric disorders	**15 (8%)**	**1 (<1%)**	**0**	**6 (3%)**	**1 (<1%)**	**0**
Depression	4 (2%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0
Renal and urinary disorders	**125 (63%)**	**8 (4%)**	**0**	**36 (17%)**	**2 (<1%)**	**0**
Dysuria	51 (26%)	3 (2%)	0	5 (2%)	0	0
Haematuria	55 (28%)	1 (<1%)	0	6 (3%)	0	0
Micturition urgency	21 (11%)	0	0	2 (<1%)	0	0
Pollakiuria	20 (10%)	0	0	6 (3%)	0	0
Urethral stenosis	1 (<1%)	1 (<1%)	0	0	0	0
Urinary incontinence	17 (9%)	2 (1%)	0	9 (4%)	1 (<1%)	0
Urinary retention	29 (15%)	3 (2%)	0	1 (<1%)	1 (<1%)	0
Reproductive system and breast disorders	**112 (57%)**	**9 (5%)**	**0**	**37 (18%)**	**4 (2%)**	**0**
Ejaculation failure	14 (7%)	2 (1%)	0	1 (<1%)	0	0
Erectile dysfunction	72 (37%)	2 (1%)	0	21 (10%)	3 (1%)	0
Perineal pain	29 (15%)	1 (<1%)	0	1 (<1%)	0	0

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Prostatic pain	5 (3%)	1 (<1%)	0	0	0	0
Prostatitis	7 (4%)	3 (2%)	0	9 (4%)	1 (<1%)	0
Respiratory, thoracic, and mediastinal disorders	**14 (7%)**	**0**	**1 (<1%)**	**7 (3%)**	**0**	**0**
Bronchospasm	0	0	1 (<1%)	0	0	0
Skin and subcutaneous tissue disorders	**12 (6%)**	**1 (<1%)**	**0**	**10 (5%)**	**0**	**0**
Purpura	0	1 (<1%)	0	0	0	0
Surgical and medical procedures	**5 (3%)**	**8 (4%)**	**3 (2%)**	**3 (1%)**	**2 (<1%)**	**1 (<1%)**
Cataract operation	2 (1%)	1 (<1%)	0	1 (<1%)	0	0
Facial operation	0	1 (<1%)	0	0	0	0
Knee arthroplasty	0	1 (<1%)	0	0	0	0
Vascular disorders	**20 (10%)**	**0**	**0**	**8 (4%)**	**2 (<1%)**	**0**
Phlebitis	0	0	0	2 (<1%)	1 (<1%)	0
Thrombosis	1 (<1%)	0	0	0	1 (<1%)	0

VTP: vascular-targeted photodynamic therapy.

Data are n (%). Grade 1–2 (when the event occurred in ≥10% of the patients in at least one group) and all grade 3 and 4 randomisation-emergent adverse events that occurred during the study period. The worst grade reported for each patient is listed. Events are listed by preferred terms (Medical Dictionary for Regulatory Activities version 18·0), and graded by National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). One patient in the VTP group died due to myocardial infarction during mountain climbing about 8 months after completing treatment; the death was assessed to be not related to treatment.

*Nine men randomly assigned to VTP did not receive treatment and were excluded from the safety analysis.

†One patient in the AS group had missing data regarding the grade of the adverse event for nervous system disorders/headache and is not included in the table

Source: CLIN1001 PCM301 Clinical Study Report[1]

A4. CS, section B.2.10, table 23 (page 57).

Table 23 refers to the adverse events in the 'indication population'.

- It states that the number of participants in the active surveillance group is 207. Please clarify.
- Please clarify the difference between the groups 'VTP' and 'VTP drug, device or VTP procedure related'.

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- The number of participants reporting Grade 1 AEs are higher in the 'VTP drug, device or VTP procedure related' group (n=22) than the 'VTP' group (n=18). Please clarify.

Response:

- Table 23 states that the number of participants in the active surveillance group is 207, which is a typo. The number of participants in the active surveillance group should have been written as N=78 (see **Table 4**).
- The 'VTP' group includes adverse events, regardless of relationship to the treatment (drug, device, or procedure). The 'VTP drug, device or VTP procedure related' group includes only adverse events related to the drug, device, or procedure, based on the evaluation of the investigator.
    - In any of the groups, patients are assigned to the Grade severity group based on the highest Grade AE they encountered. As, the 'VTP drug, device or VTP procedure related' group includes a narrower set of AEs, patients can be assigned to lower grade group that in the 'VTP' group. For example, if a patient randomized to VTP had a grade 1 adverse event related to the drug, device, or VTP procedure and a grade 2 adverse event unrelated to the drug, device, or procedure, the patient would have been reported as having a grade 2 adverse event in the 'VTP' group and a grade 1 adverse event in the 'VTP drug, device or VTP procedure related' group. To be more accurate, row headers have been updated (see **Table 4**) to "Subjects with at least one Grade X AE, but no higher" for clarification.

Table 4 Adverse events (AEs) by severity (indication population)

Number of Subjects with AE in Category	**VTP N = 79 n (%)**	**VTP drug, device or VTP procedure related N = 79 n (%)**	**Active surveillance N = 78 n (%)**
Subjects with at least one Grade 1 (mild) AE, but no higher	18 (22.8)	22 (27.8)	13 (16.7)
Subjects with at least one Grade 2 (moderate) AE, not no higher	44 (55.7)	36 (45.8)	19 (24.4)
Subjects with at least one Grade 3 (severe) AE, but no higher	11 (13.9)	5 (6.3)	6 (7.7)
Subjects with at least one Grade 4 (life-threatening) AE, but no higher	1 (1.3)	0	1 (1.3)
Subjects with at least one Grade 5 (death) AE, but no higher	0	0	0

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Number of Subjects with AE in Category	VTP N = 79 n (%)	VTP drug, device or VTP procedure related N = 79 n (%)	Active surveillance N = 78 n (%)
AE: adverse event; VTP: vascular-targeted photodynamic therapy Source: EMA Assessment Report Tookad[2]			

Loss to follow up

A5. CS, section B.2.10, 'Limitation' (page 61).

The company submission states " *… radical therapy was considered a failure in the PCM301 trial, which led to discontinuation of follow-up in some cases*". Please provide the number of participants whose follow up was discontinued because of having radical therapy.

Response: The number of participants whose follow up was discontinued after radical therapy is presented in **Table 5**. In total, about 13% (9 out of 72) of patients who had radical therapy during the initial RCT period of 24 months had subsequent loss to follow up. Out of the 60 and 12 patients who radical therapy in PCM301 during the randomized clinical trial time period in the AS and VTP group, 6 (10%) and 3 (25%) had follow up discontinued after radical therapy, respectively.

In addition, reporting at M24 of prostate-specific antigen (PSA) testing and health-related quality of life (HRQoL) instruments was 15% to 17% lower among patients who ever received radical therapy during the RCT time period compared to patients who did not receive radical therapy during the RCT time frame. The difference was statistically significant for all parameters, as illustrated in **Table 6**.

Table 5 Number of participants with loss to follow-up after radical therapy

	AS N = 207	VTP N = 206	Total N = 413
Patients ever receiving RT during RCT	60	12	72
Patients ever receiving RT during RCT with no visit after date of RT, n (%)	6 (10%)	3 (25%)	9 (13%)
AS, active surveillance; VTP, vascular-targeted photodynamic therapy; RT, radical therapy; RCT, randomized clinical trial *Exclude patient 52811-24 who had RT at 26.9 months and patient 52811-08 who had RT at 27 months			

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Table 6 Data availability among patients ever receiving RT vs patients never receiving RT

Description	RT reported during RCT time period* Total N = 72	No RT reported during RCT time period Total N = 341	Difference RT vs. No RT Total	Comparison RT vs. No RT Total p-value
Available record of M24 PSA test, n (%)	49 (68%)	290 (85%)	17%	<0.01
Available record of M24 IPSS score, n (%)	48 (67%)	281 (82%)	16%	<0.01
Available record of M24 IIEF score, n (%)	48 (67%)	280 (82%)	15%	<0.01
Available record of M24 EQ-5D score, n (%)	47 (65%)	274 (80%)	15%	<0.01

RT, radical therapy; RCT, randomised clinical trial; AS, active surveillance; VTP, vascular-targeted photodynamic therapy; PSA, prostate-specific antigen; IPSS, International Prostate Symptom Score; IIEF, International Index of Erectile Function
Note: Patient 25042-05 receiving 'ELIGARD.45' hormonal therapy was not counted as patient ever receiving RT
* Excludes patient 52811-24 who had RT at 26.9 months and patient 52811-08 who had RT at 27 months

Appendix D

Search strategy

A6. Appendix D, section D.1.1, Tables 1 and 2 (pages 7-8).

Table 1 specifies the time frame of the searches as '2008 or later' while table 2 specifies time frames of '2008 to 2017/18' and for conference abstracts only, '2014-2017'. Please provide the rationale for the time frames specified in the search strategy eligibility criteria.

Response: Table 1 provides the framework used in the literature search for the clinical evidence of padeliporfin VTP and active surveillance. The time frame was restricted to 2008 or later because:

i) The first trial of padeliporfin VTP (known then as WST11-mediated VTP), CLIN801 PCM201, had a study start date of September 2008,

ii) Based on input from clinicians, it appeared that the first significant results from active surveillance cohorts were published by Dall'Era 2008,[3] based on patients enrolled from 1989 to 2007 at UCSF

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Table 2 provides the framework used in the literature search for clinical evidence (in particular, safety) of radical therapies (i.e., radical prostatectomy, external beam radiation therapy and brachytherapy). The time frame was restricted to 2008 for three reasons:

1. Radical therapy techniques have evolved rapidly over the past few decades. Publications prior to 2008 would have reported results based on outdated techniques that do not reflect the current practice, with an increased use of robotic surgery over time. Changes in external beam radiation therapy have occurred progressively over the past few decades with the introduction of three-dimensional conformal radiotherapy (3D-CRT) in the 1980s, intensity-modulated radiation therapy (IMRT) in the 1990s, and image-guided radiation therapy (IGRT) in the early 2000s.[4]
2. Earlier publications are either covered well in other high-quality systematic literature reviews or no longer relevant. This includes a review by Centre hospitalier universitaire de Québec (CHU de Québec) and the Institut national d'excellence en santé et en services sociaux (INESSS) published in 2016[5] and another review by the Agency for Healthcare Research and Quality (AHRQ) published in 2014.[6]
3. Limited resources necessitated an approach that would limit the number of results to a reasonable number that could be reviewed by the submission deadline while mitigating the possibility of missing a relevant article. As stated in the Centre for Reviews and Dissemination (CRD) guidance for undertaking systematic reviews:[7] "The extent of searching is determined by the research question and the resources available to the research team."

Before full-text review, conference abstracts published before 2014 were excluded under the assumption that high quality congress abstracts from more than 3 years ago would have since been published as full-text journal articles.

Flow diagram

A7. Appendix D, section D.1.2, Tables 16-19 (pages 32-45).

The flow diagrams (labelled Tables 16 and 17) report that 215 and 270 full-text articles were excluded respectively. However, tables 18 and 19 which provide the 'complete reference list of excluded studies' only include 68 and 53 references respectively. Please clarify and provide the correct versions, if necessary.

Response: Tables 18 and 19 did not include the final list of references. The updated tables (see 'ID866_Padeliporfin VTP_Appendices_Table 18' and 'ID866_Padeliporfin VTP_Appendices_Table 19') have been uploaded as supporting documents to NICE Docs/Appraisals.

Extracted data

A8. Appendix D, section D.1.2, Tables 20-22 (pages 46-134).

Tables 20 to 22 provide raw extracted data on the efficacy and safety (table 20) and rate of radical therapy (table 21) for VTP and active surveillance, and radical therapy safety (table 22).

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- Please clarify how these tables have been used to inform the main submission.
    - If not provided in the main submission, please provide a summary of the results from these tables.
- The tables are truncated on the right margins. Please provide complete versions of these tables.

Response:

- A summary of results from tables 20, 21 and 22 from Appendix D are provided below.
- Tables 20 to 22 are truncated on the right margins. The complete version of these tables (see 'ID866_Padeliporfin VTP_Appendices_Table 20', 'ID866_Padeliporfin VTP_Appendices_Table 21' and 'ID866_Padeliporfin VTP_Appendices_Table 22') have been uploaded as supporting documents to NICE Docs/Appraisals.

Tables 20 to 21 have not been directly used to inform the main submission as the PCM301 trial provided the primary body of evidence for clinical effectiveness in the main submission, being the only phase III randomized controlled trial comparing the efficacy and safety of VTP with active surveillance. Since PCM301 is a direct comparison between VTP and active surveillance that included relevant outcomes (i.e., rate of radical therapy and adverse events), an indirect comparison did not have to be conducted and Tables 20 and 21 were not used to directly inform the main submission.

Below is a summary of the results for each of the tables.

Table 20 Clinical evidence: Padeliporfin VTP and active surveillance (search strategy #1), extracted data on efficacy and safety

69 publications have been selected for review and extraction of study design information, number of patients, intervention, inclusion criteria (prostate cancer risk status, Gleason Score (GS), maximum number of positive cores, maximum cancer core length, PSA at entry, clinical stage at entry), efficacy outcomes (time to metastasis, prostate cancer related death) and safety outcomes (reporting of AEs, SAEs, TEAEs, urinary symptoms, erectile dysfunction, bowel symptoms).

Out of the 69 publications, 18 had no relevant outcomes for this data extraction. The remaining 51 were extracted.

- There were 8 publications based on interventional studies: 6 included VTP (of which 1 was a comparison vs. active surveillance based on the PCM301 study), 2 included a comparison of active surveillance, prostatectomy, and radiotherapy (both publications based on the ProtecT study).
- The remaining 43 publications were all derived from observational studies, of which 10 were retrospective and 33 were prospective. Among these, 1 included VTP and 42 included active surveillance either alone (34 publications) or in comparison with radical therapies (8 publications)

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- 18,166 patients were reported as initially managed under active surveillance in total, of which 9,237 were exclusively very low risk, 6,480 were low risk (including some very low risk) and 2,449 were mostly low risk with some patients with higher grade disease
    - For efficacy outcomes: 9 publications reported progression to metastasis (5,536 patients) and 25 publications reported prostate cancer specific mortality (11,856 patients)
    - For safety outcomes: 2 publications reported AEs (385 patients), but only 1 publication (207 patients from PCM301 study), reported SAEs and the details of AEs by grade
    - For quality of life outcomes:
        - 15 publications (1,792 patients) reported QoL using EORTC QLQ-C30, ICIQ-SF, EPIC, SF-36, SF-12, ICSmaleSF, HADS, MAX-PC, IIEF-15, IIEF-5, IPSS, BAI, BDI, BHS, emotional thermometers, DCS, CES-D, STAI-6, EQ-VAS, MUIS, or EQ-5D – of note EQ-5D was only used in the PCM301 study
        - 10 publications (1,485 patients) reported urinary symptoms, erectile dysfunction, and/or bowel symptoms
- 589 patients were reported as with VTP in total, of which 503 were low risk and 86 were mostly low risk with some patients with low volume intermediate risk disease
    - For efficacy outcomes: no publication reported time to metastasis or prostate cancer specific mortality
    - For safety outcomes: 6 publications reported AEs (470 patients), 5 publications reported SAEs (440 patients), 4 publications reported TEAEs (398 patients), and 2 publications (314 patients) reported the details of AEs by grade
    - For quality of life outcomes:
        - 4 publications (493 patients) reported QoL using IIEF-5, IPSS, FACT-P, or EQ-5D – of note EQ-5D was only used in the PCM301 study
        - 6 publications (470 patients) reported urinary symptoms, erectile dysfunction, and/or bowel symptoms
- For active surveillance, the key results are:
    - Efficacy outcomes: freedom from metastases at 10 years ranged from 97% to 100%, while prostate cancer specific survival at 10 years was always greater than 98.8% (Godtman et al 2013; Tosoian et al 2015; Preston et al 2015; Hamdy et al 2016; Godtman et al 2016; Bul et al 2012; Scott et al 2015)
    - Safety outcomes: the most common AEs experienced by patients were erectile dysfunction (12%), urinary incontinence (5%), prostatitis (5%), haematuria (3%) (Azzouzi et al 2017 and PCM301 CSR for additional details).
    - Quality of life outcomes: patients managed with AS have minimal impact on their quality of life prior to progression to radical therapy. They maintain good urinary and sexual function. The main quality of life issue faced by AS

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patients prior to radical therapy is anxiety and / or fear of disease progression associated with the absence of treatment, which can favour progression to radical therapy in absence of progression (~25% to 36% of patients crossing over) (Herden et al 2017; Lee et al. 2014; Marenghi et al 2017). After radical therapy, patients typically experience urinary symptoms, erectile dysfunction, and/or bowel syndrome (see below).

- For VTP, the key results are:
    - Efficacy outcomes: no study reported progression to metastases or prostate cancer specific mortality
    - Safety outcomes: the most common AEs experienced by patients were erectile dysfunction (38%, with 1% Grade 3), haematuria (28%, with <1% Grade 3), dysuria (26%, with no Grade 3), urinary retention (16%, with 2% Grade 3), perineal pain (15%, with <1% Grade 3), miction urgency (11%, no Grade 3), pollakiuria (10%, no Grade 3), urinary incontinence (10%, with 1% Grade 3). Overall, most of the AEs were mild or moderate in severity, occurred during the procedure or in the days immediately after the procedure, and resolved quickly without sequelae (Azzouzi et al 2017 and PCM301 CSR for additional details).
    - Quality of life outcomes: patients who received VTP experienced a limited and transitory decrease in their IIEF-5 score. At 24 months the mean IIEF-5 score was identical to the one in the AS group and the differences over time were never statistically significant. The IPSS score also worsened transiently at 3 months after VTP and then recovered to a slightly better level than baseline. At 24 months, the mean IPSS score of the VTP group was slightly better than in the AS group, but the difference was not statistically significant (Azzouzi et al 2015, Azzouzi et al 2017 and PCM301 CSR for additional details).

Table 21 Clinical evidence: Padeliporfin VTP and active surveillance (search strategy #1), extracted data on rate to RT

Out of 69 articles selected, 49 had relevant outcomes for progression to radical therapy. Upon further review 22 articles included details about follow-up schedule and criteria for recommendation of radical therapy (RT), which allowed comparison with PCM301 study. Finally, 16 articles were retained for analysis after exclusion of 6 studies, which included a systematic confirmatory biopsy in their selection criteria. In fact, such a procedure was not included in PCM301 and it has an impact on the rate of disease upgrade and subsequently the level of progression to RT.

Each study was further reviewed and categorized according to:

- The prostate cancer risk group of the patients:
    - Very low risk only
    - Very low and low risk
    - Low risk only (similar to PCM301 indication population)
    - Low and intermediate risk

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- The strength of its follow-up schedule, as it can have a direct impact on disease upgrade
    - Limited: routine PSA testing, but no pre-scheduled re-biopsy
    - Standard: routine PSA testing with a systematic re-biopsy at 1 year, and subsequent re-biopsy every 3 years and/or ad-hoc based on PSA kinetics
    - Strong: routine PSA testing and at least 2 re-biopsies during the first 2 years (similar to PCM301 protocol) and then at regular intervals

Table 7 and **Table 8** display the distribution of articles along these two dimensions (of note some articles are counted several times when they include details for several patient sub-groups). Out of 14,849 patients covered in the selected articles, the majority belonged to the very low risk subgroup (11,127 patients) and a majority was monitored with a standard follow-up schedule (10,214 patients). When considering studies that were the most closely aligned with PCM301 characteristics, there were 568 patients that were low risk only (i.e. not very low risk) and 3,505 monitored with a strong follow-up schedule. Still, all of the studies with a strong follow-up included a significant portion (often a majority) of very low risk patients. Hence, none were directly comparable to PCM301.

Table 7 Distribution of analysed studies according to patient risk and strength of follow-up protocol (note: some studies include several subgroups)

	Very low risk only	**Very low risk & low risk**	**Low risk only**	**Low & intermediate risk**	**TOTAL**
Limited follow-up	1	-	-	2	**3**
Standard follow-up	7	1	4	1	**13**
Strong follow-up	2	4	-	-	**6**
TOTAL	**10**	**5**	**4**	**3**	**22**

Table 8 Distribution of patients in analysed studies according to patient risk and strength of follow-up protocol

	Very low risk only	**Very low risk & low risk**	**Low risk only**	**Low & intermediate risk**	**TOTAL**

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Limited follow-up	381			749	**1,130**
Standard follow-up	9,190	302	568	154	**10,214**
Strong follow-up	1,556	1,949			**3,505**
TOTAL	**11,127**	**2,251**	**568**	**903**	**14,849**

The ranges of reported rates of progression to RT at 2, 4, and 5 years have been reported in **Table 9** according to the patient risk group and the strength of the follow-up. Additionally, the rates of progression to RT from the AS arm in PCM301 have also been reported for easy direct comparison.

Among the very low risk only subgroup, the strength of follow-up does not seem to have a significant impact on rate of progression to RT, as the ranges of the different follow-up categories overlap significantly at each time point.

When comparing patient groups who had a similar strength of follow-up but different risk levels, it appears:

- Patients who received limited follow-up tended to have similar rates of progression to RT over time regardless of the risk subgroup
- The same observation was also valid for patients with standard follow-up
- For patients with strong follow-up, a higher risk level was associated with a higher rate of progression to RT (see below “very low and low risk” vs. “very low risk only”)

As a result, when reviewing rates of progression to RT from the AS arm of PCM301, the most relevant comparison appears to be with the very low and low risk group that received a strong follow-up schedule. When considering either the whole study population, which included very low risk and low risk patients, or the indication population (low risk only) the rates of progression to RT at 2 and 5 years are within the range of published data, with values close to the top of the range when focusing on the indication population only (higher risk profile than the closest comparator group from the literature).

Table 9 Ranges of progression to RT over time according to patient risk group and strength of follow-up

	2 years	**4 years**	**5 years**
Very low risk only			
Limited follow-up	18%	29%	32%

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Standard follow-up	14%-29%	26%-45%	29%-52%
Strong follow-up	12%-17%	25%-34%	29%-41%
Very low and low risk			
Limited follow-up	-	-	-
Standard follow-up	25%	34%	-
Strong follow-up	22%-46%	33%-58%	37%-65%
Low risk only			
Limited follow-up	-	-	-
Standard follow-up	10%-28%	36%-42%	42%-46%
Strong follow-up	-	-	-
Low and intermediate risk			
Limited follow-up	15%-20%	31%-31%	33%-38%
Standard follow-up	12%	30%	38%
Strong follow-up	-	-	-
AS from PCM301 (strong follow-up)			
Very low and low risk (entire study)	33%	53%	-
Low risk only (indication population)	39%	57%	-
Note: a single figure was included when only one study was available in a given category, while the minimum and maximum reported values were reported when several studies where available			

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Table 22 Clinical evidence: Radical therapy (search strategy #2), extracted data on RT safety

Out of 53 articles selected, 42 had relevant outcomes (reporting of AEs and/or QoL for urinary, sexual, and/or, bowel functions) and involved the use of radical prostatectomy (RP), EBRT (RT), or brachytherapy (BT) among low-risk prostate cancer patients. 13 articles were further excluded as they involved use of adjuvant or neoadjuvant androgen deprivation therapy with EBRT or brachytherapy, which typically affects the safety profile of these procedures. Most of the articles covered several types of procedures and functional outcomes. A total of 29 articles and 3,914 patients were analysed. The breakdown by type of procedure and type of outcome is summarized in **Table 10**.

Table 10 Number of articles and number of patients analysed according to procedure (RP, RT, BT) and to functional outcomes (urinary, sexual, bowel)

n articles *(n patients)*	**Urinary function**	**Sexual function**	**Bowel function**	**All functional outcomes**
Radical prostatectomy	16 (1,720)	17 (1,720)	6 (885)	17 (1,720)
EBRT	10 (1798)	9 (1798)	9 (1798)	10 (1,798)
Brachytherapy	10 (396)	8 (321)	6 (387)	10 (396)
All procedures	28 (3,914)	26 (3,839)	15 (3,070)	29 (3,914)

There was significant variation across studies in the type of endpoint used to measure functional outcomes and in the time frame of the assessment (from immediately after procedure to 10 years after). The measures used included:

- **Urinary function:** patients reporting use of ≥1 pad/day, EPIC urinary function, EORTC-QLQ-PR25 urinary symptoms, ICIQ-SF, IPSS, acute and late genitourinary (GU) toxicities of Grade ≥2, patient-reported incontinence
- **Sexual function:** IIEF-15, IIEF-6, IIEF-5, EPIC sexual function, EORTC-QLQ-PR25 sexual function, SHIM, erection firm enough for penetration, erection firm enough for sexual intercourse, acute and late GU toxicities of Grade ≥2
- **Bowel function:** EPIC bowel function, EORTC-QLQ-PR25 bowel function, acute and late gastrointestinal (GI) toxicities of Grade ≥2, patient-reported faecal inconvenience

Interestingly, one article indicated that the response rate on functional outcomes was lower among patients treated with RP and EBRT (66% for both) compared to patients on active surveillance or patients without prostate cancer (74% and 75% respectively).[8]

Table 11 summarizes the findings for radical prostatectomy. There is significant variation across the types of measures and for the same measure across the different studies. Overall:

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- 19% to 68% of patients had to wear at least 1 pad/day just after RP and at 1 year 3% to 20% of patients had not recovered full continence
- 30% to 61% of patients had potency issues (IIEF-5 ≤17) at 1 month after RP and 19% to 57% at 1 year, even with use of PDE5 inhibitors
- Bowel function was not impacted in the short and long term after RP

Table 11 Summary of functional outcomes among patients treated with radical prostatectomy

Type of outcome	Type of measure	Short term (less than 1 year) outcomes	Long term (1 year and over) outcomes
Urinary function	Use of ≥1 pad/day	19% to 68% after catheter removal / 1 month	3% to 20% at 1 year
	EPIC urinary function	39% decrease in mean score at 1mo	• 9% to 40% decrease in mean score at 1yr • 0% to 6% decrease in mean score at 2yrs
	ICIQ	34% increase of patients with ICIQ≥7 at 1mo	8.2% decrease in mean score at 1.9yrs
	EORTC-QLQ-PR25 urinary symptoms	Mean score of 17 at 6mos vs 9 at baseline	No significant difference vs. baseline at 1 and 5yrs
	IPSS	Mean score of 4.9 at 6mos vs 4.6 at baseline	No significant difference vs. baseline at 1 and 5yrs
Sexual function	IIEF	• 30% to 61% of patients with IIEF-5≤17 at 6mos with 51% of patients with PDE5 inh. • 60% of patients not recovering baseline potency at 6mos (incl. use of PDE5 inh.) • 40% decrease in mean IIEF-15 score at 6mos	• 19% to 57% of patients with IIEF-5≤17 at 1yr (incl. use of PDE5 inh) • 32% to 90% of patients not recovering baseline potency at 1yr (incl. use of PDE5 inh.) – 35% at 5yrs
	EPIC sexual function	67% decrease in mean score at 1mo	• 50% to 58% decrease in mean score at 1yr • 39% to 58% decrease in mean score at 2yrs
	EORTC-QLQ-PR25 sexual function	Mean score of 9 at 6mos vs 5 at baseline	Mean score of 7 at 1yr vs 5 at baseline

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Type of outcome	Type of measure	Short term (less than 1 year) outcomes	Long term (1 year and over) outcomes
	Erection firm enough for penetration or sexual intercourse	na	44% to 88% at 1yr (incl. use of PDE5 inh.)
	SHIM	na	SHIM>15 for 87% of patients at 1yr
Bowel function	EPIC bowel function	98% of baseline mean score at 1mo	98% to 100% of baseline mean score at 1 and 2yrs
	EORTC-QLQ-PR25 bowel symptoms	Mean score of 3 at 6mos vs 2 at baseline	No significant change at 1yr

Table 12 summarizes the findings for EBRT. There is significant variation across the types of measures and for the same measure across the different studies. Overall:

- 7% to 27% of patients had acute genitourinary toxicities of Grade 2 or above, and 23% to 31% had late toxicities
- 34% of patients lost potency at some point after EBRT
- 2% to 11% of patients had acute gastrointestinal toxicities of Grade 2 or above, and 2% to 30% had late toxicities

Table 12 Summary of functional outcomes among patients treated with EBRT

Type of outcome	Type of measure	Short term (less than 1 year) outcomes	Long term (1 year and over) outcomes
Genitourinary toxicities	Grade≥2 GU toxicities	7% to 27% of patients with acute toxicities	23% to 31% of patients with late toxicities
Urinary function	EPIC urinary function	6% decrease in mean score at 1mo	• 3% decrease to 6% increase in mean score at 1yr • 35% of patients with a change in score >2 at 1yr
	Patient reported incontinence	29% of patients with reported incontinence (timing unknown)	
Sexual function	EPIC sexual function	13% decrease in mean score at 1mo	• 4% to 14% decrease in mean score at 1yr • 20% to 30% decrease in mean score at 2yrs

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Type of outcome	Type of measure	Short term (less than 1 year) outcomes	Long term (1 year and over) outcomes
	Erection firm enough for penetration or sexual intercourse	14% with erection firm enough after EBRT vs. 48% before	na
Bowel function	Grade≥2 GI toxicities	2.3% to 10.7% of patients	2.4% to 30% of patients
	EPIC bowel function	4% decrease in mean score at 1mo	• 0% to 8% decrease in mean score at 1yr • 23% of patients with a change in score >5 at 1yr

Table 13 summarizes the findings for brachytherapy. There is significant variation across the types of measures and for the same measure across the different studies. Overall:

- 27% to 54% of patients had acute genitourinary toxicities of Grade 2 or above, and 19% to 49% had late toxicities
- 42% of patients experience a decrease in potency at 6mos after brachytherapy, and 22% to 39% had not fully recovered at 1yr
- 2% of patients had acute gastrointestinal toxicities of Grade 2 or above, and 8% had late toxicities, while faecal inconvenience was reported among 10% of patients at 3mos and 4% at 1yr

Table 13 Summary of functional outcomes among patients treated with brachytherapy

Type of outcome	Type of measure	Short term (less than 1 year) outcomes	Long term (1 year and over) outcomes
Genitourinary toxicities	Grade≥2 GU toxicities	27% to 54% of patients with acute toxicities	19% to 49% of patients with late toxicities
Urinary function	EPIC urinary function	15% decrease in mean score at 1mo	No significant change at 1yr
	ICIQ	4% increase of patients with ICIQ≥7 at 1mo	9.5% decrease in mean score at 1.9yrs
	EORTC-QLQ-PR25 urinary symptoms	Mean score of 36 at 6mos vs 8 at baseline	Mean score of 15 at 1yr vs 8 at baseline
	IPSS	Mean score x3 at 3-6mos compared to baseline	• Mean score x1.8-2.1 at 1yr

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Type of outcome	Type of measure	Short term (less than 1 year) outcomes	Long term (1 year and over) outcomes
			• 38% of patients without recovery of baseline score at 1yr
	Patient reported incontinence	49% of patients with reported incontinence (timing unknown)	
Sexual function	IIEF	42% of patients not recovering baseline potency at 6mos (incl. use of PDE5 inh.)	22% to 39% of patients not recovering baseline potency at 1yr (incl. use of PDE5 inh.)
	EPIC sexual function	9% decrease in mean score at 1mo	12% decrease in mean score at 1mo
	EORTC-QLQ-PR25 sexual function	Mean score of 10 at 6mos vs 6 at baseline	Mean score of 7 at 1yr vs 6 at baseline
	Patient reported erectile dysfunction	Increase of 10% of patients at 3mos vs. baseline	Increase of 16% of patients at 3mos vs. baseline
Bowel function	Grade≥2 GI toxicities	1.9% of patients with acute toxicities	7.9% of patients with late toxicities
	EPIC bowel function	4% decrease in mean score at 1mo	1% decrease in mean score at 1mo
	EORTC-QLQ-PR25 bowel symptoms	Mean score of 6 at 6mos vs 2 at baseline	Mean score of 5 at 1yr vs 2 at baseline
	Patient-reported faecal inconvenience	10% of patients at 3mos	4% of patients at 1yr

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Section B: Clarification on cost-effectiveness data

B0. REVISED BASE CASE

Based on the questions raised by The Evidence Review Group, Aberdeen HTA and the technical team at NICE, the Company concludes that its base case economic model needs to be revised as follows:

- Inclusion of costs for second VTP treatment (see question B1),
- Adjustment of the TTM curve for AS and VTP to take into account the differences in populations between PCM301 indication population (low-risk only) and ProtecT population (very low-risk, low-risk, and intermediate-risk) (see question B2),
- Use of baseline utility values derived from EQ-5D data from PCM301 (see question B6),
- Using secondary care costs for physical examinations and nurse consultations in the VTP administration costs (see question B8), and
- Incorporating adjustment of TTM for general mortality (see question B9)

Whilst the Company provides a cost-effectiveness comparison vs. active surveillance for the sake of completeness, it is important to remember that because of TOOKAD® VTP's positioning, the relevant comparisons are vs. radical prostatectomy (RP), radiotherapy (EBRT), and brachytherapy (BT). As indicated in the initial submission, about 50% of newly diagnosed low-risk prostate cancer patients currently elect to active surveillance and the other half elects to radical therapy. In this context, TOOKAD® VTP is primarily positioned to offer a new, effective, and safer alternative to this second group of patients who seeks active treatment. Additionally, it can provide a solution to patients who initially elect to active surveillance but want to discontinue it and seek active treatment in absence of disease progression.

When taking into account all the adjustments listed above, the revised base case analysis yields a slightly higher ICER for the comparison of VTP vs. AS (£49,415/QALY) than in the initial submission and slightly lower ICERs for the comparisons of VTP vs. RP, EBRT and BT (£15,946/QALY, £26,728/QALY, and £21,533/QALY respectively; see **Table 15**).

In addition to individual comparisons, the Company provides the overall cost effectiveness in the comparison of world without VTP vs world with VTP, where VTP is assumed to displace 30% of patients with 20% currently electing to radical prostatectomy and 10% to brachytherapy, without moving patients from the AS group. This ICER is also improved compared to the initial base case submission and is now £17,287/QALY (see **Table 16)**.

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Table 14 Revised base case: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	16,650	13.673	12.269	-	-	-	-	-
EBRT	17,522	13.673	12.113	872	0.000	-0.156	Dominated by AS	Dominated by AS
RP	19,334	13.673	11.970	2,684	0.000	-0.299	Dominated by AS	Dominated by AS
BT	20,554	13.673	12.162	3,904	0.000	-0.107	Dominated by AS	Dominated by AS
VTP	27,652	13.673	12.492	11,002	0.000	0.223	49,415	49,415

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

Table 15 Revised base case: pairwise comparisons against VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	27,652	13.673	12.492	-	-	-	-
AS	16,650	13.673	12.269	-11,002	0.000	-0.223	49,415
RP	19,334	13.673	11.970	-8,318	0.000	-0.522	15,946
EBRT	17,522	13.673	12.113	-10,130	0.000	-0.379	26,728
BT	20,554	13.673	12.162	-7,097	0.000	-0.330	21,533

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

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Table 16 Revised base case: world without vs with VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	17,889	13.673	12.163	-	-	-	-
World with VTP†	20,263	13.673	12.301	2,373	0.000	0.137	17,287

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively

Economic model

B1. CS, section B.2.10, table 19 (page 51) and B.3.2 (page 86).

The company submission did not include a second VTP treatment in its model because it is not recommended and "*There are insufficient patients who have underwent retreatment of the ipsilateral lobe … to determine the efficacy and safety of a second VTP procedure*" (CS, page 86). However, in the 'indication population', 5 people had received retreatment with VTP (Table 19).

- Please provide further rationale for excluding second VTP treatments in the model.
- Please clarify how second VTP treatments were accounted for in the 'time to radical therapy' analysis.
- Please explore the impact of adding the costs of second VTP treatments in the model.

Response:

- Steba Biotech excluded second VTP treatments in the model because it is not recommended in the Summary of Product Characteristics (SmPC). Per the SmPC: *"Retreatment of the same lobe or sequential treatment of the contralateral lobe of the prostate are not recommended."*[9]
- In the "time to radical therapy" analysis in the CS, patients with second VTP treatment were not accounted for differently than patients without second VTP treatment. However, a sensitivity analysis was conducted in which patients were censored at time of second VTP treatment (see **Figure 1**), which yields a relative benefit in the VTP arm similar to the "time to radical therapy" analysis used in the CS (HR=0.31, 95%CI=0.17-0.55 vs HR=0.29, 95%CI=0.16-0.53, respectively).
- **Table 17**, **Table 18** and **Table 19** present the impact of adding the costs of second VTP treatments in the model.

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- In this scenario, the cost effectiveness of VTP is maintained when comparing to RP (ICER = £19,377/QALY) and is at threshold in the comparison to brachytherapy (ICER = £30,993/QALY)
- The overall cost effectiveness in the comparison of world without VTP vs world with VTP is also maintained (ICER = £21,869/QALY)

Figure 1 Estimated cumulated risk of receiving a radical therapy over 48 months – indication population with censoring of patients with 2nd VTP

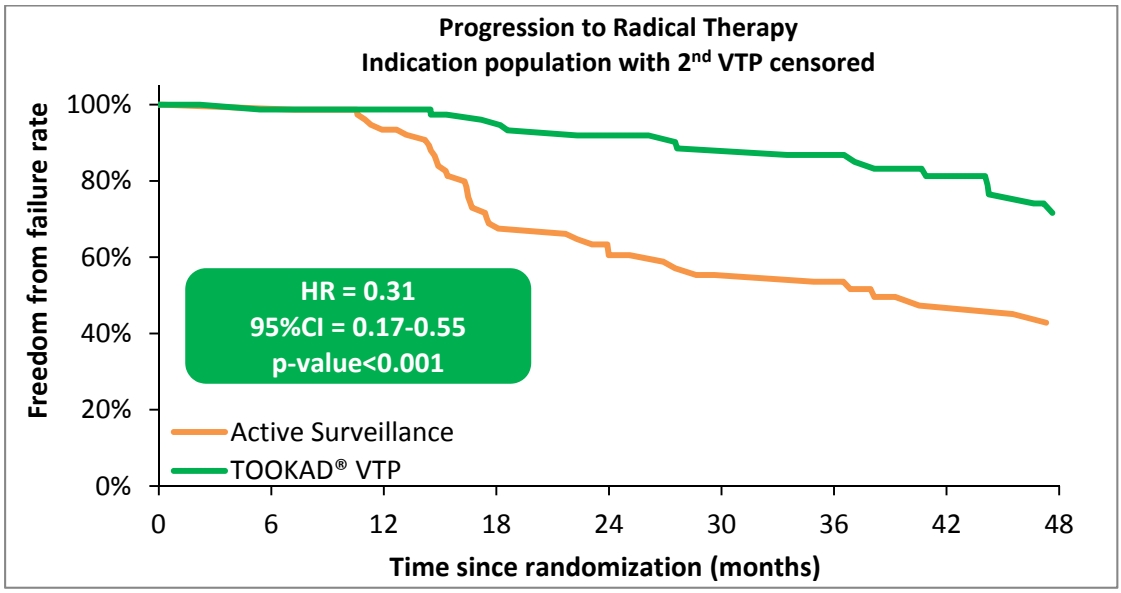

Table 17 Exploring costs of 2nd VTP treatments: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	16,609	13.673	11.413	-	-	-	-	-
EBRT	16,999	13.673	11.340	390	0.000	-0.073	Dominated by AS	Dominated by AS
RP	18,752	13.673	11.185	2,143	0.000	-0.227	Dominated by AS	Dominated by AS
BT	19,871	13.673	11.393	3,262	0.000	-0.020	Dominated by AS	Dominated by AS
VTP	27,614	13.673	11.643	11,005	0.000	0.230	47,876	47,876

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

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Table 18 Exploring costs of 2nd VTP treatments: pairwise comparisons against VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	27,614	13.673	11.643	-	-	-	-
AS	16,609	13.673	11.413	-11,005	0.000	-0.230	47,876
RP	18,752	13.673	11.185	-8,862	0.000	-0.457	19,377
EBRT	16,999	13.673	11.340	-10,615	0.000	-0.303	35,055
BT	19,871	13.673	11.393	-7,743	0.000	-0.250	30,993
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy							

Table 19 Exploring costs of 2nd VTP treatments: world without vs with VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	17,579	13.673	11.345	-	-	-	-
World with VTP†	20,126	13.673	11.461	2,547	0.000	0.116	21,869
VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year * Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively † Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively							

Clinical parameters and variables

PCM301 and ProtecT

B2. PRIORITY QUESTION. CS, section B.3.3 (page 93).

The proportion of patients in each health state at each time point in the partitioned survival model is derived using 3 parametric survival curves; time to radical therapy (TTRT), time to metastasis (TTM) and time to prostate cancer-related death (overall survival, OS). PCM301 is used to derive TTRT for the 'indication' subgroup, while the ProtecT trial is used to derive TTM and OS.

- Please further clarify to what extent the populations in PCM301 and ProtecT are comparable. In particular, please consider risk status, stage of disease, prostate specific antigen (PSA) levels and any other observable factors that could influence the risk of disease progression.

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Response: The indication population in PCM301 and the population of ProtecT have a comparable mean age at randomization (64 vs. 62), with a somewhat wider range in the indication population of PCM301. When looking at initial risk staging parameters, the indication population of PCM301 is more homogenous, as it only includes unilateral low risk patients and no very low risk patients, whereas the population in ProtecT encompasses very low risk and low risk patients, along with some intermediate (20% based on Gleason Score 7) and even a few high risk patients, more specifically:

- In the active monitoring group of the ProtecT trial, patients have a lower median PSA compared to patients in the indication population of PCM301, but with a wider range, which includes patients with intermediate risk level PSA (i.e. between 10 and 20 ng/mL).
- The distributions of T1c/T2clinical stage are similar with a greater proportion of T2 stage in ProtecT (25% vs. 13%)
- While the PCM301 study enrolled only patients with Gleason Score ≤ 6, ProtecT also included 20% of patients with Gleason score 7 at baseline and 2% with Gleason score 8-10, which are associated with intermediate and high risk disease respectively.

Table 20 Observable factors in PCM301 and ProtecT that could influence risk of disease progression

	Indication population in PCM301 N = 158	**Active monitoring in ProtecT N = 545**
Median age (range)	64 (46–74)	62 (50–69)
Median PSA (range; ng/mL)	7.1 (1.0 – 10.0)	4.6 (3.0 – 20.9)*
Clinical stage		
T1c	127 (87%)	410 (75%)
T2	21 (13%)	135 (25%)
Gleason score		
≤6	158 (100%)	421 (77%)
7	0 (0%)	111 (20%)
8-10	0 (0%)	13 (2%)
Inclusion of very low risk patients?	No	Yes
ProtecT, Prostate testing for cancer and Treatment * One patient from the feasibility study had a serum PSA concentration of 20.9 µg/L at the specialist nurse visit; the concentration fell to 17.6 µg/L on repeat measurement and he became eligible for recruitment.		

The inclusion of a meaningful proportion of patients with intermediate risk disease in ProtecT is likely to have an impact on the risk of disease progression of the AS arm, but not of the radical prostatectomy (RP) arm. In fact, the PIVOT study, a randomized controlled trial

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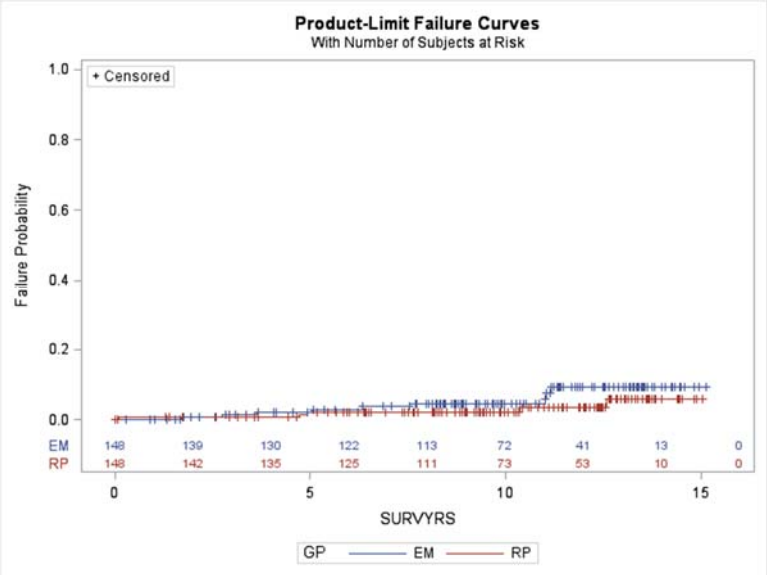
comparing observation to radical prostatectomy, recently reported the following in its 15-year follow-up (Wilt et al NEJM 2017 main article and supplementary material):[10]

- Among low risk patients (which also encompasses very low risk patients), there was no significant difference in metastatic progression of disease between the observation and RP arm (see **Figure 2A**)
- Among intermediate risk patients, the metastatic progression of disease was greater in the observation arm than in the RP arm (see **Figure 2B**). The point estimate of the hazard ratio is lower in the intermediate-risk group compared to the low-risk group (0.42 vs. 0.54); the 95% confidence interval is narrower, but the limited number of patients, low event rate, and late occurrence of event don't allow it to reach statistical significance (95%CI=0.17-1.04). A similar trend was reported among high risk patients with an even lower point estimate for the hazard ratio (see **Figure 2C**)
- For patients in the RP arm, there was no significant difference in metastatic progression between the low risk and intermediate risk subgroups (see **Figure 2D**)

Figure 2 Metastatic disease progression reported over 15 years by risk subgroups in PIVOT study

A. Low risk subgroup (including very low risk). HR=0.54, 95%CI=0.18, 1.62



B. Intermediate risk subgroup. HR=0.42, 95%CI=0.17, 1.04

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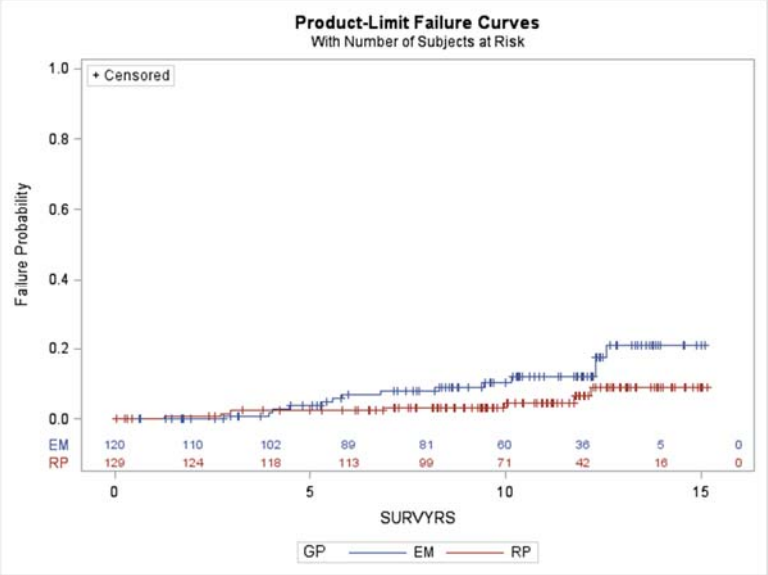
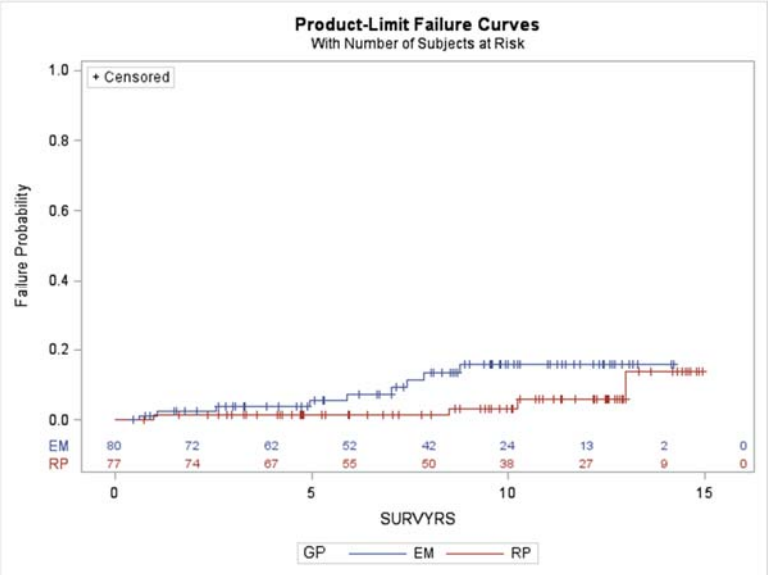


C. High risk subgroup. HR=0.37, 95%CI=0.11, 1.20



D. Low and intermediate risk subgroups combined

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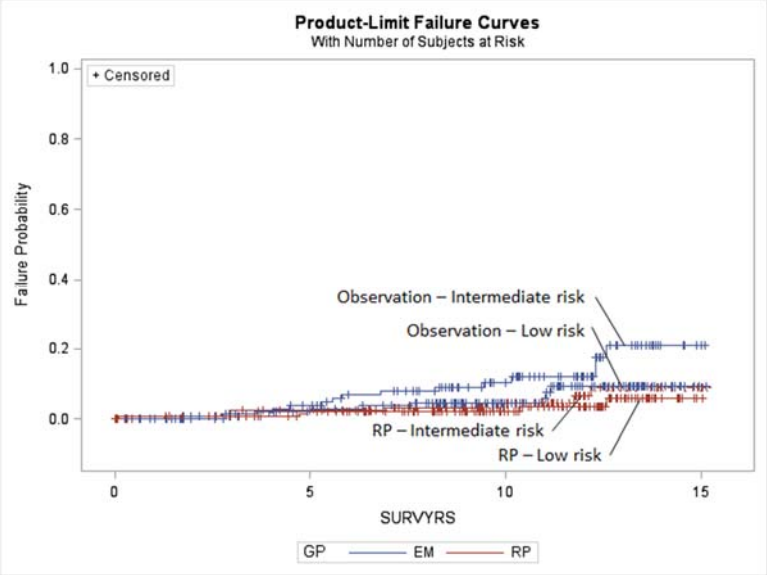

Based on these additional data and the differences in populations between PCM301 indication population and ProtecT population (low-risk only for PCM301 vs. very low-risk, low-risk, some intermediate-risk and a few high-risk for ProtecT), the Company concludes the following regarding the TTM curves:

- For radical prostatectomy, EBRT, and brachytherapy, the curve of the RP arm in ProtecT is appropriate to describe the expected disease progression in a UK, low-risk only population, as the differences in patient populations do not affect disease progression
- For active surveillance (and as a result for VTP), the curve of the RP arm in ProtecT is also the appropriate one to describe the expected disease progression in a UK, low-risk only population, once one takes into account the impact of excluding intermediate-risk patients on disease progression

Furthermore, the Company reviewed this assessment with an expert clinician in the UK who agreed that radical therapy would have a similar effect on progression among patients with low risk and intermediate risk disease, but patients on active surveillance with low risk vs intermediate risk disease would have differential risk to progression as no treatment is involved.

Based on this conclusion, the Company has updated its base case with revised TTM curves for AS and VTP. The results are described in **Table 21**, **Table 22** and **Table 23**. This update has no meaningful impact in the comparison of VTP vs AS since TTM was already equivalent between these two treatment groups. However, this results in a meaningful reduction in the pairwise ICERs of VTP vs each radical therapy. The most notable difference is the ICER of VTP vs. EBRT at £24,028/QALY, instead of above the £30,000/QALY threshold as in the previous version. As a result, the ICER in the world without vs with VTP comparison is also reduced (£19,549/QALY vs £15,088/QALY in the base case vs updated model, respectively).

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Table 21 Using equivalent TTM across treatment groups: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	16,072	13.673	11.492	-	-	-	-	-
EBRT	16,999	13.673	11.340	926	0.000	-0.152	Dominated by AS	Dominated by AS
RP	18,752	13.673	11.185	2,680	0.000	-0.307	Dominated by AS	Dominated by AS
BT	19,871	13.673	11.393	3,799	0.000	-0.099	Dominated by AS	Dominated by AS
VTP	26,175	13.673	11.722	10,103	0.000	0.230	43,958	43,958

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

Table 22 Using equivalent TTM across treatment groups: pairwise comparisons against padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	26,175	13.673	11.722	-	-	-	-
AS	16,072	13.673	11.492	-10,103	0.000	-0.230	43,958
RP	18,752	13.673	11.185	-7,423	0.000	-0.536	13,837
EBRT	16,999	13.673	11.340	-9,176	0.000	-0.382	24,028
BT	19,871	13.673	11.393	-6,304	0.000	-0.329	19,166

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

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Table 23 Using equivalent TTM across treatment groups: without vs with padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	17,304	13.673	11.385	-	-	-	-
World with VTP†	19,419	13.673	11.525	2,115	0.000	0.140	15,088

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively

Time to metastasis and disease progression

B3. CS, section B.3.3 (page 105).

Time to metastasis (TTM) is derived from the outcome 'disease progression' defined as "*death due to prostate cancer or its treatment; evidence of metastatic disease; long-term androgen-deprivation therapy; clinical T3 or T4 disease; and ureteric obstruction, rectal fistula, or the need for a permanent catheter when those are not considered to be a complication of treatment in the ProtecT trial*" (CS, page 105).

- Please clarify to what extent ProtecT's 'disease progression' definition is consistent with the health state costs and utility values applied to people who progress in the model. For example, do progression costs assume that everyone who progresses have distant metastases, although in ProtecT's definition, some people progressing have local progression?

Response: In **Table 24**, the estimated cost and utility value of each 'disease progression' event as defined in ProtecT are compared relative to metastatic disease. Aside from long-term androgen deprivation therapy (ADT), 'disease progression' events in ProtecT are likely less costly and likely have higher utility values compared to metastatic disease. Unless the distribution of patients with 'disease progression' events in ProtecT skew towards long-term ADT events, then the costs and negative impact on HRQoL are likely overestimated in the economic model for patients in the metastatic disease health state. However, the distribution of 'disease progression' events in ProtecT is unclear and the effect of each 'disease progression' event on costs and QALYs is based on limited evidence. Thus, the Company is unable to make a definitive statement about the impact on the ICER in the initial base case. Still, based on the revised base case from answer to question B2, where disease progression (TTM) is the same for all treatment options, adjusting costs and/or utilities of post-progression (metastatic) state will not impact the ICERs of VTP vs. other treatment options.

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Table 24 Comparing disease progression in ProtecT to metastasis

Description of disease progression event	Effect on costs compared to metastasis	Effect on utility compared to metastasis
Evidence of metastatic disease	None	None
Long-term androgen-deprivation therapy (ADT)	In Ramsay et al. 2015, cost of second-line abiraterone-based (Zytiga®) regimen was £24,670 (cost unadjusted to 2018 price levels), which is **more costly** than the cost attributed to metastatic disease in the economic model.	Per NICE guidelines,[11] ADT may be considered as adjuvant therapy for up to 3 years in men with high-risk localised prostate cancer and is recommended in metastatic disease. The average long-term ADT patient is likely to have utility that is **similar to, or higher** than, the average metastatic patient with prostate cancer because the latter doesn't include patients with locally advanced disease but may include hormone-relapsed patients on chemotherapy.
Clinical T3 or T4 disease	Per NICE guidelines,[11] T3b and T4 disease fall under locally advanced prostate cancer. The majority of patients with locally advanced prostate cancer recurrence should be treated with radiation therapy, combined with hormone therapy for most men, for at least part of their treatment. Since not all men will receive hormone therapy, nor will it be given long-term, treating T3 or T4 disease is likely to be **somewhat less costly** then treating metastatic disease.	Utility for T3 and T4 disease, which is defined as locally advanced disease per NICE guidelines, [11] would be **somewhat higher** than utility associated with metastatic disease.
Ureteric obstruction	Per NICE guidelines:[11] • Offer decompression of the upper urinary tract by percutaneous nephrostomy or by insertion of a double J stent to men with obstructive uropathy secondary to hormone-relapsed prostate cancer. [2008] • The option of no intervention should also be discussed with men with obstructive uropathy secondary to hormone-relapsed prostate cancer and	Ureteric obstruction (as well as rectal fistula and need for permanent catheter below) is likely not associated with metastatic disease in the context of disease progression in the ProtecT trial since "evidence of metastatic disease" should then occur first and thereby supersedes ureteric obstruction as the event included in the disease progression analysis in ProtecT. As symptoms of ureteric obstruction may range from no symptoms at all to severe pain to loss of kidney function,

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	remains a choice for some. [2008] Based on National Schedule of Reference Costs Year: 2016-17 • Unilateral, Percutaneous Insertion of, Ureteric Stent or Nephrostomy (HRG code YL11Z): £973.59 • Bilateral or Multiple, Percutaneous Insertion of, Ureteric Stent or Nephrostomy (HRG code YL10Z): £1298.20 Both are **less costly** than treating metastatic disease.	sepsis or even death, it is difficult to ascertain its impact on HRQoL. Thus, whether it's average associated utility value would be lower or higher than the utility associated with metastatic disease is **unknown** as it depends on the cause, location, degree, and duration of obstruction, as well as the presence of a urinary tract infection.
Rectal fistula	Per NHS:[12] • Surgery is usually necessary to treat an anal fistula as very few heal by themselves. • Surgery for an anal fistula is usually carried out under general anaesthetic. In many cases, it's not necessary to stay in hospital overnight afterwards. • The most common type of surgery for anal fistulas is a fistulotomy. According to BMI Healthcare's (independent healthcare group in the UK) website, anal fistula surgery ranges between £2,692 and £3,714,[13] which is **less costly** than the cost of treating metastatic disease.	Symptoms of anal fistula include:[12] • skin irritation around the anus • a constant, throbbing pain that may be worse when you sit down, move around, have a bowel movement or cough • smelly discharge from near your anus • passing pus or blood when you poo • swelling and redness around your anus and a high temperature (fever), if you also have an abscess • difficulty controlling bowel movements (bowel incontinence) in some cases Based on the list of possible symptoms, rectal fistula would potentially have a **somewhat higher** utility value compared to the utility of metastatic disease.
Need for a permanent catheter	The need for a permanent catheter may arise due to permanent urinary incontinence or urinary retention, which are common side effects of prostate cancer treatment. Based on National Schedule of Reference Costs Year: 2016-17, the cost of treating urinary incontinence can be as high as £3187.67, which is based on HRG currency code LB16D (Urinary	Under the assumption that the disutility associated with urinary incontinence, per the economic model, is applied to the baseline utility value for localised prostate cancer, the utility value associated with need for permanent catheter would be **higher** than that for metastatic disease.

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	Incontinence or Other Urinary Problems, with Interventions, with CC Score 7+). Under the assumption that this would approximate the cost of inserting a permanent catheter, it is **less costly** than the cost of treating metastatic disease.	
ADT, androgen deprivation therapy; NICE, National Institute for Health and Care Excellence; HRQoL, health-related quality of life; HRG, Healthcare Resource Group; NHS, National Health Services; UK, United Kingdom		

Time to radical therapy

B4. PRIORITY QUESTION. CS, section B.3.3 (pages 93-103).

The ProtecT trial shows a substantially lower rate of progression to radical therapy in patients having active surveillance recruited from UK centres compared with the observed and extrapolated rate based on data from PCM301. In particular, the base case extrapolation (lognormal) projects that ~90% of patients having active surveillance in PCM301 will undergo radical therapy by 10 years compared with 55% in ProtecT.

- Please provide a scenario analysis using the ProtecT data to model time to radical therapy on active surveillance, and estimate the time to radical therapy in the VTP arm relative to this baseline. This may require the use of time dependent hazard ratios derived from PCM301.

Response: Although the ProtecT trial shows a substantially lower rate of progression to radical therapy compared to PCM301, at least some of this difference can be explained by the following four criteria, which can affect the reported rate of progression to radical therapy: monitoring schedule, compliance with monitoring schedule, pre-planned criteria for recommendation to initiate radical therapy and baseline risk of progression in patient population. In **Table 25**, the exploration of each factor shows that the differences in design along 3 out 4 factors explain why lower rates of progression to radical therapy are observed in ProtecT compared to PCM301 (the 4th factor is likely to have no impact).

Table 26, **Table 27** and **Table 28** present the results of a scenario analysis using the ProtecT data to model time to radical therapy on active surveillance. In order to model time to radical therapy for the VTP group, cycle-specific transition probabilities were estimated from the parametric models used to fit the Kaplan-Meier curves of the VTP and AS groups in PCM301. Then, the ratio of these transition probabilities between VTP and AS was applied to time to radical therapy of the active surveillance arm derived from ProtecT on a per-cycle basis. In addition, **Table 29**, **Table 30** and **Table 31** present similar results, but using the Weibull distribution rather than the lognormal distribution (base case in original economic model) to model time to radical therapy since it has the lowest BIC fit statistics (**Table 32**) in the updated analysis. Of note, in coherence with answer to question B2 and the revised base case, the TTM curves for AS and VTP have been revised and aligned on the one for RP, EBRT and BT. In both cases, the ICER of VTP vs. AS increases significantly, while the ICERs of VTP vs each radical therapy option decreases significantly, leading to VTP being cost effective vs. EBRT. As a result, the ICER in the world without vs with VTP comparison

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is also reduced (£3,633/QALY using lognormal distribution and £4,728/QALY using Weibull distribution)

Table 25 Criteria that affect the rate to radical therapy in PCM301 compared to ProtecT

Criteria	PCM301	ProtecT	Conclusion
Monitoring schedule	In PCM301 RCT, PSA and DRE measured every 3 months. TRUS-guided biopsy at Month 12 and Month 24. In PCM301 FU5 observational study, PSA testing frequency was based on current practice, which would typically be every 3 to 12 months, depending on patient status and profile of PSA kinetics.	In the active monitoring group, PSA every 3 months in first year and twice yearly thereafter. Rise of at least 50% in PSA during previous 12 months triggered repeat testing within 6-9 weeks No scheduled re-biopsies, only ad-hoc.	While PCM301 and ProtecT have similar PSA schedules, PCM301 includes scheduled biopsies at M12 and M24, which are not included in ProtecT. These lead to earlier detection of disease upgrade and as a result earlier progression to radical therapy
Compliance with monitoring schedule	High compliance	No detailed data, but likely high compliance since ProtecT is an RCT.	Both PCM301 and ProtecT are RCTs with likely similar and high compliance with monitoring schedule. Hence, this parameter should not result in different rate of progression to radical therapy between the two studies.
Pre-planned criteria for consideration to initiate radical therapy	In PCM301, disease progression was defined through the composite co-primary endpoint that included any departure from the inclusion criteria. Specifically: • Any Gleason primary or secondary pattern of 4 or more • More than 3 cores definitively positive for cancer when considering all histological results available during	In the AM group, an increase of at least 50% of PSA level during the previous 12 months triggered a review. Management options included continued monitoring or further tests and radical or palliative treatments as required.	Criteria to consider initiation of radical therapy in ProtecT seem to be based on looser guidelines compared to PCM301. It is not clear how frequently PSA increase was associated with re-biopsy and subsequently with treatment decision. Also, it is unclear how baseline disease (in particular Gleason Score 6 vs. greater than 6) impacted subsequent considerations of

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	follow-up in the study • At least 1 cancer core length > 5 mm • PSA > 10 ng/mL in 3 consecutive measures • Any T3 prostate cancer • Metastasis		disease progression and treatment decisions. Therefore, it is likely that the tighter set of criteria in PCM301 led to more frequent detections of disease upgrade and progression to radical therapy than in ProtecT. Of note, initiation of radical therapy in PCM301 closely followed disease upgrade.
Baseline risk of progression in patient population	See **Table 20**	See **Table 20**	The patient population in ProtecT is more heterogeneous, i.e. it includes very low risk and intermediate risk patients, compared to the patient population in the indication population of PCM301, which is all unilateral low risk, but not very low risk. As shown in Godtman 2016,[14] low risk and intermediate risk patients initially managed with active surveillance tend to have similar profiles of progression to radical therapy, while very low risk patients have a lower likelihood of progression to radical therapy. As a result, this parameter is likely to result in a lower rate of progression to radical therapy in the ProtecT trial compared to PCM301
PSA, prostate specific antigen; DRE, digital rectal exam; TRUS, transrectal ultrasound; AM, active monitoring; EBRT, external; beam radiation therapy; RP, radical prostatectomy; RCT, randomized clinical trial.			

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Table 26 Using ProtecT data to model TTRT on AS (lognormal) and assuming equivalent TTM across all treatments: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	10,356	13.673	11.799	-	-	-	-	-
EBRT	16,999	13.673	11.340	6,643	0.000	-0.459	Dominated by AS	Dominated by AS
RP	18,752	13.673	11.185	8,397	0.000	-0.614	Dominated by AS	Dominated by AS
BT	19,871	13.673	11.393	9,516	0.000	-0.406	Dominated by AS	Dominated by AS
VTP	21,537	13.673	11.918	11,182	0.000	0.119	93,729	93,729

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

Table 27 Using ProtecT data to model TTRT on AS (lognormal) and assuming equivalent TTM across all treatments: pairwise comparisons against padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	21,537	13.673	11.918	-	-	-	-
AS	10,356	13.673	11.799	-11,182	0.000	-0.119	93,729
RP	18,752	13.673	11.185	-2,785	0.000	-0.733	3,799
EBRT	16,999	13.673	11.340	-4,539	0.000	-0.579	7,843
BT	19,871	13.673	11.393	-1,666	0.000	-0.526	3,170

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

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Table 28 Using ProtecT data to model TTRT on AS (lognomal) and assuming equivalent TTM across all treatments: without vs with padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	14,377	13.673	11.543	-	-	-	-
World with VTP†	15,101	13.673	11.742	724	0.000	0.199	3,633

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively

Table 29 Using ProtecT data to model TTRT on AS (Weibull) and assuming equivalent TTM across all treatments: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	10,514	13.673	11.796	-	-	-	-	-
EBRT	16,999	13.673	11.340	6,485	0.000	-0.456	Dominated by AS	Dominated by AS
RP	18,752	13.673	11.185	8,238	0.000	-0.611	Dominated by AS	Dominated by AS
BT	19,871	13.673	11.393	9,357	0.000	-0.403	Dominated by AS	Dominated by AS
VTP	22,185	13.673	11.902	11,671	0.000	0.106	110,610	110,610

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

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Table 30 Using ProtecT data to model TTRT on AS (Weibull) and assuming equivalent TTM across all treatments: pairwise comparisons against padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	22,185	13.673	11.902	-	-	-	-
AS	10,514	13.673	11.796	-11,671	0.000	-0.106	110,610
RP	18,752	13.673	11.185	-3,433	0.000	-0.716	4,792
EBRT	16,999	13.673	11.340	-5,186	0.000	-0.562	9,231
BT	19,871	13.673	11.393	-2,314	0.000	-0.509	4,547

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

Table 31 Using ProtecT data to model TTRT on AS (Weibull) and assuming equivalent TTM across all treatments: without vs with padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	14,458	13.673	11.541	-	-	-	-
World with VTP†	15,376	13.673	11.735	918	0.000	0.194	4,728

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively

Table 32 Goodness of fit statistics for parametric models fitted to TTRT curve in active monitoring group of ProtecT trial

Distribution	AIC	BIC
Weibull	1987.70	1996.30
Gamma	1988.36	2001.27
Lognormal	1989.14	1997.75
Loglogistic	1990.62	1999.22

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Gompertz	2000.21	2008.82
Exponential	2020.10	2024.40
AIC, Akaike information criterion; BIC, Bayesian information criterion		

B5. PRIORITY QUESTION. CS, section B.3.3, figures 18-20 (pages 100-102).

The tails of the Kaplan Meier curves for time to radical therapy in PCM301 appear to be converging slightly and the 'best fitting' generalised gamma curves appear to be a good visual fit to the observed data.

- Please provide an exploratory scenario analysis using the generalised gamma function for time to radical therapy, and allow the curves for active surveillance and VTP to converge but not cross.

Response: The Company would contest the assessment that the tails of the Kaplan-Meier (KM) curves for time to radical therapy in PCM301 appear to be converging. However, the results of a scenario analysis using the generalised gamma function for time to radical therapy, and allowing the curves for active surveillance and VTP to converge but not cross, are presented in **Table 33**, **Table 34** and **Table 35**. Of note, in coherence with answer to question B2 and the revised base case, the TTM curves for AS and VTP have been revised to use the same one as for RP, EBRT and BT. In this scenario, VTP remains cost effective vs radical prostatectomy (£20,845/QALY). The comparison of a world without vs a world with VTP yields to an ICER of £23,697/QALY.

The Company believes that the generalized gamma distribution should be rejected based on lack of clinical plausibility. In fact, when using the generalised gamma function, the curve for VTP has an extreme downward trajectory (evident by the crossing of the curves at an early time point), which would require a strong acceleration of progression to radical therapy in the VTP group after Month 36. Based on expert review by a UK clinician, this profile of progression to radical therapy is unlikely as it would require acceleration of the hazard of disease upgrade over time (see **Figure 3** for unadjusted VTP curve and **Figure 4** with adjustment to allow "*the curves for AS and VTP to converge but not cross"* as requested by the ERG). Instead, in the disease progression and progression to radical therapy profile after focal therapy, it is expected that the vast majority of in-field progressions occur in the first 2 years after treatment, and that mostly out-of-field progressions (i.e. contralateral lobe) occur after this initial period at a fairly constant rate (typically 1-2% per year). Based on this review, it appears that the lognormal progression profile, which has a steadier hazard of progression to radical therapy over time after the first couple of years, appears to have higher clinical plausibility, as it is be better aligned with the experience in clinical practice than the generalized gamma one.

Furthermore, the generalised gamma distribution is the second to last best-fitting distribution in the VTP group based on Bayesian information criterion (BIC) fit statistics. Hence, while it has a good fit for the AS group, it does not reflect at best the trend of the VTP group.

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Additionally, the Company is providing an additional scenario analysis where the generalised gamma distribution was used for the AS TTRT curve and a lognormal distribution for the VTP TTRT curve. In this scenario, no adjustment was made to either the VTP or AS curve, and the VTP curve remained above the AS curve over the time horizon. Under this scenario, VTP is cost effective vs. RP, EBRT, BT (£13,837/QALY, £24,028/QALY, and £19,166/QALY respectively) and the comparison of a world without vs a world with VTP yields to an ICER of £15,088/QALY (**Table 36**, **Table 37** and **Table 38**).

Figure 3 Hazards of generalised gamma and lognormal models for time to radical therapy

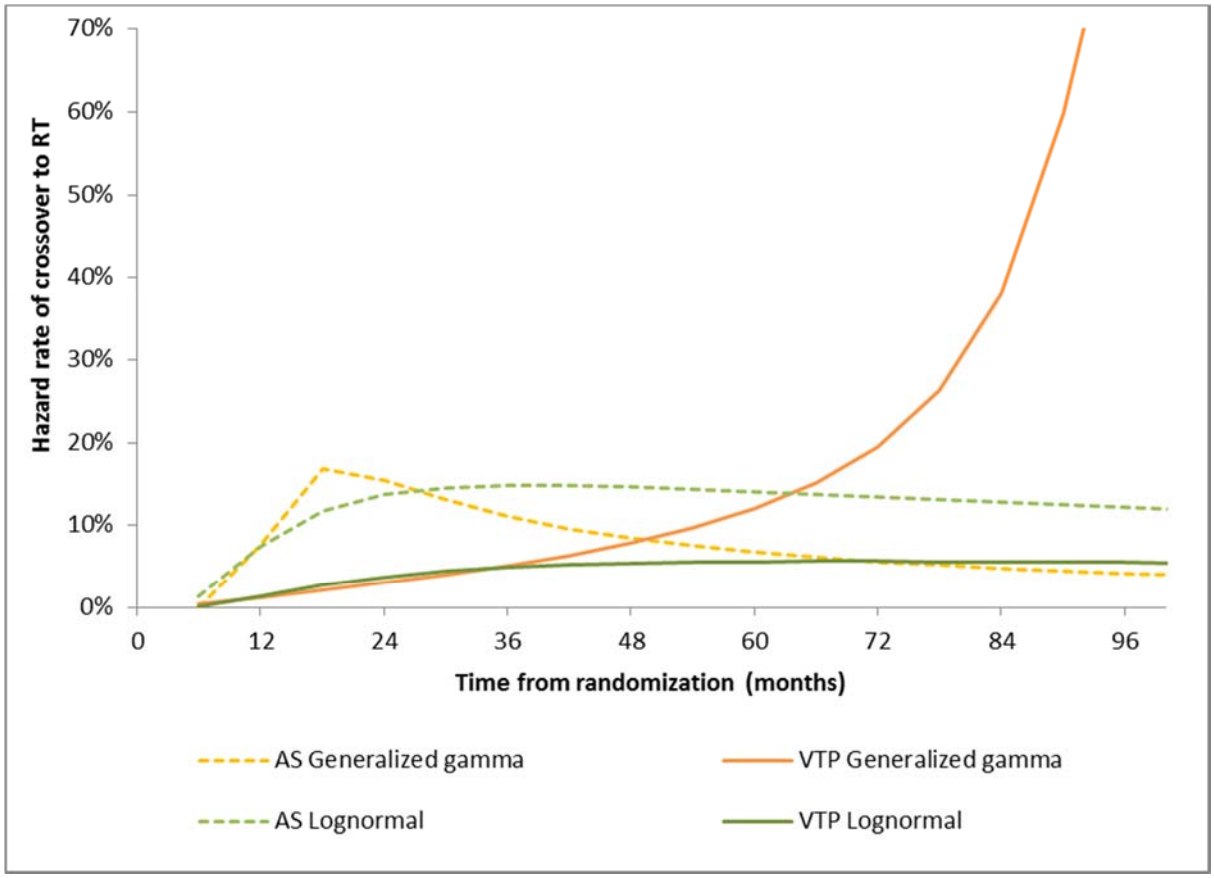

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Figure 4 Hazards of generalised gamma (adjusted for VTP) and lognormal models for time to radical therapy

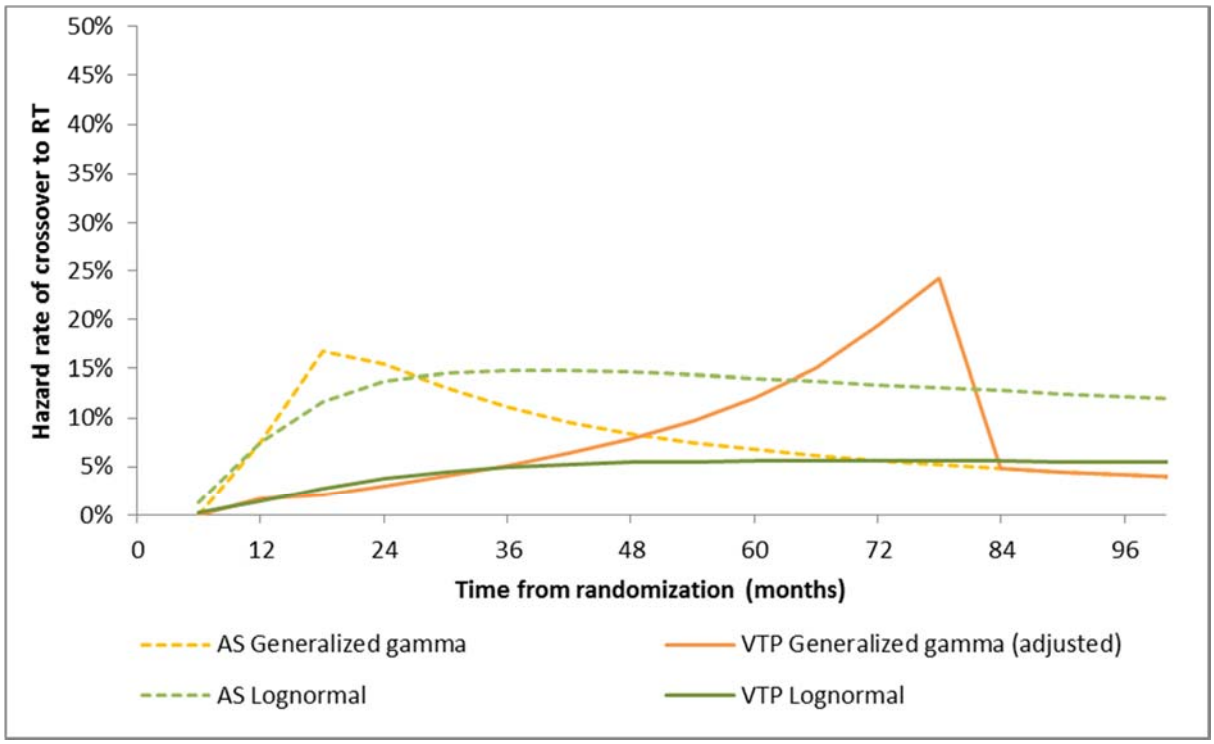

Table 33 Using generalized gamma to model TTRT and assuming equivalent TTM across all treatments: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	13,816	13.673	11.611	-	-	-	-	-
EBRT	16,999	13.673	11.340	3,182	0.000	-0.271	Dominated by AS	Dominated by AS
RP	18,752	13.673	11.185	4,936	0.000	-0.426	Dominated by AS	Dominated by AS
BT	19,871	13.673	11.393	6,055	0.000	-0.218	Dominated by AS	Dominated by AS
VTP	28,009	13.673	11.629	14,193	0.000	0.018	776,992	776,992

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

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Table 34 Using generalized gamma to model TTRT and assuming equivalent TTM across all treatments: pairwise comparisons against padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	28,009	13.673	11.629	-	-	-	-
AS	13,816	13.673	11.611	-14,193	0.000	-0.018	776,992
RP	18,752	13.673	11.185	-9,257	0.000	-0.444	20,845
EBRT	16,999	13.673	11.340	-11,011	0.000	-0.290	38,025
BT	19,871	13.673	11.393	-8,138	0.000	-0.237	34,401

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

Table 35 Using generalized gamma to model TTRT and assuming equivalent TTM across all treatments: without vs with padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	16,149	13.673	11.446	-	-	-	-
World with VTP†	18,814	13.673	11.559	2,665	0.000	0.112	23,697

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively

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Table 36 Using generalized gamma for AS and lognormal for VTP to model TTRT and assuming equivalent TTM across all treatments: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	13,816	13.673	11.611	-	-	-	-	-
EBRT	16,999	13.673	11.340	3,182	0.000	-0.271	Dominated by AS	Dominated by AS
RP	18,752	13.673	11.185	4,936	0.000	-0.426	Dominated by AS	Dominated by AS
BT	19,871	13.673	11.393	6,055	0.000	-0.218	Dominated by AS	Dominated by AS
VTP	26,175	13.673	11.722	12,359	0.000	0.111	111,735	111,735

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

Table 37 Using generalized gamma for AS and lognormal for VTP to model TTRT and assuming equivalent TTM across all treatments: pairwise comparisons against padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	26,175	13.673	11.722	-	-	-	-
AS	13,816	13.673	11.611	-12,359	0.000	-0.111	111,735
RP	18,752	13.673	11.185	-7,423	0.000	-0.536	13,837
EBRT	16,999	13.673	11.340	-9,176	0.000	-0.382	24,028
BT	19,871	13.673	11.393	-6,304	0.000	-0.329	19,166

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

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Table 38 Using generalized gamma for AS and lognormal for VTP to model TTRT and assuming equivalent TTM across all treatments: without vs with padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	16,149	13.673	11.446	-	-	-	-
World with VTP†	18,264	13.673	11.586	2,115	0.000	0.140	15,088

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively

Utility values

B6. CS, section B.3.2, tables 36 and 37 (pages 90-92) and section B.3.4 (pages 114-116).

The company's model used baseline utility values from Ramsay (2015), a literature review of studies that derived utility values using different methods (EQ-5D, HUI, SF-6D and direct preference elicitation methods). PCM301 collected EQ-5D data at baseline, 12 and 24 months for the 'indication population' (preferred approach for deriving utilities by NICE).

- Please clarify the rationale for not using the EQ-5D data from PCM301 to derive the baseline utility values in the partitioned survival model.
- Please explore the impact of adverse events on utility and cost-effectiveness estimates using the available EQ-5D data from PCM301.

Response:

- The rationale for using Ramsay (2015) rather than EQ-5D data from PCM301 to derive baseline utility values was for consistency since the other utility values and disutility values were derived from Ramsay (2015). However, scenario analyses using EQ-5D data from PCM301 to derive baseline utility values was explored in Tables 68 to 71 in the CS. In pairwise comparison against VTP, this led to ICERs of £43,960/QALY, £18,462/QALY, £35,110/QALY and £30,587/QALY vs AS, RP, EBRT and brachytherapy, respectively. Results are presented in **Table 39**, **Table 40** and **Table 41**.
- EQ-5D data from PCM301 was not used to explore the impact of adverse events on utility and cost-effectiveness estimates because of the limited data availability and lack of sensitivity of EQ-5D assessments to the adverse events of interest (UI, ED and BD). Given the number of data points available where EQ-5D was collected prior to, and after, a relevant adverse event (see **Table 42**), and the limited granularity of

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this data (measured every 12 months), the EQ-5D is unlikely to be able to capture the impact of the adverse events. The EQ-5D assessments would not likely capture the impact of transient AEs given the instantaneous recall period of EQ-5D assessments and period between date of AE and next EQ-5D assessment (see **Table 43**), which ranged from 7.5 to 9.7 months. In addition, though it is possible that EQ-5D may capture permanent AEs, the sample size is limited (see **Table 42**) even when expanding the data to the ITT population.

Based on the utility values derived from EQ-5D data collected in the PCM301 trial for any Grade ≥ 2 UI, ED or BD event with pre- and post-EQ-5D assessments (e.g. EQ-5D assessments at baseline and M12 if an AE occurred between baseline and M12), disutility values were estimated by subtracting the post-EQ-5D value from the prior EQ-5D value. However, this results in no change for Grade ≥ 2 UI and Grade ≥ 2 BD. For Grade ≥ 2 ED, the utility values lacked face validity as the utility value increased following Grade ≥ 2 ED by 0.013 (see **Table 43**).

In the ProtecT trial, the "comparisons of health-related quality of life revealed no significant differences among the treatment groups in the physical and mental health subscores of the SF-12 general health measure" (see **Figure 5**), despite detection of significant impact on quality of life when using specific instruments for urinary, sexual, and bowel functions. Based on expert review with a UK clinician, EQ-5D would likely not be discriminatory for UI, ED and BD since SF-12 wasn't able to detect differences compared to disease-specific measures.

Due to these limitations described above, the Ramsay (2015) disutility values appear to be the more valid choice to use in the cost-effectiveness model. Nevertheless, the impact of adverse events on utility and cost-effectiveness estimates using the available EQ-5D data from PCM301 were explored in **Table 44**, **Table 45** and **Table 46**.

Table 39 Using baseline utility value based on EQ-5D data from PCM301: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	16,609	13.673	12.491	-	-	-	-	-
EBRT	16,999	13.673	12.445	390	0.000	-0.047	Dominated by AS	Dominated by AS
RP	18,752	13.673	12.290	2,143	0.000	-0.201	Dominated by AS	Dominated by AS
BT	19,871	13.673	12.498	3,262	0.000	0.006	530,260	530,260
VTP	26,714	13.673	12.721	10,105	0.000	0.230	43,960	30,587

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

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Table 40 Using baseline utility value based on EQ-5D data from PCM301: pairwise comparisons against padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	26,714	13.673	12.721	-	-	-	-
AS	16,609	13.673	12.491	-10,105	0.000	-0.230	43,960
RP	18,752	13.673	12.290	-7,962	0.000	-0.431	18,462
EBRT	16,999	13.673	12.445	-9,715	0.000	-0.277	35,110
BT	19,871	13.673	12.498	-6,843	0.000	-0.224	30,587

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

Table 41 Using baseline utility value based on EQ-5D data from PCM301: without vs with padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	17,579	13.673	12.436	-	-	-	-
World with VTP†	19,856	13.673	12.545	2,277	0.000	0.109	20,959

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively

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Figure 5 Outcomes for health-related quality of life in ProtecT

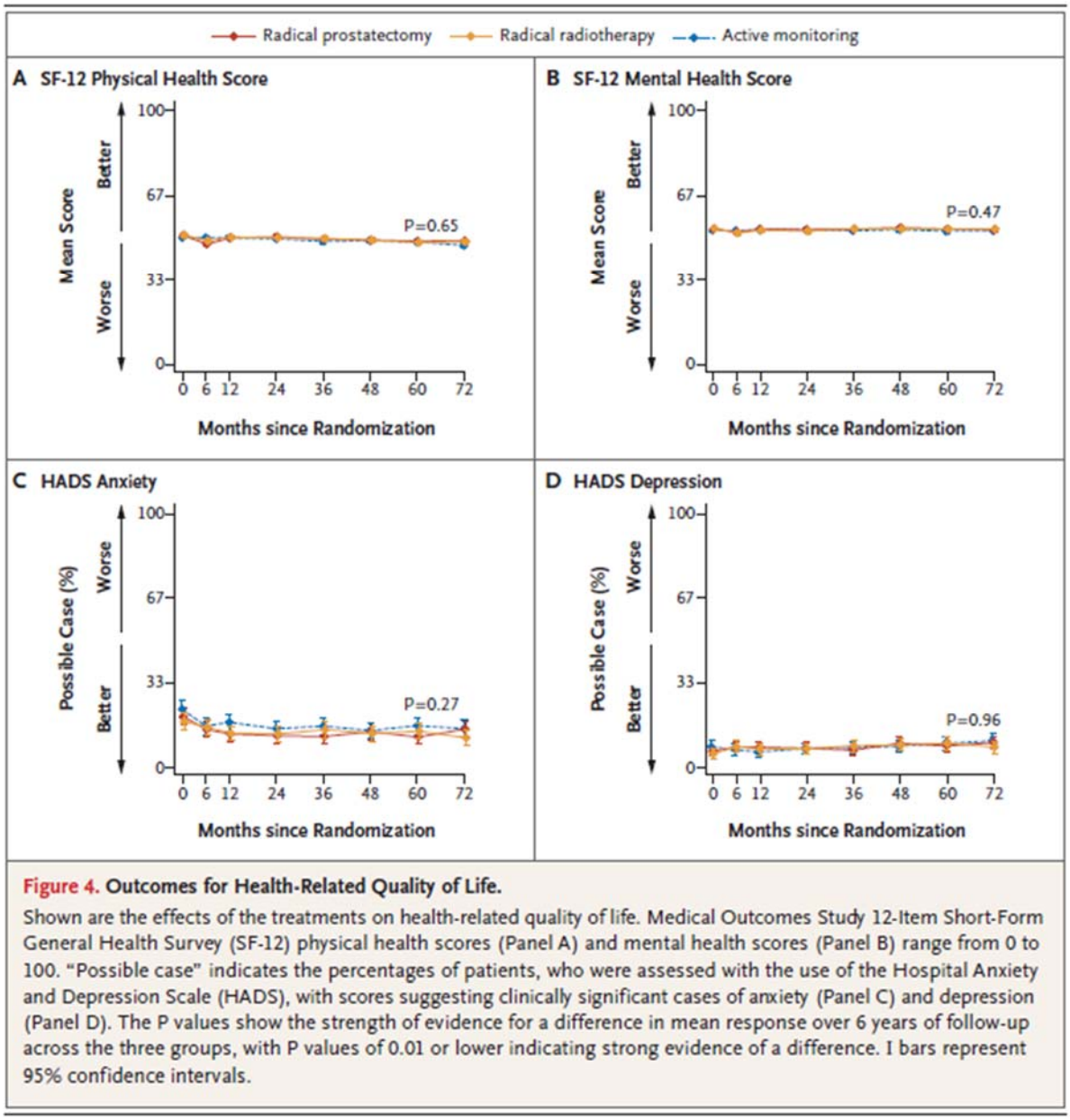

Figure 4. Outcomes for Health-Related Quality of Life.

Shown are the effects of the treatments on health-related quality of life. Medical Outcomes Study 12-Item Short-Form General Health Survey (SF-12) physical health scores (Panel A) and mental health scores (Panel B) range from 0 to 100. "Possible case" indicates the percentages of patients, who were assessed with the use of the Hospital Anxiety and Depression Scale (HADS), with scores suggesting clinically significant cases of anxiety (Panel C) and depression (Panel D). The P values show the strength of evidence for a difference in mean response over 6 years of follow-up across the three groups, with P values of 0.01 or lower indicating strong evidence of a difference. I bars represent 95% confidence intervals.

Table 42 Number of events: ED, UI, or BD, Grade ≥ 2 (by duration type) with adjacent EQ-5D assessments (ITT population)

Adverse event	Transient	Permanent
Grade ≥ 2 ED	16	21
Grade ≥ 2 UI	6	6
Grade ≥ 2 BD	4	1
ED, erectile dysfunction; UI, urinary incontinence; BD, bowel dysfunction		

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Table 43 Utility values based on EQ-5D data for adverse events

Adverse event	Utility values			Mean duration between EQ-5D and AE dates	
	EQ-5D assessment prior to AE	EQ-5D assessment post-AE	Difference	Prior EQ-5D and AE (months)	Post-EQ-5D and AE (months)
Grade ≥ 2 ED	0.962	0.975	0.013	3.8	8.4
Grade ≥ 2 UI	0.954	0.954	0.000	4.8	7.5
Grade ≥ 2 BD	0.958	0.958	0.000	3.1	9.7

AE, adverse event; ED, erectile dysfunction; UI, urinary incontinence; BD, bowel dysfunction

Table 44 Using estimated disutility values based on EQ-5D data for adverse events from PCM301 (per Table 43): fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	16,609	13.673	12.000	-	-	-	-	-
EBRT	16,999	13.673	12.105	390	0.000	0.105	3,710	3,710
RP	18,752	13.673	12.158	2,143	0.000	0.157	13,614	33,456
BT	19,871	13.673	12.079	3,262	0.000	0.079	41,329	Dominated by RP
VTP	26,714	13.673	11.977	10,105	0.000	-0.023	Dominated by AS	Dominated by RP

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

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Table 45 Using estimated disutility values based on EQ-5D data for adverse events from PCM301 (per Table 43): pairwise comparisons against padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	26,714	13.673	11.977	-	-	-	-
AS	16,609	13.673	12.000	-10,105	0.000	0.023	Dominates VTP
RP	18,752	13.673	12.158	-7,962	0.000	0.181	Dominates VTP
EBRT	16,999	13.673	12.105	-9,715	0.000	0.128	Dominates VTP
BT	19,871	13.673	12.079	-6,843	0.000	0.102	Dominates VTP

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

Table 46 Using estimated disutility values based on EQ-5D data for adverse events from PCM301 (per Table 43): without vs with padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	17,579	13.673	12.061	-	-	-	-
World with VTP†	19,856	13.673	12.015	2,277	0.000	-0.046	Dominated by world without VTP

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively

Adverse events

B7. PRIORITY QUESTION. CS, section B.2.10 (page 59), section B.3.4 (pages 114-122) and section B.3.5 (pages 130-132).

The company's model includes costs and utility decrements associated with three specific adverse events; urinary incontinence (UI), bowel dysfunction (BD) and erectile dysfunction

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(ED). PCM301 provides adverse event rates for the pre-radical therapy health state, while Ramsey (2015) provides these rates for the post-radical therapy health state.

- Please clarify to what extent the original study populations used in Ramsay (2015) are comparable to the 'indication population' from PCM301. In particular, please consider stage of disease, baseline prevalence of UI, BD and ED and any other factors that might influence the prevalence of UI, BD and ED at follow-up.
- Please further justify excluding the costs and utility decrements associated with VTP-specific adverse events listed in Table 25 (CS, page 59).

Response:

- The patient population included in Ramsay et al. 2015 (**Figure 6**) is more heterogeneous compared to that of PCM301. The Ramsay et al. 2015 population consists of patients with very low-risk, low-risk, intermediate-risk and high-risk disease so it is difficult to make an assessment as to what extent the two populations are comparable and therefore factors that may influence the prevalence of UI, ED and BD. Baseline patient age in PCM301 is comparable with the RP group in Ramsay et al. 2015 (63.1 vs 62.1 years, respectively) and slightly younger than the BT, AS and EBRT groups (66.1, 66.1 and 69.2 years, respectively). Mean PSA in PCM301 was similar to the BT and RP groups in Ramsay et al. 2015 (7.05 vs 7.19 and 6.68 ng/ml, respectively), but higher than the AS group (7.05 vs 5.55 ng/ml) and lower than the EBRT group (7.05 vs 8.49 ng/ml). Due to missing data in Ramsay et al. 2015, it is difficult to estimate the distribution of patients by clinical stage or Gleason score. However, all patients in PCM301 had Gleason score ≤6, but Ramsay et al. 2015 also includes some patients with Gleason score >6.
- Costs and utility decrements associated with VTP-specific adverse events listed in Table 25 of the CS were excluded for the following reasons:
    - Although Table 25 in the CS lists serious adverse events, these include adverse events of all grades, including grade 1 adverse events that typically do not require treatment nor have an impact HRQoL (see **Table 47**).
    - The economic model does not include radical therapy-specific adverse events such as hematuria, post-operative pain, urinary infection as this information is not readily available from literature. Including it for VTP only would create an inconsistency between the intervention studied and the comparators. In addition, VTP-specific adverse events listed in Table 25 of CS are generally less likely, or as likely, to occur following VTP than following treatment with radical therapy based on expert clinical review by a UK clinician (see **Table 48**).
    - Time to resolution indicates that these are transient adverse events that quickly resolve (see **Table 49**).

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Figure 6 Summary of the characteristics of the study participants included in the primary review, where data were combinable, from the information reported by the study authors

Variable	BT	CRYO	HIFU	Laser therapy	PDT	EBRT	RP	AS
Number of studies	41	19	21	1	1	34	30	10
Number of participants	26,129	3995	4000	12	23	12,547	19,961	5592
Mean age, years (SD/IQR)	66.05 (2.97)	68.56 (2.45)	67.58 (3.53)	56.5[a] (51–62)		69.17 (2.03)	62.09 (2.68)	66.09 (2.52)
n (%)	13,397 (51.3)	2773 (69.4)	3155 (78.9)	12 (100.0)		7394 (58.9)	15,046 (75.4)	5511 (98.6)
Missing/unknown, *n* (%)	12,732 (48.7)	1222 (30.6)	845 (21.1)		23 (100.0)	5153 (42.0)	4915 (24.6)	81 (1.4)
Clinical stage, *n* (%)								
T1	14,399 (55.1)	802 (20.1)	1994 (49.9)	12 (100.0)		3959 (31.6)	10,709 (53.6)	4304 (77.0)
T2	9313 (35.6)	1493 (37.4)	1554 (38.9)			4619 (36.8)	4653 (23.3)	761 (13.6)
≤T2a[b]	12 (0.1)	50 (1.3)	21 (0.5)		23 (100.0)			
T3–T4	219 (0.8)	223 (5.6)	86 (2.2)			232 (1.8)	83 (0.4)	4 (0.1)
Missing/unknown	2186 (8.4)	1427 (35.7)	345 (8.6)			3737 (29.8)	4516 (22.6)	523 (9.4)
PSA								
Mean, ng/ml (SD)	7.19 (1.60)	8.43 (2.63)	7.77 (1.13)	5.7 (1.1)		8.49 (2.39)	6.68 (1.46)	5.55 (0.5)
n (%)	9771 (37.4)	695 (17.4)	3713 (92.8)	12 (100.0)		5056 (40.3)	9822 (49.2)	3773 (67.5)
Missing/unknown, *n* (%)	16,358 (62.6)	3300 (82.6)	287 (7.2)		23 (100.0)	7491 (59.7)	10,139 (50.8)	2009 (32.5)
Gleason score, *n* (%)								
≤6	9538 (36.5)	1695 (42.4)	1116 (27.9)	12 (100.0)	23 (100.0)	5686 (45.3)	7515 (37.6)	4920 (88.0)
7	2091 (8.0)	883 (22.1)	541 (13.5)			1931 (15.4)	2719 (13.6)	116 (2.1)
8–10	101 (0.4)	187 (4.7)	165 (4.1)			691 (5.5)	637 (3.2)	29 (0.5)
Missing/unknown	14,399 (55.1)	1230 (30.8)	2178 (54.5)			4239 (33.8)	9090 (45.5)	527 (9.4)
Prostate size								
Mean, ml (SD/IQR)	37.48 (2.51)	36.6 (8.16)	26.5 (6.87)	37 (16–85)		42.67 (6.77)	45.03 (0.93)	44 (35–57)
n (%)	893 (3.4)	221 (5.5)	3875 (96.9)	12 (100.0)		456 (3.6)	361 (1.8)	2494 (44.6)
Missing/unknown, *n* (%)	25,236 (96.6)	3774 (94.5)	125 (3.1)		23 (100.0)	12,091 (96.4)	19,600 (98.2)	3098 (55.4)

BT, brachytherapy; CRYO, cryotherapy; IQR, interquartile range; SD, standard deviation.
a Median.
b Clinical stage for all patients as reported by Barret 2013.[103] This group could not be included in any other category.

Table 47 Serious adverse events related to study drug, device, or procedure, by grade (indication population, N=79)

System Organ Class Preferred Term	Grade 1		Grade 2		Grade 3	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
All SAEs related to study drug, device, or procedure	**2 (2.5)**	**2**	**6 (7.6)**	**7**	**3 (3.8)**	**5**
Infections and infestations	**0 (0)**	**0**	**1 (1.3)**	**1**	**2 (2.5)**	**2**
Orchitis	0 (0)	0	1 (1.3)	1	0 (0)	0
Urinary tract infection	0 (0)	0	0 (0)	0	2 (2.5)	2
Nervous system disorders	**0 (0)**	**0**	**1 (1.3)**	**1**	**0 (0)**	**0**

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Transient global amnesia	0 (0)	0	1 (1.3)	1	0 (0)	0
Renal and urinary disorders	**2 (2.5)**	**2**	**4 (5.1)**	**4**	**1 (1.3)**	**2**
Dysuria	1 (1.3)	1	0 (0)	0	0 (0)	0
Haematuria	0 (0)	0	0 (0)	0	1 (1.3)	1
Urinary retention	1 (1.3)	1	4 (5.1)	4	1 (1.3)	1
Reproductive system and breast disorders	**0 (0)**	**0**	**1 (1.3)**	**1**	**1 (1.3)**	**1**
Penile pain	0 (0)	0	1 (1.3)	1	0 (0)	0
Prostatitis	0 (0)	0	0 (0)	0	1 (1.3)	1

SAE: serious adverse event; VTP: vascular-targeted photodynamic therapy.

Note: SAEs with assessments of very likely, probable, or possible or with missing relationship are considered related.

Source: EMA Assessment Report Tookad[2]

Table 48 Likelihood that serious adverse events related to study drug, device, or procedure (indication population, N=79) would occur following radical therapy

System Organ Class Preferred Term	All-grade		Clinical expert review on likelihood of occurrence following radical therapy
	Subjects n (%)	Events n	
All SAEs related to study drug, device, or procedure	11 (13.9)	14	
Infections and infestations			
Orchitis	1 (1.3)	1	Catheter-related event, which occurs following RP and BT, but is much more rare following EBRT (~5% of men are catheterized). The SAE incidence after VTP is very modest compared to RP and BT
Urinary tract infection	2 (2.5)	2	Same as for orchitis.
Nervous system disorders			

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Transient global amnesia	1 (1.3)	1	Unusual adverse event likely due to anaesthesia, so risk would apply to RP and BT. Importantly, this event is transient.
Renal and urinary disorders			
Dysuria	1 (1.3)	1	This would typically apply to any procedure (RP, BT and EBRT) at a higher rate and with longer duration compared to VTP (e.g., it can last for 3-6 months after BT). There is also an increased risk of dysuria after biopsy.
Haematuria	1 (1.3)	1	This would typically occur in ~5% of patients following RP. It can occur following BT and EBRT at similar or greater rates than after VTP.
Urinary retention	6 (7.6)	6	This can occur following EBRT and BT, but is less common after RP where urinary incontinence is more of an issue. It can also occur in ~5% of patients after biopsy.
Reproductive system and breast disorders			
Penile pain	1 (1.3)	1	The incidence is similar to the one of VTP across radical treatments.
Prostatitis	1 (1.3)	1	This also occurs following EBRT or BT with similar incidence, but not after RP, as the prostate has been removed (nonetheless neuropathic pain can occur).

SAE: serious adverse event; VTP: vascular-targeted photodynamic therapy; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy.

Note: SAEs with assessments of very likely, probable, or possible or with missing relationship are considered related.

Source: EMA Assessment Report Tookad[2]

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Table 49 Duration of serious adverse events related to study drug, device, or procedure (indication population, N=79)

System Organ Class Preferred Term	All-grade		Duration of adverse event	
	Subjects n (%)	Events n	Mean (SE) days	Median (min, max) days
All SAEs related to study drug, device, or procedure	11 (13.9)	14	14 (3.2)	12 (1, 32)
Infections and infestations				
Orchitis	1 (1.3)	1	3 (.)	3 (3, 3)
Urinary tract infection	2 (2.5)	2	16 (6)	16 (10, 22)
Nervous system disorders				
Transient global amnesia	1 (1.3)	1	1 (.)	1 (1, 1)
Renal and urinary disorders				
Dysuria	1 (1.3)	1	1 (.)	1 (1, 1)
Haematuria	1 (1.3)	1	14 (.)	14 (14, 14)
Urinary retention	6 (7.6)	6	19 (5)	20.5 (4, 32)
Reproductive system and breast disorders				
Penile pain	1 (1.3)	1	1 (.)	1 (1, 1)
Prostatitis	1 (1.3)	1	30 (.)	30 (30, 30)

SAE: serious adverse event; VTP: vascular-targeted photodynamic therapy.

Note: SAEs with assessments of very likely, probable, or possible or with missing relationship are considered related.

Source: EMA Assessment Report Tookad[2]

Costs

B8. CS, section B.3.5, table 49 (pages 123-124).

- The cost of physical examinations and nurse consultations in the VTP administration costs are based on primary care, not secondary care. Please justify the rationale for using primary care costs.

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- The company submission states that a lease will be offered for the use of laser generator at a unit cost per VTP procedure.
    - Please clarify whether the leasing fee includes maintenance.
    - Please provide the full cost of a laser generator.
        - Please explore the impact of using the full cost of a laser generator on the cost-effectiveness estimates.

Response:

- The company acknowledges that the costs for physical examinations and nurse consultations should have used secondary care costs. In addition, nurse consultation was estimated based on a 9.22 minute consultant rather than 15.5 minute consultant. Both updates have been made and the results are reported in **Table 50**, **Table 51** and **Table 52**.
- The Company does not plan to commercialise the laser generator by offering it up for purchase. Instead, it plans to lease the laser generator on a per-procedure basis. However, the impact of using the full cost of the laser generator on the cost-effectiveness estimates is presented in **Table 53**, **Table 54** and **Table 55** based on the following assumptions:
    - £[redacted] per laser generator
    - 10 year life span
    - Conservative assumption of [redacted] patients treated over the ten year life span, based on [redacted] patients treated over the first five years (per BIM) and assuming a constant number of [redacted] of patients treated per year after year 5
    - [redacted] centres where patients are treated
    - ~£[redacted] per procedure based on [redacted] procedures per centre per year

  During the NICE clarification teleconference with the ERG and NICE technical team, it was explained to the Company that the primary objective was to understand the Company's commercialization plan. In response, the Company is providing the following details:
    - The Company plans to make the laser generator available in 15 to 20 centres across England during a 3 year roll-out.
    - In terms of roll-out priority, the Company has assigned a priority to centres in **Table 56** below based on geographic location and expertise of centres. In order to facilitate equity, quality and safety of care, the Company will connect into existing cancer referral networks to ensure effective roll-out at the relevant centres. Recommendations are based on profile of hospitals as Centres of Excellence for prostate cancer (as per HCP mapping); interest of lead clinicians in adopting TOOKAD® VTP (reviewed with two expert clinicians); and geographic spread (**Figure 7**).

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Table 50 Using costs of physical examinations and nurse consultations based on secondary care: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	16,609	13.673	11.413	-	-	-	-	-
EBRT	16,999	13.673	11.340	390	0.000	-0.073	Dominated by AS	Dominated by AS
RP	18,752	13.673	11.185	2,143	0.000	-0.227	Dominated by AS	Dominated by AS
BT	19,871	13.673	11.393	3,262	0.000	-0.020	Dominated by AS	Dominated by AS
VTP	26,673	13.673	11.643	10,064	0.000	0.230	43,781	43,781

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

Table 51 Using costs of physical examinations and nurse consultations based on secondary care: pairwise comparisons against padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	26,673	13.673	11.643	-	-	-	-
AS	16,609	13.673	11.413	-10,064	0.000	-0.230	43,781
RP	18,752	13.673	11.185	-7,921	0.000	-0.457	17,319
EBRT	16,999	13.673	11.340	-9,674	0.000	-0.303	31,947
BT	19,871	13.673	11.393	-6,802	0.000	-0.250	27,226

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

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Table 52 Using costs of physical examinations and nurse consultations based on secondary care: without vs with padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	17,579	13.673	11.345	-	-	-	-
World with VTP†	19,844	13.673	11.461	2,264	0.000	0.116	19,444

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively

Table 53 Using purchase option for laser: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	16,609	13.673	11.413	-	-	-	-	-
EBRT	16,999	13.673	11.340	390	0.000	-0.073	Dominated by AS	Dominated by AS
RP	18,752	13.673	11.185	2,143	0.000	-0.227	Dominated by AS	Dominated by AS
BT	19,871	13.673	11.393	3,262	0.000	-0.020	Dominated by AS	Dominated by AS
VTP	26,740	13.673	11.643	10,131	0.000	0.230	44,072	44,072

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

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Table 54 Using purchase option for laser: pairwise comparisons against padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	26,740	13.673	11.643	-	-	-	-
AS	16,609	13.673	11.413	-10,131	0.000	-0.230	44,072
RP	18,752	13.673	11.185	-7,988	0.000	-0.457	17,465
EBRT	16,999	13.673	11.340	-9,741	0.000	-0.303	32,168
BT	19,871	13.673	11.393	-6,869	0.000	-0.250	27,493

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

Table 55 Using purchase option for laser: without vs with padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	17,579	13.673	11.345	-	-	-	-
World with VTP†	19,864	13.673	11.461	2,284	0.000	0.116	19,616

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively

Table 56 Suggested NHS Centres best suited to provide TOOKAD® to patients with a good geographical spread across England*

Lead clinician	Clinician role	NHS Institution	City	Geography
Emberton	Professor of Interventional Oncology, Division of Surgery and Interventional Science, UCL	University College Hospitals NHS Foundation Trust (UCLH)	London	South East England
Hamdy	Professor of Urology & Consultant Urological Surgeon	Nuffield Department of Surgical Sciences, University of Oxford, Oxford	Oxford	Central Southern England

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Cornford	Consultant Urological Surgeon	Royal Liverpool and Broadgreen Hospitals NHS Trust, Liverpool	Liverpool	North West England
Ahmed	Consultant Urologist at Imperial College Healthcare NHS Trust	Imperial College London	London	South East England
Rosario	Clinical Senior Lecturer, University of Sheffield and Honorary Consultant Urological Surgeon to Sheffield Teaching Hospitals Trust	Academic Department of Urology, University of Sheffield, Royal Hallamshire Hospital, Sheffield	Sheffield	North England
Clarke	Professor of Urological Oncology at the Christie and Salford Royal Hospital NHS Foundation Trust in Manchester	Christie and Salford Royal Hospital NHS Foundation Trust in Manchester	Manchester	North West England
Gnanapragasam	Honorary Consultant Urologist	Cambridge University Hospitals NHS Foundation Trust; Department of Urology, Addenbrooke's University Hospital, Cambridge	Cambridge	South East England
Persad	Consultant Urologist	Bristol Royal Infirmary and Southmead Hospital	Bristol	South West England
Dudderidge	Urological Surgeon	Department of Urology, University Hospital Southampton, Southampton	Southampton	South, Central England
Parker	Consultant Clinical Oncologist	Royal Marsden NHS Foundation Trust	London	South East England
Heer	Hon Consultant in Urology	Freeman Hospital (Newcastle upon Tyne Hospitals NHS Foundation Trust)	Newcastle	North East England

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Henry	Associate Professor in Clinical Oncology	Leeds Cancer Centre, St. James's University Hospital, Leeds	Leeds	North England
Kockelbergh	Honorary Professor of Urology	Department of Urology, University Hospitals of Leicester, Leicester, UK.	Leicester	Midlands, England
Streeter	Lead Clinician of East Kent Urology MDT and a Consultant Urological Surgeon.	Kent and Canterbury Hospital, Canterbury and Royal Victoria Hospital, Folkestone.	Canterbury	South East England
Oliver	Consultant Oncologist	The Royal London Hospital School of Medicine and Dentistry	London	South East England

*Recommendations based on profile of hospitals as Centres of Excellence for prostate cancer (as per HCP mapping); interest of lead clinicians in adopting TOOKAD® VTP (reviewed with an expert clinician); geographic spread.

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Figure 7 Map of suggested NHS Centres for TOOKAD® VTP roll-out in England

Excel model

B9. PRIORITY QUESTION. Excel spreadsheet "ID866_Padeliporfin VTP_CE Model_2018Feb27_ACIC - JP 280218 [ACIC]".

The company uses ProtecT trial data on 'prostate cancer specific survival' and 'freedom from disease progression' (including prostate cancer specific deaths) to model overall survival and disease progression (time to metastasis). Survival curves from the ProtecT trial on 'prostate cancer specific survival' and 'freedom from disease progression' are used to partition the cohort between pre-progressed, progressed (to metastasis) and dead states. The company adjusts the 'prostate cancer specific survival' curve to include general

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population all-cause mortality, but it does not adjust the 'freedom from disease progression' curve. As a result, for people starting the model on radical treatment, overall survival is always lower than 'freedom from disease progression'. The apparent consequence is that no one in the radical treatment arms progress to metastasis before they die.

- Please check the calculations and inputs used in cells K4:V164 of the 'CurveOverview' worksheet in the company's model.

Response: The Company agrees that the 'freedom from disease progression' curve needs to be adjusted to include general population all-cause mortality. The results of a scenario analysis adjusting the 'freedom from disease progression' curve to include general population all-cause mortality are presented in **Table 57**, **Table 58** and **Table 59**. Of note, in coherence with answer to question B2 and the revised base case, the TTM curves for AS and VTP have been revised and aligned on the one for RP, EBRT and BT. In this scenario, the comparison of a world without vs a world with VTP yields to an ICER of £15,415/QALY.

Table 57 Adjusting TTM for general mortality and assuming equivalent TTM across all treatments: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	16,650	13.673	11.246	-	-	-	-	-
EBRT	17,522	13.673	11.089	872	0.000	-0.156	Dominated by AS	Dominated by AS
RP	19,334	13.673	10.947	2,684	0.000	-0.299	Dominated by AS	Dominated by AS
BT	20,554	13.673	11.139	3,904	0.000	-0.107	Dominated by AS	Dominated by AS
VTP	26,795	13.673	11.468	10,145	0.000	0.223	45,566	45,566

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

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Table 58 Adjusting TTM for general mortality and assuming equivalent TTM across all treatments: pairwise comparisons against padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	26,795	13.673	11.468	-	-	-	-
AS	16,650	13.673	11.246	-10,145	0.000	-0.223	45,566
RP	19,334	13.673	10.947	-7,461	0.000	-0.522	14,303
EBRT	17,522	13.673	11.089	-9,273	0.000	-0.379	24,467
BT	20,554	13.673	11.139	-6,240	0.000	-0.330	18,934

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

Table 59 Adjusting TTM for general mortality and assuming equivalent TTM across all treatments: without vs with padeliporfin VTP

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	17,889	13.673	11.140	-	-	-	-
World with VTP†	20,006	13.673	11.277	2,116	0.000	0.137	15,415

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively

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Professional organisation submission

Padeliporfin for treating localised prostate cancer [ID866]

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 Association of Urological Surgeons (BAUS)

3. Job title or position	Reader in Urology and Consultant Urological Surgeon
4. Are you (please tick all that apply):	**X** ☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? **X** ☐ 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).	BAUS is a registered charity whose charitable objective is to promote the highest standard in the practice of urology for the benefit of patients by fostering education, research and clinical excellence. The main income streams for BAUS are membership subscriptions and income from the Annual Scientific meeting and other educational meetings and courses. Charity registration number 1127044. Annual report and financial statements are available at: https://www.baus.org.uk/about/governance/trustees_annual_report.aspx
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment of localised prostate cancer is to stop the disease from progressing to disease outside of the prostate, where it would not be amenable to cure, and to do this with minimum side effects.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The absence of any clinically significant prostate cancer on biopsy or MRI criteria in the treated area. Thresholds for the definitions of clinically significant cancer vary, with established definitions requiring on standard transrectal biopsy. Emerging definitions usually incorporate the presence of at least Gleason grade 3+4 disease, with discussions about the relative importance of maximum cancer core length versus grade.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – the aim is to find a treatment that will eradicate all clinically significant cancer in the prostate whilst allowing a patient to maintain good urinary and sexual function. Current radical treatments (radiotherapy and surgery) have significant effects on urinary, sexual and bowel function. Current focal treatments (principally high intensity focussed ultrasound and cryotherapy) show a significant advantage in urinary and sexual function, but there is a lack of equality of access to these across the NHS.
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	Men with low or intermediate risk localised prostate cancer often have a choice between a range of treatment options – traditionally these are: 1. Active surveillance This requires ongoing monitoring consisting of blood tests and clinic visits with MRI scans and biopsies during surveillance. Around 1 in 3 men will change to an active treatment strategy by 5 years, often because of progression defined by biopsy, PSA, clinical examination or MRI. A minority (usually <20%) will choose active treatment despite objective evidence of progression, based on 'surveillance fatigue', preferring treatment to surveillance because of the psychological and practical burden of surveillance. 2. Radical radiotherapy This is usually done with a combination of hormone treatment followed by a course of external beam radiotherapy requiring daily visits taking 4-7 weeks to complete. Hormone therapy will usually be continued for some time after treatment. This is used for clinically significant localised and locally advanced prostate cancer. The rate of urine leakage is low, although men can experience blood in the urine and strictures. 1 in 10 men will have had one or more significant gastro-intestinal events in the first 2 years after treatment. There is a significant impact on sexual function. Radiotherapy can also be given as an implantation of radioactive seeds in a one off procedure without hormones (seed brachytherapy). This approach is used for low and intermediate risk prostate cancer. It has a lower side effect profile than external beam radiotherapy and bowel side effects are rare. The effects on urinary and sexual function are less marked than for external beam radiotherapy.

	3. Radical prostatectomy (surgical removal of the prostate) This involves a general anaesthetic procedure to remove the prostate. The hospital stay is usually 1 -2 days with a catheter for 7-10 days afterwards. Many men have problems with urine leakage immediately after catheter removal, of whom many will have significant recovery by 1 year. The majority of men will not have erections sufficient for intercourse after radical prostatectomy, despite the use of medications and devices. 4. Focal ablative therapy Some UK NHS centres offer focal therapy, using different ablative techniques to treat clinically significant cancer and leaving the rest of the prostate untreated. This can be in the form of freezing (cryotherapy) , ultrasound (high intensity focussed ultrasound, or HIFU) or other modalities. These are permitted by NICE on the condition that the data on these treatments and their functional and oncological outcomes are collected within a registry, to enable further assessment to be done. Typically, urine leakage occurs in 1-2% of men, with 2 in 3 men maintaining erections without the need for tablets and 1 in 3 needing tablets to support the erections. 1 in 4 men need a second treatment by 5 years, and 1 in 10 men will require radical treatment despite an initial ablation approach.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The NICE guidelines on prostate cancer diagnosis and treatment (CG 175), which are due for updating (April 2019). The NICE guidelines on interventional procedures are also relevant (IPG 424 Focal HIFU 2012, IPG 423 2012 Focal cryotherapy and IPG132 2005 on low dose rate brachytherapy).
• Is the pathway of care well defined? Does it vary or are there differences of opinion between	Traditional risk stratification uses Gleason grade (based on pathological examination of biopsy tissue), the prostate specific antigen (PSA) blood test and examination of the prostate by a doctor or nurse (digital rectal examination). Current risk stratification also includes an estimate of the volume of the disease in the prostate,

professionals across the NHS? (Please state if your experience is from outside England.)	based on the maximum length of cancer in a core, and findings on MRI. The appropriate threshold between low and intermediate risk disease is not well established when current tools are used eg low volume Gleason 3 + 4 may carry less risk than high volume Gleason 3 + 3 in all cores of a biopsy sample. For men with low risk disease (particularly low volume Gleason 6 eg ≤5mm cancer core length on biopsy) there is widespread agreement that active surveillance is the most appropriate form of initial management, although the NICE guidelines CG175 do allow men to be offered radical treatment. The latest National Prostate Cancer Audit report shows that a minority of men (275 men, 8%) diagnosed with low risk disease had radical treatment (performance indicator 2, NPCA Report 2017). For men with intermediate risk disease (Gleason 7) there are differences of opinion on whether focal therapy should be offered or not. For those centres who offer focal therapy, the relative benefits of a dramatically reduced side effect profile, particularly in terms of maintaining urinary and sexual function are balanced against the potential need for a second focal treatment, or, occasionally radical treatment.
• What impact would the technology have on the current pathway of care?	The technology would offer another form of focal therapy for prostate cancer. As a needle based technique it would be particularly helpful for anterior tumours. The low side effect profile seen in studies to date is attractive to men with prostate cancer and their clinicians. Due to the short learning curve, and availability of randomised trial data, the widespread availability of this technology across the NHS may be faster than other focal therapy technologies.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology would be used for focal prostate ablation, which is not available to all suitable men in the NHS. The indications would be similar to those for other focal therapies – well defined, often unilateral, clinically significant prostate cancer.

• How does healthcare resource use differ between the technology and current care?	The technology requires a general anaesthetic procedure, with administration of a drug, activated by laser fibres in the prostate. The procedure requires theatre time, and a specialist operator (usually a urologist). This is similar to other focal ablation technologies. It differs from other focal therapies in the use of a drug (padeliporfin), in addition to a device (laser). An alternative active treatment would be radical prostatectomy or radical radiotherapy which both require more complex expensive equipment (robotic assistance for surgery, and radiotherapy machines for radiotherapy). The procedure costs would be expected to be significantly lower for the technology than for either radical surgery or radical radiotherapy. In addition, the expected number of healthcare visits would be much less for the technology, especially because of the low side effect profile. One in 10 men after radical treatment will have at least one significant adverse event in the first 2 years after treatment (genito-urinary events for radical prostatectomy, gastro-intestinal events for radical radiotherapy) according to the National Prostate Cancer Audit report 2017.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist urology practice in secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will be a need to train urologists in the procedure, but as the technical skills are identical to those required for placing needles in the prostate during transperineal biopsy and high dose-rate brachytherapy the training need is not onerous, with many centres having these skills. There would need to be an investment in the laser used to activate the drug – high volume prostate cancer treatment centres would expect to have one of their own, whilst others could hire the equipment as needed, as happens with other urological lasers and focal prostate cancer treatment equipment.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – it offers a significant reduction in side effects compared to standard radical treatment. In the randomised study (Azzouzi et al, 2016) there was no difference in mean sexual and urinary function scores between the active surveillance and treatment groups at 2 years.
• Do you expect the technology to increase length of life more than current care?	As the majority of men with intermediate risk disease do not have a reduced length of life, as long as medical recommendations for treatment are followed, the technology would be unlikely to affect this.
• Do you expect the technology to increase health-related quality of life more than current care?	The technology has significant potential to increase health-related quality of life compared to standard radical treatment. It would usually be offered as a focal treatment where only significant cancer in the prostate is treated and leaving insignificant cancer and non-cancerous areas to reduce the likelihood of side effects. The side effect profile in the randomised study of padeliporfin versus active surveillance showed that there was only a transient reduction in urinary and sexual function in the treatment arm, with no difference between the two groups at baseline and month 24[1]. The majority of men having radical surgery in the UK will experience significant deterioration in sexual function and temporary urine leakage is common, with many men recovering in the first year after surgery. Recent UK data shows that 1 in 10 men having persistent urine leakage requiring more than a pad a day at 1 year, and 1 in 3 men wearing a pad for some leakage or concerns about leakage at 1 year, with 90% of men having surgery wearing pads for urine leakage at 1 month. Men having radical radiotherapy have a lower risk of urine leakage than men having radical surgery (use of >1 pad per day similar to men in active monitoring by 12 months in the PROTECT study[2]). Men having radical radiotherapy will experience significant reduction in sexual function with around one third of men in PROTECT having a significant problem, compared to 2 thirds of men having surgery in PROTECT having a significant problem).

	1. Azzouzi, Abdel-Rahmène, Sébastien Vincendeau, Eric Barret, Antony Cicco, François Kleinclauss, Henk G van der Poel, Christian G Stief, *and others.* "Padeliporfin Vascular-targeted Photodynamic Therapy Versus Active Surveillance in Men with Low-risk Prostate Cancer (CLIN1001 PCM301): An Open-label, Phase 3, Randomised Controlled Trial." *The Lancet. Oncology* 18, no. 2 (2017): doi:10.1016/S1470-2045(16)30661-1. 2. Donovan, Jenny L, Freddie C Hamdy, J Athene Lane, Malcolm Mason, Chris Metcalfe, Eleanor Walsh, Jane M Blazeby, *and others.* "Patient-Reported Outcomes After Monitoring, Surgery, or Radiotherapy for Prostate Cancer." *The New England journal of medicine* 375, no. 15 (2016): doi:10.1056/NEJMoa1606221.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be less effective for men with low volume low risk prostate cancer as they have little to gain from it. It may be less effective for men with high volume high grade (Gleason 4 + 3) cancer on both sides of the prostate, as it is less likely to be able to eradicate that cancer due to a need to treat the cancer using an appropriate treatment margin, but it has not been studied in that group.
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	The technology is easier to use than the current treatment standards of robotic radical prostatectomy or radical radiotherapy. It requires a pharmacy on the site of the operating theatre, but this is standard in hospital treatment facilities.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As treatment is a one off procedure, I would not expect any start/stop rules to be developed once as patient has been assessed as suitable and chosen the padelifporfin treatment.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The substantial benefits would include significant improvements in urinary and sexual function over radical treatment, which is not usually fully captured in QUALYs.
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 – it is an innovative approach to prostate cancer, and has shown a low side effect profile. It could improve the option for men with intermediate risk disease, or high volume low risk disease, offering them a cancer treatment with much fewer side effects than are seen in standard radical treatments.
• Is the technology a 'step-change' in the management of the condition?	Yes – although it is one of a number of ways to deliver focal therapy to prostate cancer, it is particularly straight forward from a technical view point meaning that the learning curve for delivering the treatment is very short, particularly for clinicians who have expertise in placing transperineal needles. In addition, access to focal therapy

	is not equitable across the UK with a minority of centres offering it, and many patients travelling long distances for it.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – to treat localised intermediate risk cancers with a low likelihood of significant reduction in urinary, sexual and bowel function. Whilst other focal therapies seek to offer this, this technology is the only one to have been assessed in a randomised controlled trial. In addition it has a short learning curve compared to the other two most commonly used focal therapies of high intensity focussed ultrasound (HIFU) and cryotherapy.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The risk of side effects with the technology are significantly lower than those reported for standard radical treatment. They are higher than those seen in men on active surveillance, but there was no significant effect on bowel function, and only a temporary reduction in urinary and sexual function scores[1]. Men who have radical treatment for prostate cancer often have troublesome urinary, sexual and bowel side effects with 1 in 10 men experiencing at least one severe complication after radical treatment[2]. 1. Azzouzi, Abdel-Rahmène, Sébastien Vincendeau, Eric Barret, Antony Cicco, François Kleinclauss, Henk G van der Poel, Christian G Stief, *and others.* "Padeliporfin Vascular-targeted Photodynamic Therapy Versus Active Surveillance in Men with Low-risk Prostate Cancer (CLIN1001 PCM301): An

	Open-label, Phase 3, Randomised Controlled Trial." *The Lancet. Oncology* 18, no. 2 (2017): doi:10.1016/S1470-2045(16)30661-1. 2. National Prostate Cancer Audit. Annual Report 2017. https://www.npca.org.uk/annual-report-2017/
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials of the technology began in men who had prostate cancer recurrence after radiotherapy[1,2,]. It was then used in men with no previous treatment for prostate cancer, and men with both Gleason 3 + 3 and Gleason 3 + 4 prostate cancer were included in the development studies[3,4]. The randomised study of the technology versus active surveillance was carried out in men with low volume Gleason 3 + 3 disease confirmed on repeat standard biopsy and without protocol based MRI within the active surveillance arm[5]. This differs from current UK clinical practice in that men on active surveillance would routinely be offered an MRI at the start of surveillance, to detect the 1 in 3 men who have more significant disease than initial standard biopsy showed[6]. Men who have low volume Gleason 3 + 3 which is confirmed as low risk by virtue of having no visible disease on MRI would then routinely be encouraged to have active surveillance rather than active treatment. A significant proportion of men in the study had more significant disease than the baseline biopsy detected, and this is reflected

	in the fact that 44% of men in the surveillance showed Gleason 4 disease at the end of study biopsy, with only 14% of men on active surveillance having a negative biopsy and 49% of men having treatment who had a negative biopsy. 1. Trachtenberg, J, A Bogaards, R A Weersink, M A Haider, A Evans, S A McCluskey, A Scherz, *and others.* "Vascular Targeted Photodynamic Therapy with Palladium-bacteriopheophorbide Photosensitizer for Recurrent Prostate Cancer Following Definitive Radiation Therapy: Assessment of Safety and Treatment Response." *The Journal of urology* 178, no. 5 (2007): doi:10.1016/j.juro.2007.07.036. 2. Trachtenberg, John, Robert A Weersink, Sean R H Davidson, Masoom A Haider, Arjen Bogaards, Mark R Gertner, Andrew Evans, *and others.* "Vascular-targeted Photodynamic Therapy (padoporfin, WST09) for Recurrent Prostate Cancer After Failure of External Beam Radiotherapy: A Study of Escalating Light Doses." *BJU international* 102, no. 5 (2008): doi:10.1111/j.1464-410X.2008.07753.x. 3. Moore, Caroline M, A R Azzouzi, E Barret, A Villers, G Muir, N Barber, J Trachtenberg, *and others.* "Determination of Optimal Drug Dose and Light Dose Index to Achieve Minimally Invasive Focal Ablation of Localized Prostate Cancer Using WST11-Vascular Targeted Photodynamic (VTP) Therapy." *BJU international* (2014)doi:10.1111/bju.12816. 4. Azzouzi, A R, E Barret, J Bennet, C Moore, S Taneja, G Muir, A Villers, *and others.* "TOOKAD® Soluble Focal Therapy: Pooled Analysis of Three Phase II Studies Assessing the Minimally Invasive Ablation of Localized Prostate Cancer." *World journal of urology* 33, no. 7 (2015): doi:10.1007/s00345-015-1505-8. 5. Ayres, Benjamin E, Bruce S I Montgomery, Neil J Barber, Nicola Pereira, Stephen E M Langley, Philippa Denham, and Simon R J Bott. "The Role of Transperineal Template Prostate Biopsies in Restaging Men with Prostate Cancer Managed by

	Active Surveillance." *BJU international* 109, no. 8 (2012): doi:10.1111/j.1464-410X.2011.10480.x. 6. Azzouzi, Abdel-Rahmène, Sébastien Vincendeau, Eric Barret, Antony Cicco, François Kleinclauss, Henk G van der Poel, Christian G Stief, *and others.* "Padeliporfin Vascular-targeted Photodynamic Therapy Versus Active Surveillance in Men with Low-risk Prostate Cancer (CLIN1001 PCM301): An Open-label, Phase 3, Randomised Controlled Trial." *The Lancet. Oncology* 18, no. 2 (2017): doi:10.1016/S1470-2045(16)30661-1.
• If not, how could the results be extrapolated to the UK setting?	Men with MRI visible lower intermediate risk prostate cancer (Gleason 3 + 4 and smaller volume unilateral 4+3) could be treated with the technology, based on the fact that men with known 3 + 4 disease were treated in the development studies, and that a significant proportion of men in the randomised study would have had intermediate risk disease not detected at baseline standard biopsy.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are: • The ability of the technology to eradicate the disease that it is intended to treat • The side effect profile particularly the effects on urinary, sexual and bowel function in comparison to men having radical treatment. Both of these were measured in the trials.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The outcome measure in the RCT was a comparison of progression between the treatment and surveillance, where progression was defined as the presence of 3 or more positive cores on standard biopsy, Gleason pattern 4, or cancer core length ≥ 5mm, PSA rise on 3 consecutive occasions, T3 disease or metastasis. Progression was 58% in the active surveillance arm, and 28% in the treatment arm. The presence of Gleason pattern 4 of high burden may predict long-term clinical outcomes. T3 disease and metastasis are very predictive of a poorer long-term clinical outcome. The presence of 3 or more positive cores, cancer core length of ≥ 5mmand PSA rise on consecutive occasions are less likely to be adequately predict long-term clinical outcomes, in the presence of Gleason 3 + 3 disease.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	A systematic review should include the data of the different names of the product over time (padeliporfin, Tookad, and WST-11).

20. How do data on real-world experience compare with the trial data?	As the technology isn't yet available in the UK there are no data outside of the development and randomised trials.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Men could only be offered treatment by those trained in the technique, who have the appropriate equipment (ultrasound and stepper for transperineal needle placement, laser). As the technique is easier to learn than other focal therapies then it should be available to more men in the UK than current focal treatments.
21b. Consider whether these issues are different from issues with current care and why.	Current focal treatments are concentrated in a few centres across the UK. As many centres have equipment for transperineal needle biopsy of the prostate then learning the technique for the technology assessed here will not be onerous.
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- The technology has been shown to have a safe side effect profile
- Urinary and sexual function is preserved much more effectively with the technology than with radical treatment
- The RCT included men with Gleason 3 + 3 disease with no MRI which differs from UK practice.
- Earlier development work included treatment of men with Gleason 3 + 4 disease
- Other focal therapies are approved by NICE if men are entered into an online registry
-

Thank you for your time.

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

NICE National Institute for Health and Care Excellence

Clinical expert statement

Padeliporfin for treating localised prostate cancer [ID866]

Thank you for agreeing to give us 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.

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 expert statement

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- 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	**Caroline Moore**
2. Name of organisation	**Submitting on behalf of the British Association of Urological Surgeons**

3. Job title or position	**Reader in Urology, University College London**
4. Are you (please tick all that apply):	**Yes** an employee or representative of a healthcare professional organisation that represents clinicians? Yes a specialist in the treatment of people with this condition? Yes a specialist in the clinical evidence base for this condition or technology? ☐ 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 I wrote it,
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

Topic-specific questions	
7. How are low and intermediate risk localised prostate cancer defined in clinical practice?	They are often defined as: Low risk Gleason 3 + 3 AND PSA 10ng/ml or less AND T2c or less Intermediate risk Gleason 3 +4 or 4+3 OR PSA up to 20ng/ml T3a or greater However, the classical risk stratification does not take modern MpMRI into account, and less emphasis is placed on the PSA alone than the Gleason score and MRI findings in clinical practice.
8. What treatment options are available for low and intermediate risk localised prostate cancer?	Active surveillance is recommended for men with low risk prostate cancer, in most cases. Men with intermediate risk localised prostate cancer often have a choice between standard radical treatments (radical prostatectomy or radical radiotherapy, including seed brachytherapy). Some centres offer focal therapy (leaving part of the prostate untreated), which can be delivered using high intensity focussed ultrasound (HIFU), or cryotherapy , or other modalities. Some men with lower intermediate risk disease (eg low volume Gleason 3 + 4) might choose active surveillance.

Thank you for your time.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Mark Emberton**
2. Name of organisation	**UCLH NHS Foundation Trust / UCL**

3. Job title or position	**Dean Faculty of Medical Sciences UCL / Honorary Consultant urologist UCLH NHS Foundation Trust**
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):
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 didn't submit one, I don't 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

Topic-specific questions	
7. How are low and intermediate risk localised prostate cancer defined in clinical practice?	This is changing as the diagnostic pathway is, as a result of recent clinical studies published by our group (PROMIS, Lancet 2017 and PRECISION, NEJM 2018), moving away from random biopsy to an image directed pathway that incorporates MRI. This is under consideration by the NICE Guidelines Committee (Prostate Cancer). There is no overall agreement on the upper and lower threshold for low and intermediate risk prostate cancer. The consensus currently is that the presence of some Gleason pattern 4 is necessary to confer intermediate risk.
8. What treatment options are available for low and intermediate risk localised prostate cancer?	For well-characterised – and this is the key issue - low risk lesions the consensus is that active surveillance is the best strategy to mitigate over-treatment. The over-treatment being conferred by surgery and radiotherapy. In low volume Gleason 4 there is considerable uncertainty as to how these men should be treated. They are at fairly low risk of PC related death (1-8% over 10 years) but the tumour is capable of metastasis.
The aim of treatment for this condition	
9. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	To achieve long term remission or ‘cure’ in the window when ‘cure’ is possible. Once prostate cancer has spread beyond the prostate ‘cure’ is not possible.

disability.)	
10. 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.)	Freedom from progression (biochemical and/or radiological)
11. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Clearly. Nowhere in oncology is there more under-diagnosis and under-treatment (less talked about) as well as the more commonly appreciated over-diagnosis and over-treatment. To date all treatments have directed at the organ not the cancer. The last and only solid tumour in which this is tolerated. Because of this all treatments have been associated with significant – and to many patients – unacceptable side-effect profiles
What is the expected place of the technology in current practice?	
12. How is the condition currently treated in the NHS?	Treatment allocation is based on age, risk but mainly patient preference as the side-effects of treatment tend to drive shared decision making.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE, European Association of Urology, American Urological Association,

• 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.)	No, there is considerable room fro patient and physician preference.
• What impact would the technology have on the current pathway of care?	It would offer a therapeutic opportunity without the attendant side-effects
13. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No, it would be an alternative to current options.
• How does healthcare resource use differ between the technology and current care?	This would have the potential to reduce resource utilisation by avoiding active surveillance and reducing the need for radical whole gland therapies and the acute and chronic toxicities that are associated with them.
• In what clinical setting should the technology be used? (For example, primary or secondary	Secondary care which these days is concentrated in expert regional high volume centres.

care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Very little as the technology required (apart from the drug and laser) are available in most regional centres
14. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, by reducing short and long term toxicity.
• Do you expect the technology to increase length of life more than current care?	No.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes.

15. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Intermediate risk patients or patients with lower risk disease that cannot consent to active surveillance or fail on it.
The use of the technology	
16. 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.)	Should be easier to use than current standard of care given the short learning curves seen in the Phase III multi-centre study

17. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	MRI will increasingly be used to define a target for treatment.
18. 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?	There are some disease specific toxicities that result from surgery that are sometimes not captured. These comprise: ejaculatory function, orgasmic sensation, penile shortening, climacturia (urinary leakage during sexual climax). These are all associated with surgery and to a less extent radiotherapy but not with TOOKAD VTP.
19. 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	Yes, for the reasons described above.

need is met?	
• 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. Men, like all patients everywhere, want treatments that are less invasive and better tolerated.
20. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Urinary incontinence and loss of sexual function has a dramatic effect on quality of life. The impact may be under-representative in the literature because of cognitive dissonance. In other words, patients believe they have been cured by their surgery and, as a result, are willing to tolerate the 'cost' of the cure.
Sources of evidence	
21. Do the clinical trials on the technology reflect current UK clinical practice?	To a degree. The diagnostic pathway is changing very quickly.
• If not, how could the results be extrapolated to	They need to be applied to the new pathway – MRI based.

the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The degree to which the new treatment is tolerated by patients.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Freedom from clinically significant disease and avoidance of radical therapy are both useful and predictive.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
22. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
23. How do data on real-world experience compare with the trial data?	It should be better as within the trial there were many centres who did not have any prior expertise. The treatment, if approved, would be administered in specialist centres.

Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
24b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • A new class of therapy that has a superior toxicity profile than any current therapy • A class of therapy that can adapt to the new diagnostic pathway (MRI based). Surgery and radiotherapy can't. • A high value option for men that have to make the impossible choice between the extremes of radical therapy and Active surveillance • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Padeliporfin for treating localised prostate cancer

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

No competing interests to disclose.

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Graham Scotland acted as the lead health economist for this appraisal: critiqued and reviewed the cost-effectiveness evidence, checked and re-analysed the economic model. Maria Dimitrova contributed to the critique of the cost-effectiveness evidence and the checking of the economic model, and conducted further sensitivity analyses. Dolapo Ayansina acted as statistician: critiqued the statistical methods presented in the submission, checked the numerical results, analyses, tables, and figures related to the review of the clinical effectiveness evidence. Moira Cruickshank and Mari Imamura acted as systematic reviewers: critiqued the company's definition of the decision problem and the clinical effectiveness evidence. Cynthia Fraser acted as information scientist: critiqued the methods used for identifying relevant studies and checked the search strategies used in the submission. Thomas Lam acted as clinical

expert: provided clinical advice and general guidance. Miriam Brazzelli acted as project lead for this appraisal: contributed to the critique of the clinical effectiveness methods, checked the final report and supervised the work throughout the project.

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List of abbreviations

AE	Adverse event
AIC	Akaike information criteria
AS	Active surveillance
AUC	Area under the curve
AUS	Artificial urinary sphincter
BD	Bowel dysfunction
BIC	Bayesian information criteria
BT	Brachytherapy
CI	Confidence interval
CRD	Centre for reviews and dissemination
CS	Company's submission
DRE	Digital rectal examination
DSU	Decision support unit
EBRT	External beam radiotherapy
ED	Erectile dysfunction
EQ-5D	Euroqol 5-dimension
ERG	Evidence review group
HIFU	High intensity focused ultrasound
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IIEF	International index or erectile function
IPSS	International prostate symptom score
IQR	Inter-quartile range
ITT	Intention to treat
IV	Intravenous
LDI	Light Density Index
LYG	Life years gained

MDT	Multi-disciplinary team
mITT	Modified intention to treat
MRI	Magnetic resonance imaging
NHS	National health service
NICE	National institute for health and care excellence
OS	Overall survival
OWSA	One-way sensitivity analysis
PCa	Prostate cancer
PSA	Prostate specific antigen
PSA	Probability sensitivity analysis
PSS	Personal social services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RP	Radical prostatectomy
RR	Risk ratio
RT	Radical therapy
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-12	Medical outcomes study 12-item short-form general health survey
TA	Technology assessment
TEAE	Treatment-emergent adverse event
TNM	Tumour, node, metastasis
TRUS	Transrectal ultrasound
TTM	Time to metastasis
TTO	Time trade off
TTRT	Time to radical therapy
UI	Urinary incontinence
VTP	Vascular-targeted photodynamic therapy
WTP	Willingness to pay

1 Summary

The prostate is a walnut-sized gland at the base of the bladder that is involved in the production of the fluid making up semen. Prostate cancer is the most common cancer diagnosis in males, with the majority being in the 65 to 74 age range. Low risk localised prostate cancer is defined as PSA<10mg/mL and Gleason score<7 and T1-2a (by the TNM classification). Recommended treatment for low risk localised prostate cancer is active surveillance, with radical treatment offered to people with evidence of disease progression. Radical treatments are associated with damage to urinary, bowel and sexual functioning; active surveillance circumvents these consequences in the short term but carries the risk of missing the chance of successful radical treatment. In recent times, focal therapy (i.e., ablation of the dominant or index lesion only) for treating localised prostate cancer has gained increasing attention.

Padeliporfin (TOOKAD®, Steba Biotech S.A., Luxembourg) is a derivative of a photosynthetic pigment of particular aquatic bacteria that source their energy from the sun, which requires illumination by light to become pharmaceutically active. Padeliporfin vascular photodynamic therapy (VTP) is a focal therapy involving intravenous administration of padeliporfin and immediate local activation by 753nm wavelength laser light. A series of pathophysiological events then lead to focal necrosis within a few days. Padeliporfin was granted European marketing authorisation on 10th November 2017.

1.1 Critique of the decision problem in the company submission

The decision problem considered in the company's submission was broadly consistent with the NICE final scope. The outcomes considered by the company included "absence of definitive cancer", a dichotomous variable; in contrast, the NICE final scope specified "disease-free survival", a continuous variable. In addition, the ERG's clinical expert questioned the company's non-standard definition of the outcome "progression of disease".

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical evidence submitted by the company consisted of one phase III, prospective, multi-centre, open-label, randomised controlled trial, CLIN1001 PCM30,

which was administered by the company. The co-primary endpoints were absence of definitive cancer at 24 months and treatment failure (defined as progression of cancer from low to moderate risk or higher over 24-month follow-up). The company conducted both an intention to treat analysis, the "ITT population" (n=413), and an analysis of people with unilateral, low risk disease, excluding very low risk, the "indication population" (n=158).

Results for the indication population showed that 65% of the VTP group and 14.1% of the active surveillance (AS) group had a negative biopsy at 24-month follow-up in the lobe diagnosed at baseline. In the ITT population, 49% of the VTP group and 13.5% of the AS group had a negative biopsy at 24 months. The risk ratios (95%CI) for VTP vs AS were 4.61 (2.60-8.16) and 3.67 (2.53-5.33) for the indication and ITT populations, respectively. Absence of disease progression in the initially diagnosed lobe at 27 months was reported in 90% of the VTP group and 42% of the AS group, in the indication population. Disease progression at 24 months was observed in 28.2% of the VTP group and 58% of the AS group, in the ITT population (hazard ratio, 95%CI: 0.34, 0.24-0.46).

Adverse events (AEs) were common in the VTP group of the safety population, with 94.9% of participants experiencing a total of 939 events. Of these, 78.7% experienced AEs related to drug, device or VTP procedure. In the AS group, 55.1% of participants experienced 307 events in total. Serious AEs were reported in 30.5% of the VTP group and 10.1% of the AS group. At 24 months, the numbers of participants with AEs of special interest in the context of early prostate cancer were greater in the VTP group than the AS group (erectile dysfunction: 38% vs 12%; urinary incontinence: 10% vs 5%; bowel dysfunction: 7.6% vs <1%). There were no prostate cancer-related deaths at 24 months.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG has some concerns about the trial methodology of the CLIN1001 PCM301 trial. The conditions under which the trial was conducted would not be in line with current practice guidelines as the accuracy of tumour localisation in the trial did not meet the requirements for focal therapy. This point was conceded by the study investigators. The ERG is also not satisfied that the risk of false negatives with

regards biopsy sampling in the VTP arm of the trial is sufficiently assuaged by any increase in sampling density.

Analysis of the trial demonstrates significantly better clinical outcomes for padeliporfin VTP when compared with active surveillance over a relatively short period of time (2 years). The ERG notes, however, that there is currently no evidence of its effectiveness compared with radical therapy. Also, there is no available evidence of long term clinical effectiveness of padeliporfin VTP with respect to long term oncological outcomes.

The ERG also notes that disease progression of the active surveillance arm of the trial is substantially higher than what has been reported by other trials and is concerned that this could potentially skew effectiveness in favour of VTP.

The evidence from the trial in relation to health-related quality of life is equivocal. The ERG notes that the company proposal is to provide padeliporfin VTP as an alternative to radical therapy for patients choosing active treatment in order to provide health-related quality of life benefits. However, these benefits have not been adequately demonstrated by the trial results or existing evidence.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a de novo economic model, assessing the cost-effectiveness of padeliporfin VTP compared with AS and radical therapy (radical prostatectomy [RP], external-beam radio therapy [EBRT] and brachytherapy) for a population of adults with unilateral, low-risk, localised and previously untreated prostate cancer. The company reported a full incremental analysis of the five comparators and a pairwise comparison of padeliporfin VTP against each comparator. Further, the company provided an overall cost-effectiveness comparison of a world without padeliporfin VTP (current practice) and a world with padeliporfin VTP, where padeliporfin VTP was assumed to take [redacted] of the market share.

The model took the form of a partitioned survival analysis (PartSA) model, where parametric curves for time to radical therapy (TTRT), time to metastasis (TTM) and overall survival (OS) were used to partition the cohorts between four states: Pre-

radical therapy, post-radical therapy, metastasis, and death. The cohorts in the AS and padeliporfin-VTP arms of the model start in the pre-radical therapy health state, with a proportion progressing to radical therapy over time. In the radical therapy arms of the model, the cohorts start in the post-radical therapy health state.

The TTRT curves for padeliporfin VTP and active surveillance were fitted on data from the company's own CLIN1001 PCM301 trial. For time to metastasis and overall survival, the company relied on data from the ProtecT trial, which compared active surveillance with radical prostatectomy and EBRT, and showed no difference in prostate-cancer-specific survival between the therapies at ten years, but a higher rate of disease progression in the active surveillance arm. In the original model submitted by the company, it was assumed that all treatments would have equal overall survival, but that AS and padeliporfin would follow the higher rate of progression to metastasis observed for AS in ProtecT.

The company digitally extracted data ProtecT Kaplan-Meier data for prostate-cancer-specific mortality and 'freedom from disease progression' (including metastasis or death due to prostate cancer), and fitted parametric curves to the extracted data. In the originally submitted model, prostate-cancer-specific survival was adjusted down to account for general population mortality, but 'freedom from disease progression' was not. This resulted in underestimation of the proportion of patients progressing to metastasis. The company corrected this issue in response to the clarification letter, but at the same time revised a number of other assumptions in their base case. The key change was to assume that for their indication population, both AS and padeliporfin VTP have the same risk of progression to metastasis as those receiving immediate radical therapy. Thus the company's revised base case model assumed equivalent time to metastasis for all treatments.

The sole driver of QALY differences between the treatment comparators in the revised model is the prevalence of three common adverse events associated with prostate cancer treatment; urinary incontinence (UI), erectile dysfunction (ED), and bowel dysfunction (BD). These adverse events are more prevalent following each type of radical therapy (in the post-radical therapy health state) than they are with AS

and padeliporfin VTP. Utility decrements are applied to the proportions experiencing each of the adverse events over time in the model.

The main costs applied in the model include localised prostate cancer treatment costs, annual surveillance/monitoring costs, adjuvant and salvage therapy costs (post-radical therapy), adverse event management costs, metastasis treatment costs, and end-of-life (palliative care) costs.

For the company's revised base case, the ICER for padeliporfin VTP is £15,946 versus radical prostatectomy, £26,728 versus EBRT and £21, 533 versus Brachytherapy. However, all the radical therapies are dominated by active surveillance in the full incremental analysis, and the ICER for padeliporfin VTP versus AS against comes to £49,415. For the world with versus the world with padeliporfin VTP, the company's revised ICER comes to £17,287.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG reviewed the company's model and identified a number of concerns. The first of these related to the way that the prostate-cancer-specific survival and freedom from disease progression curves from ProtecT were being used to partition the cohorts. The company revised this issue at the clarification stage, but did not demonstrate its impact in isolation from their other revised assumption of equal disease progression across all the treatment arms. This is an important assumption which may be realistic given the low risk characteristics of the indication population, combined with the intensive monitoring and relatively low threshold for initiating radical therapy in CLIN1001 PCM301. However, there is a lack of long-term data from the CLIN1001 PCM301 trial to verify it.

In the revised model the key factors that affect cost-effectiveness are the relative costs of the alternative primary treatment strategies, time to radical therapy following padeliporfin VTP and AS, the prevalence of adverse events by treatment modality, and the cost and utility impact of adverse events.

The ERG identified a number of concerns with the respect to these factors:

1. The cost applied for padeliporfin VTP did not appear to very detailed, and the ERG are uncertain if all the resources involved in its administration have been adequately measured and valued (e.g. time in theatre, duration of stay, and pre-treatment planning costs). However, the same issues may apply to the planning costs for AS and the radical therapies.
2. The costs applied for the RP and EBRT are sourced from a previous study which included bottom-up costings, which appear low in comparison with the HRG based reference costs (applied in previous NICE guideline models).
3. There is uncertainty surrounding the most appropriate choice of parametric distribution for TTRT on padeliporfin VTP and AS, and the choice of distribution has a significant impact on the ICERs for padeliporfin VTP.
4. The company have sourced all their data on the prevalence of adverse events from a previous modelling study, which did not include a formal meta-analysis of adverse event rates by treatment modality. More recently published randomised data from the ProtecT trial calls into question some of the applied values and differences in prevalence between treatments. This relates particularly to the applied difference in the prevalence of bowel dysfunction between AS and RP in the model, when the ProtecT trial showed that bowel function was unchanged and no different between these groups.
5. Reviewing the original source of the applied utility decrement for bowel dysfunction, the ERG believe that the company have overestimated the reduction. In the original study, the difference in utility between those with and those without gastrointestinal toxicity was -0.1 rather than -0.16 applied in the company's model.
6. Regarding the costs of radical therapies, the ERG believe that assumptions about the proportion of patients receiving adjuvant hormone therapy (with RP and EBRT) and adjuvant EBRT (with RP) are questionable.
7. Regarding the cost of treating bowel dysfunction, the ERG believe the company may have inadvertently applied this on annual basis, when the original source suggests it may have been intended to represent a total mean treatment costs per patient rather than an annual cost per patient. It is not entirely clear from the source document.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

- The submission was generally coherent.
- The company model was relatively simple and easy to follow. Given the assumptions of equivalent survival and metastatic progression across treatment options, it is clear what is driving the model.

1.6.2 Weaknesses and areas of uncertainty

- The main source of evidence provided by the company is limited to a phase III trial.
- There is some concerns about whether this trial represents the best evidence to inform current clinical practice (see comments on section 1.3 above).
- The trial only presents short term (24 months) evidence of the effectiveness of padeliporfin VTP. Evidence for longer term effectiveness is not available.
- There a number of uncertainties surrounding key input parameters and assumptions in the cost-effectiveness model.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

In addition to the sensitivity analysis conducted by the company, the ERG carried out a number of additional scenario analyses to explore the impact of changing a number of uncertain input parameter values and assumptions. In addition to the choice of parametric function for TTRT, the ERG believe the most important uncertainties relate to:

1. The comparative prevalence of the key adverse events (UI, ED and BD) following the alternative treatment modalities; and
2. The health state utility and cost-impact of bowel dysfunction

When a number of alternative assumptions are applied simultaneously to the company's revised base case, the ICER for VTP increases above £30,000 per QALY gained against all comparators.

2 Background

2.1 Critique of company's description of underlying health problem

The Company's description of localised prostate cancer appears accurate and appropriate to the decision problem, in terms of prevalence, symptoms and complications. The company describes the prostate as a walnut-sized gland situated at the base of the bladder. The prostate surrounds part of the urethra, which carries urine from the bladder and sperm from the testicles to the penis, and it produces the fluid that makes up semen, in combination with sperm and fluids produced by other glands.

There are various types of prostate cancer, depending on the type of the cell the cancer starts in. The most common type of prostate cancer is acinar adenocarcinoma, which develops in the gland cells lining the prostate gland. This type of prostate cancer tends to be slow growing and unlikely to spread, although not in all cases.[1]

Definitive diagnosis of prostate cancer is based on histopathological verification of tissue from a biopsy, usually conducted on the basis of a digital rectal examination (DRE) and/or raised PSA level.[2]

Staging of prostate cancer is carried out by clinicians to classify the size of the tumour and whether it has spread elsewhere in the body. The 2009 TNM (Tumour, Node, Metastasis) classification is used for staging.[2] Tumour (T) describes the size of the tumour, ranging from T1 to T4 for prostate cancer. T1 indicates the tumour is too small to be seen on a scan or felt during a physical examination. T1 is further divided into T1a, T1b (found during surgery for other reasons, with cancer present in <5% [T1a] or >5% [T1b] of the tissue) and T1c (found by biopsy). T2 indicates the cancer is completely inside the prostate gland; T2 is sub-divided into T2a (cancer in only half of one side of the prostate), T2b (cancer in more than half of one side of the prostate) and T2c (cancer in both sides of the prostate). T3 indicates the cancer has broken through the capsule of the prostate gland. T4 indicates the cancer has spread into other organs of the body. The company's submission relates to people diagnosed with T1c or T2a prostate cancer only.

Node (N) classifies spread of the cancer to the lymph nodes as N0 (no spread to the nearby lymph nodes) or N1 (the cancer has spread to lymph nodes close to the prostate). This submission relates to people with no spread of prostate cancer, i.e. N0.

Metastasis (M) classifies spread of the cancer to other parts of the body out with the pelvis as M0 (no spread to body parts) or M1 (spread of the cancer to other parts of the body). The present submission describes people with M0 prostate cancer only.[1]

In addition to TNM staging, microscopic examination of tumour biopsies are carried out to determine its Gleason score, which is the grade, or histologic pattern of cells, in the tissue. The Gleason score consists of two grades from 1 to 5 (with higher numbers indicating increasing abnormality of cells); first, the most extensive pattern plus, second, the highest pattern, regardless of its extent. The lowest definitive Gleason score for prostate cancer is 6 (3+3), with 3+2, 2+3 and 2+2 all being encompassed in the Gleason score of ≤6. This report relates only to people with prostate cancer Gleason score ≤6. A Gleason score of 7 can signify a majority of well-differentiated cancer cells with a lesser amount of more poorly differentiated cancer cells (Gleason 4+3=7) or the reverse (Gleason 3+4=7). Gleason scores 8, 9 and 10 relate to well-differentiated cancer cells.[2, 3]

Prostate specific Antigen (PSA) is a protein produced by both normal and cancerous prostate cells. Raised levels of PSA in the blood may indicate prostate cancer, but can also be a sign of other conditions, and prostate cancer is not generally diagnosed solely on the basis of PSA levels. In the UK, there is no routine PSA screening as there is currently insufficient evidence to show that the benefits offset the risks.[4]

The risk of biochemical recurrence of localised prostate cancer is classified on the basis of staging, Gleason scores and PSA levels, as follows:[2, 5]

- Low risk:
  - PSA<10ng/mL and
  - Gleason score<7 and
  - T1-2a

- Intermediate risk:
  - PSA 10-20ng/mL or
  - Gleason score 7 or T2b
- High risk:
  - PSA>20ng/mL or
  - Gleason score>7 or
  - T2c.

It has been estimated that, in England in 2011, 17% of prostate cancer diagnoses were low risk, 47% intermediate risk, 26% high risk and 10% metastatic. [6]

Prostate cancer is the most frequent cancer diagnosis in males and accounts for 13.4% of all cancers in England, for all ages combined. A total of 40489 diagnoses of "malignant neoplasm of prostate" (Code C61) were registered in England in 2016. [7] Hospital Episode Statistics for admitted patient care in England for the year 2016-2017 show that there were 75276 finished consultant episodes for "malignant neoplasm of prostate" (code C61.X). In addition, there were 918 finished consultant episodes for "carcinoma in situ: prostate" (code D07.5).[8]

The majority of people diagnosed with prostate cancer in England are 50 years of age or older[6] with the most prominent age groups being 65 to 69 years and 70 to 74 years of age.[8] The risk factors for prostate cancer have yet to be definitively established.[9]

The management of localised prostate cancer continues to be contentious.[10] Treatment decisions should be made following a discussion about all options with a multidisciplinary team, and the benefits and risks of each treatment have been explored with the patient.[2] The main treatments for localised prostate cancer currently include radical treatments that aim to cure the cancer (i.e. surgery, external radiotherapy) or active surveillance, with the aim of monitoring the cancer and treating if and when it becomes clinically necessary. Radical treatments carry the risk of damage to urinary, bowel and sexual functioning, whilst active surveillance avoids these consequences in the short term but with the risk of missing the chance of successful radical treatment.[11] In recent years, focal therapy (defined as ablation of the

dominant or index lesion only)[12] has gained increasing attention in the treatment of localised prostate cancer. The key principles of focal therapy are to treat the cancer and preserve tissue whilst reducing the consequences of radical treatment to the prostate and surrounding areas.[13-16]

Padeliporfin (TOOKAD®, Steba Biotech S.A., Luxembourg) is a derivative of a photosynthetic pigment of particular aquatic bacteria that source their energy from the sun. Padeliporfin requires illumination by light to become pharmaceutically active. Padeliporfin vascular photodynamic therapy (VTP) involves intravenous administration of padeliporfin and immediate local activation by 753nm wavelength laser light. A series of pathophysiological events then lead to focal necrosis within a few days. Padeliporfin was granted European marketing authorisation on 10th November 2017.[17]

2.2 Critique of company's overview of current service provision

The company appropriately refers to the current NICE pathways (CG175) for localised prostate cancer[18] and radical treatment for localised prostate cancer.[19] For low risk localised prostate cancer, the NICE recommendation is to offer active surveillance as an option to people for whom radical prostatectomy or radical radiotherapy is suitable.[20] NICE CG175 states that the decision to proceed from active surveillance to radical treatment should take account of the individual's personal preferences, comorbidities and life expectance. Radical treatment should be offered to people with localised prostate cancer who have chosen active surveillance and who have evidence of disease progression. In addition, for people having radical treatment, NICE recommends information and support before treatment.[20]

Figure 1 presents the company's updated version of the NICE pathway with its intended position of padeliporfin.

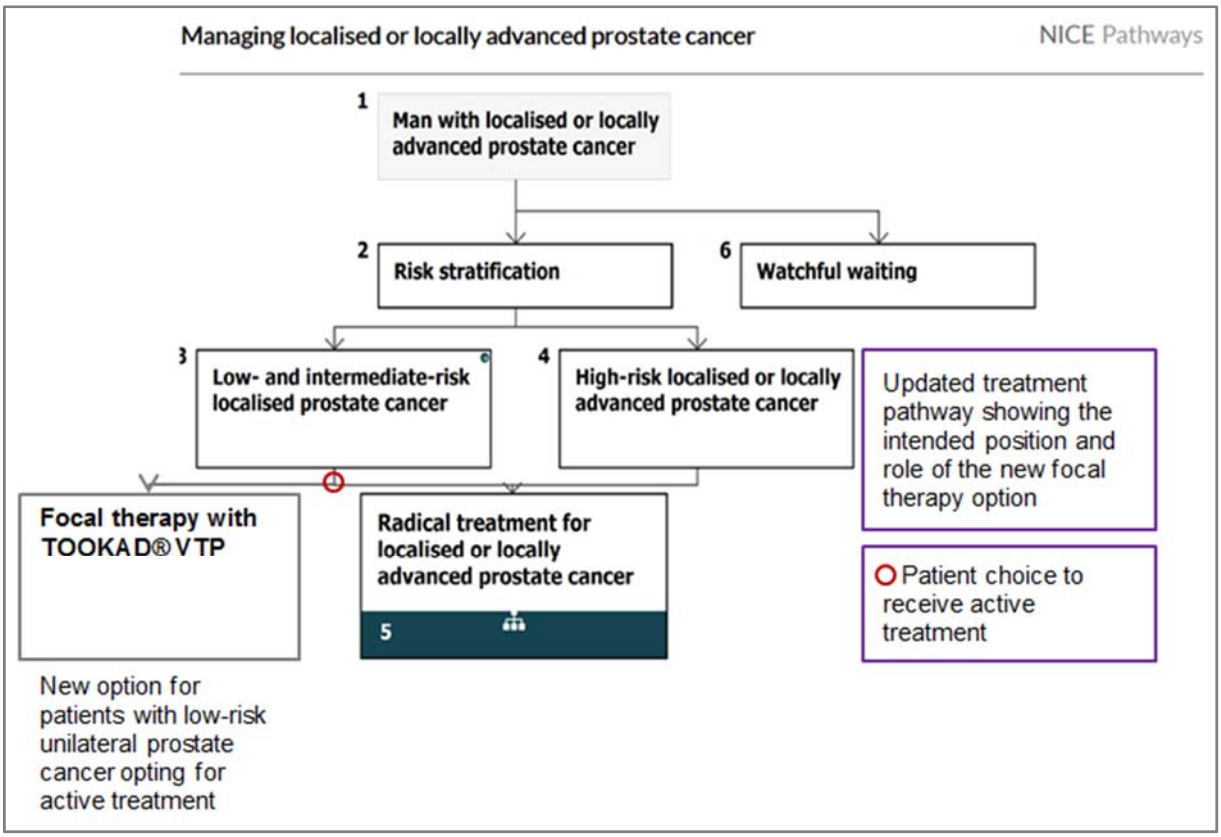

Figure 1 Company's intended positioning of padeliporfin in the NICE pathway for managing localised prostate cancer (reproduced from Figure 3 of the company's submission)

The company propose padeliporfin as an alternative to radical therapy for people choosing active treatment as a result of symptoms experienced, clinical indicators, recommendation by clinician or psychological factors. The company states that "*focal treatment with padeliporfin VTP can reduce overtreatment by radical therapies and provide HRQoL benefits*". The company further states "*It is of the utmost importance to clarify that we agree with leading clinicians who do not see focal therapy as an alternative to active surveillance in patients with confirmed, clinically insignificant, low risk disease*".

3 Critique of company's definition of decision problem

3.1 Population

The NICE final scope for this appraisal specified the population as "*adults with unilateral, low-risk localised prostate cancer*". The decision problem addressed by the company's submission specified that the population was "*as per scope*".

Inclusion criteria for the company's CLIN1001 CLIN1001 PCM301 trial were:
1. Low-risk prostate cancer diagnosed with 1 existing TRUS-guided biopsy using from 10 to 24 cores performed less than 12 months prior to enrolment and showing the following:

- *Gleason 3 + 3 prostate adenocarcinoma, as a maximum*
- *2 to 3 cores positive for cancer (subjects with only 1 positive core could be*
- *included provided they had at least 3 mm of cancer core length.)*
- *A maximum cancer core length of 5 mm in any core*

2. Cancer clinical stage up to T2a (pathological or radiological up to T2c disease permitted)
3. PSA of 10 ng/mL or less (5 ng/mL or less for subjects using a 5-α-reductase inhibitor [5-ARI])
4. Prostate volume ≥ 25 cc and < 70 cc
5. Male subjects aged 18 years or older (CSR).

The company further specified a "*restricted indication population*", defined as excluding:

1. *Patients with bilateral disease (as they would require two VTP procedures; a second VTP treatment is not recommended after detection of residual cancer, either in the ipsilateral or in the contralateral lobe, even in absence of progression)*
2. *Very low risk patients with 1 or 2 positive cores and a PSA density ≤0.15 ng/mL/cm^3 (as they have a lower likelihood of upstaging or progression, especially with modern biopsy technique).*

The restricted indication population is consistent with the approved indication.

The approved indication for padeliporfin (TOOKAD®, Steba Biotech S.A., Luxembourg) is "*monotherapy for adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and:*

- *Clinical stage T1c or T2a,*
- *Gleason Score ≤ 6, based on high-resolution biopsy strategies,*
- *PSA ≤ 10 ng/mL,*
- *3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1 -2 positive cancer cores with ≥ 50 % cancer involvement in any one core or a PSA density ≥ 0.15 ng/mL/*cm"[3] [17]

The ERG agrees that the company's definition of the population is appropriate and is consistent with current guidelines,[2] albeit the ERG's clinical expert considers the definition of the number of positive cancer cores to be irrelevant in this context.

3.2 Intervention

The NICE final scope specified the intervention as "*padeliporfin for use in vascular-targeted photodynamic therapy*", which is consistent with the decision problem addressed in the company's submission.

Padeliporfin is a water-soluble, light-activated, vascular occluding, photosensitising agent which is used in vascular-targeted photodynamic therapy (VTP). Padeliporfin is activated by 753nm light, thereby generating reactive oxygen species within blood vessels, which lead to vessel thrombosis and tissue necrosis in the vicinity of the light-delivery fibre.[21] Padeliporfin is infused intravenously and circulates systemically, remaining in the vascular system with only the targeted area of the prostate illuminated.[17, 22] Irreversible damage to cell membranes and small arterioles is thus induced and blood and nutriment supply to tumours is blocked.[23, 24]

Padeliporfin is formulated as a powder for solution for injection. It is restricted to hospital use only and should only be used by personnel trained in the VTP procedure. The recommended dose of padeliporfin is one single dose of 3.66mg/kg. Padeliporfin is administered as part of focal VTP; the procedure is performed under general

anaesthetic after rectal preparation. Prophylactic antibiotics and alpha-blockers may be prescribed at the physician's discretion. Retreatment of the same lobe or sequential treatment of the contralateral lobe of the prostate are not recommended.

The solution is administered by intravenous injection over 10 minutes. The prostate is then illuminated immediately for 22 minutes 15 seconds by laser light at 753nm delivered via interstitial optical fibres from a laser device at a power of 150mW/cm of fibre, delivering an energy of 200J/cm. Planning of optical fibre positioning should be performed at the beginning of the procedure using the treatment guidance software. During the procedure, the number and length of the optical fibres are selected depending on the shape and size of the prostate and the optical fibres are positioned transperineally into the prostate under ultrasound guidance to achieve a Light Density Index (LDI) ≥1 in the targeted tissue. Treatment should not be undertaken in patients where an LDI ≥1 cannot be achieved.

A tabulated list of adverse reactions to padeliporfin is presented in Table 1. Adverse reactions are listed by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to < 1/10), and uncommon (≥1/1000 to < 1/100).

Table 1 Summary of adverse reactions considered related to padeliporfin and/or the study device and/or the study procedure in the pooled safety analysis (reproduced from Table 1 of Summary of Product Characteristics)[25]

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Genito-urinary tract infection
	Uncommon	Prostatic abscess
Psychiatric disorders	Uncommon	Libido decreased Affective disorder Encopresis
Nervous system disorders	Uncommon	Headache Dizziness Sciatica Sensory disturbance Formication
Eye disorders	Uncommon	Eye irritation Photophobia
Vascular disorders	Common	Haematoma Hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	Exertional dyspnoea
Gastrointestinal disorders	Common	Haemorrhoids Anorectal discomfort Abdominal pain Rectal haemorrhage
	Uncommon	Abdominal discomfort Abnormal faeces Diarrhoea
Hepatobiliary disorders	Common	Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Ecchymosis
	Uncommon	Rash Erythema Dry skin Pruritus Skin depigmentation Skin reaction
Muscular and connective tissue disorders	Common	Back pain
	Uncommon	Groin pain Muscle haemorrhage Haemarthrosis Musculoskeletal pain Pain in extremity
Renal and urinary disorders	Very common	Urinary retention Haematuria Micturition disorders
	Common	Urethral stenosis Urinary incontinence
	Uncommon	Ureteric haemorrhage Urethral haemorrhage Urinary tract disorders
Reproductive system and breast disorders	Very common	Perineal pain Male sexual dysfunction

System organ class	Frequency	Adverse reaction
	Common	Prostatitis Genital pain Prostatic pain Haematospermia
	Uncommon	Genital haemorrhage Penile swelling Prostatic haemorrhage Testicular swelling
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Asthenia Catheter site pain Laser device failure Infusion site bruising Nodule Pain Application site erythema
Investigations	Common	Abnormal clotting
	Uncommon	Blood lactate dehydrogenase increased Blood triglyceride increased Gamma-glutamyltransferase increased Blood cholesterol increased Blood creatine phosphokinase increased Low density lipoprotein increased Neutrophil count increased PSA increased Weight increased White blood cell count increased
Injury, poisoning and procedural complications	Common	Perineal injury
	Uncommon	Surgical procedure repeated Contusion Post-procedural urine leak Procedural pain Post-procedural discharge Fall

The ERG's clinical expert is of the opinion that there is no place for padeliporfin VTP in the current treatment pathway for localised low risk prostate cancer. The basic premise is that most people with low risk prostate cancer do not need treatment at the outset, and for the majority of patients, treatment of such patients will lead to overtreatment. Nevertheless, there is a need to monitor such patients in the long run, such that those patients who are destined to progress must be identified and treated with radical treatment if and when it becomes necessary (i.e., before the disease becomes locally advanced or metastatic). This premise is currently fulfilled by active surveillance. The ERG's clinical expert considers that focal treatments, in order

to fit into the treatment pathway, need to demonstrate the following: oncological outcomes which are at least equivalent to radical treatment, whilst having better QoL outcomes; and better oncological outcomes than active surveillance (including the radical treatment pathway for those who progress or are reclassified while on active surveillance).

3.3 Comparators

The NICE final scope specified the comparator as active surveillance, with radical surgery or radical radiotherapy for people who chose radical treatment. The decision problem addressed by the company was consistent with the NICE final scope.

3.4 Outcomes

The outcomes specified in the NICE final scope were disease-free survival; progression of disease; need for radical treatment; mortality; adverse effects of treatment (for example, erectile dysfunction or incontinence); health-related quality of life. The decision problem addressed by the company's submission specified that the outcomes addressed were "*as per scope*". The co-primary outcomes in the phase III trial, the CLIN1001 PCM 301 trial, which has been included in the company submission as main source of evidence for the effectiveness and safety of padeliporfin are:

- Absence of definitive cancer (specified as absence of any histology result definitively positive for cancer at 24 months)
- Treatment failure (specified as progression of cancer from low to moderate or higher risk over the 24 months of follow-up).

The secondary efficacy endpoints of the CLIN1001 PCM 301 trial were:

- Total number of cores positive for cancer
- Notification of initiation of any radical therapy (any radical treatment for prostate cancer other than the treatment to which the subject was randomised, including surgery, radiotherapy [external beam, brachytherapy, focused], high-intensity focused ultrasound, cryotherapy, hormonal therapy for cancer, or chemotherapy for cancer)

- Proportion of subjects with a severe prostate cancer-related event: cancer extension to T3, metastasis, or prostate cancer-related death

The secondary safety endpoints of the CLIN1001 PCM 301 trial were:

- AEs
- Rate of special AEs: incontinence, erectile dysfunction, urinary symptoms
- Laboratory tests (haematology, serum chemistry, and urinalysis)
- Vital signs (oral body temperature, blood pressure, and pulse rate)
- Physical examination
- ECG data
- The proportion of subjects with significant changes in scores of IIEF-15 or IPSS questionnaires and EQ-5D.

The ERG's clinical expert notes the company's co-primary endpoint of progression, in that it either delays or avoids the need for radical treatment. This is considered an assumption in the context of the basic premise of the need to treat people who definitively do require radical treatment. For such people, radical treatment has to be performed as soon as it becomes necessary and is proven to be effective oncologically. The outcomes of these patients in the long run, following treatment with padeliporfin, is currently unknown; the enforced delay in receiving radical treatment may potentially adversely affect oncological outcomes. The ERG's clinical expert further notes that previous studies in this population of focal therapy (using HIFU or cryotherapy) have used absence of disease (i.e., histologically proven) as the primary outcome of treatment efficacy. The ERG's clinical expert questions the company's non-standard definition of the outcome 'progression'.

The ERG further notes that the outcome described in the scope as "disease-free survival" (a continuous outcome) is reported by the company as "absence of definitive cancer" (a dichotomous outcome).

3.5 Other relevant factors

No subgroups were specified in the NICE final scope. The company performed two subgroup analyses:

- A pre-planned subgroup efficacy analysis of disease status at baseline (unilateral or bilateral disease) in the ITT population
- A post-hoc subgroup analysis in people with unilateral low risk disease (excluding very low risk), which was ultimately the approved indication and, therefore, reported in the main efficacy and safety outcomes sections of the company's submission.

Table 2 presents the NICE final scope and the decision problem addressed by the company and includes both the company's and the ERG's comments.

Table 2 Comparison of NICE final scope and decision problem addressed by the company

	Final scope issued by NICE	**Decision problem addressed in the company's submission**	**Comments from the company**	**Comments from the ERG**
Population	Adults with unilateral, low risk localised prostate cancer	Adults with unilateral, low risk localised prostate cancer	None	None
Intervention	Padeliporfin for use in vascular-targeted photodynamic therapy	Padeliporfin for use in vascular-targeted photodynamic therapy	None	None
Comparators	• Active surveillance For people who choose radical treatment: • Radical surgery • Radical radiotherapy	• Active surveillance For people who choose radical treatment: • Radical surgery • Radical radiotherapy	None	None
Outcomes	• Disease-free survival • Progression of disease • Need for radical treatment • Mortality	• **Disease-free survival (reported as "absence of definitive cancer")** • Progression of disease • Need for radical treatment • Mortality	None	The ERG's clinical expert questions the use of the outcome "progression" and its definition, as specified by the company. The ERG notes that "disease-free survival" (a

	Final scope issued by NICE	Decision problem addressed in the company's submission	Comments from the company	Comments from the ERG
	• Adverse effects of treatment (for example, erectile dysfunction or incontinence) • HRQoL	• Adverse effects of treatment (for example, erectile dysfunction or incontinence) • HRQoL		continuous variable) is reported by the company as "absence of definitive cancer" (a dichotomous variable)
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. 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. The cost of the laser equipment needed to deliver this technology needs to be included in the cost effectiveness analysis. Costs will be considered from an NHS and Personal Social Services perspective	Cost effectiveness is expressed in terms of incremental cost per quality-adjusted life year. A lifetime horizon (40 years) for estimating clinical and cost effectiveness was used. The cost of the necessary laser equipment was included in the cost effectiveness analysis. Costs from an NHS and Personal Social Services perspective are considered	None	None

	Final scope issued by NICE	Decision problem addressed in the company's submission	Comments from the company	Comments from the ERG
Subgroups	None specified	Pre-planned subgroup analysis: disease status at baseline (unilateral vs bilateral) Post-hoc subgroup analysis: people with unilateral, low risk disease	None	None

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company submission provides full details of the searches that were undertaken to identify studies for the clinical effectiveness review. The major relevant databases were searched: MEDLINE, MEDLINE In-Process, EMBASE and CENTRAL for primary studies and CDSR, DARE and HTA Database via the Cochrane Library for evidence syntheses. The searches were undertaken in November 2017 for reports published since 2008 in the English language. The company undertook two systematic reviews: the first for randomised controlled trials, comparative studies or evidence syntheses on padeliporfin or active surveillance for low risk localised prostate cancer and the second for adverse events (specifically urinary incontinence, erectile dysfunction and radiation-induced enteropathy) following radical therapy for low risk localised prostate cancer. The search strategies are documented in full in Appendix D of the company submission and are reproducible.

The main search strategies for 'review 1' combined three facets: low risk prostate cancer; padeloporfin or active surveillance; and relevant study designs (Table 1). A supplementary section of the search identified a subset of the records retrieved from the main search and is described as a "pragmatic search". This restricted the full search to reports relating to disease progression or metastases. The ERG was unclear as to why this was done but may have facilitated efficient screening of records.

The search strategies for 'review 2' combined four facets: low risk prostate cancer; prostatectomy, radiotherapy or brachytherapy; adverse events including urinary incontinence, erectile dysfunction or radiation-induced enteropathy; and relevant study designs (Table 2).

The search strategies were considered fit for purpose, including both relevant controlled vocabulary and a comprehensive set of text terms with appropriate use of the Boolean operators.

4.1.2 Inclusion criteria

The inclusion criteria for the searches are presented in Table 3 below.
One publication, the CLIN1001 PCM301 trial, met all the inclusion criteria and was included as main source of evidence in the company's review of clinical effectiveness.[26]

At clarification, the company stated that the first study of padeliporfin VTP commenced in September 2008 and that the first significant results for AS cohorts were also published in 2008. The company further clarified its 2008 start date for the searches by explaining that publications prior to that date would have been on outdated techniques that do not reflect current practice and that earlier publications were covered in high-quality systematic reviews or are no longer relevant. The 2014 start date for the conference abstract search was justified by the company on its assumption that high-quality abstracts from more than three years earlier would have since been published as full-text articles. The ERG is broadly satisfied with the company's approach.

The company provided raw extracted data on the efficacy and safety (Table 20, Appendix D) and rate of radical therapy (Table 21, Appendix D) for padeliporfin VTP and active surveillance (AS), and radical therapy safety (Table 22, Appendix D). At clarification, the company explained that these data were not used directly to inform the main submission as the CLIN1001 PCM301 study provided the primary body of evidence for clinical effectiveness.[26] The company further provided summaries of the studies. The ERG noted that while these studies were not used to inform the company's review of clinical effectiveness evidence or the economic model.

Table 3 Inclusion criteria for the company's systematic review of clinical effectiveness (reproduced from Tables 4 and 5, Document B of company's submission)

	Search #1	**Search #2**
Population	Low-risk localised prostate cancer	
Intervention	Padeliporfin Active surveillance	Radical therapies • Radical prostatectomy • Radical radiotherapy o EBRT o Brachy therapy
Comparator	No restriction	
Outcomes	**Systematic search:** • Rate of radical treatment (events per patient year) • Adverse events **Pragmatic search within overall search:** • Time to metastasis	Specific adverse events: • Urinary incontinence • Erectile dysfunction • Radiation-induced enteropathy
Study design	Systematic search: • RCTs • Non-RCTs/ observational studies • Systematic reviews, meta-analyses & HTAs for screening reference lists Pragmatic search within overall search: • RCTs & comparative studies only	• RCTs • Non-RCTs/ observational studies • Systematic reviews, meta-analyses & HTAs for screening reference lists
Time frame	2008 or later	• Publication date for journal articles, HTA reports etc: 2008-2017/18 • Publication date for conference abstracts: 2014-2017

Note. EBRT: external beam radiotherapy; RCT: randomised controlled trial; HTA: health technology assessment.

The ERG further noted that the numbers of excluded studies reported in the PRISMA flow diagrams relating to the two searches (Tables 16 and 17, Appendix D) were not consistent with the reference lists of excluded studies (Tables 18 and 19, Appendix D). At clarification, the company explained that the Tables 18 and 19 did not include the final list of references of excluded studies, and updated versions were provided.

In general, the ERG found the company's description of the systematic review of clinical effectiveness somewhat difficult to follow, both due to inaccuracies and omissions in the text and provision of data which were not particularly pertinent to the submission.

4.1.3 Critique of data extraction

The company did not report whether the methods of the systematic review of clinical effectiveness were based on published guidance. The company did not report the number of reviewers involved in the key stages of the systematic review process (i.e., title/abstract screening, full-text screening, and data extraction) and the level of independence of researchers at each stage. It is, therefore, unclear to the ERG whether the company's methods were appropriate.

4.1.4 Quality assessment

The company does not report whether its quality assessment process was based on published guidance or the number of reviewers involved. It appears to the ERG that the company's quality assessment of CLIN1001 PCM301 is based upon the recommendations of the Cochrane and CRD handbooks. The company's assessment of CLIN1001 PCM301 is summarised in Table 4.

Table 4 The company's quality assessment of the included study (CLIN1001 PCM301) (reproduced with modification from Table 2, Document B of company's submission)

Assessment criteria	CLIN1001 PCM301
Selection bias	
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Observation bias	
Were the care providers, participants and outcome assessors blind to treatment allocation?	No. Treatment was open-label (participants and investigational site staff were not masked to study treatment). Investigators assessing primary efficacy outcomes were masked to treatment allocation.
Other bias	
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
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
Did the authors of the study publication declare any conflicts of interest?	Yes

In general, the ERG agrees with the company's quality assessment of CLIN1001 PCM301, with some exceptions. First, the company states that baseline demographic and disease characteristic were well balanced between the VTP and AS groups. The ERG notes that, in the ITT population, the mean baseline PSA level in the VTP group (6.19ng/mL, SD 2.114) was higher than that of the AS group (5.91 ng/mL, SD 2.049). The difference between groups was also evident in the indication population, albeit in the opposite direction, with the VTP mean PSA (6.98 ng/mL, SD 1,796) being lower than the mean PSA in the AS group (7.12 ng/mL, SD 1.704). In the indication population the proportion of people with T2a staging was higher in the VTP group (17.5%) than in the AS group (9%). Some baseline characteristics were balanced across groups but showed a difference between the ITT and indication

populations. For example, estimated prostate volume in the ITT population was 42.5cm^3 for both VTP and AS groups, whilst, in the indication population, was 37.2 cm^3 and 37.6 cm^3, respectively. Time since diagnosis was longer for the ITT population (6.34 and 6.02 months, respectively) than for the indication population (4.92 and 4.81 months, respectively). In addition, the ranges of values for time since diagnosis suggests some heterogeneity in the population, with some participants having been diagnosed up to around four years earlier than others in the ITT population. In the indication population, however, the range of time since diagnosis was up to around 20 months only. Second, the company states that "*investigators assessing primary efficacy outcomes were masked to treatment allocation*". The ERG clinical expert notes that the prostate lobe is known to shrink after treatment with VTP, thus possibly introducing bias into the outcome assessment process, despite assessors not definitively knowing the treatment allocation.

The ERG conducted a broad assessment of the methods used by the company for the systematic review of clinical effectiveness evidence using the CRD criteria. Results are presented in Table 5.

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.1.5 Evidence synthesis

The company's clinical effectiveness evidence focused upon a phase III, prospective, multi-centre, open-label, randomised controlled trial, the CLIN1001 PCM301trial, which was sponsored by the company.[26]

4.1.6 Characteristics and findings of included trial(s)

Summary characteristics of the CLIN1001 PCM301 trial are presented in Table 6.

Table 6 Characteristics of the RCT (CLIN1001 PCM301) included in the company's review of clinical effectiveness

Characteristic	CLIN 1001 PCM301 details
Countries/no of centres	Belgium, Finland, France, Germany, Italy, Netherlands, Spain, Sweden, Switzerland, UK; 47 centres (4 UK centres, with 17 participants)
Main inclusion criteria	• Low-risk prostate cancer diagnosed with TRUS-guided biopsy; maximum Gleason 3+3; 2 to 3 cores positive for cancer (people with 1 positive core could be included provided they had at least 3mm of cancer core length); maximum 5mm cancer core length in any core • Cancer clinical stage up to T2a (pathological or radiological up to T2c disease permitted) • PSA ≤10ng/mL • Prostate volume ≥25cc and < 70cc • Age ≥18 years
Main exclusion criteria	• Any prior or current treatment for prostate cancer • Life expectancy <10 years • Contra-indication to MRI (e.g. pacemaker, history of allergic reaction to gadolinium) • Factors excluding accurate reading of pelvic MRI (e.g. hip prostheses) • Any condition or history of illness or surgery that may pose an additional risk to men undergoing the VTP procedure
Intervention	Padeliporfin VTP (n=206); single 10-minute IV infusion of 4mg/kg padeliporfin followed by local illumination with laser light at 753nm with a fixed power of 150mW/cm over 22 minutes 15 seconds
Comparator	Active surveillance (n=207). Included: • PSA testing at 3-monthly intervals • Annual prostate biopsy
Co-primary endpoints	• Absence of definitive cancer: absence of any histology result definitely positive for cancer at 24 months

Characteristic	CLIN 1001 PCM301 details
	• Treatment failure: Progression of cancer from low to moderate or higher risk over the 24 months of follow-up. Moderate or higher risk is defined as one or more of: o More than 3 cores definitively positive for cancer when considering all histological o results available during follow-up in the study o Any Gleason primary or secondary pattern of 4 or more o At least 1 cancer core length > 5 mm o PSA > 10 ng/mL in 3 consecutive measures o Any T3 prostate cancer o Metastasis o Prostate cancer-related death
Secondary efficacy endpoints	• Total number of cores positive for cancer • Notification of initiation of any radical therapy (any radical treatment for prostate cancer other than the treatment to which the subject was randomised, including surgery, radiotherapy [external beam, brachytherapy, focused], high-intensity focused ultrasound, cryotherapy, hormonal therapy for cancer, or chemotherapy for cancer) • Proportion of subjects with a severe prostate cancer-related event: cancer extension to T3, metastasis, or prostate cancer-related death
Other outcomes	Used in economic model and specified in scope: • Frequency of adverse events Specified in scope: • Total number of cores positive for cancer • Proportion of patients with a severe prostate cancer-related event • Proportion of patients with significant changes in scores of the IPSS questionnaire or the IIEF questionnaire and EQ-5D
Subgroup analyses	Post-hoc subgroup analysis: • Patients with unilateral low risk disease excluding very low risk (ultimately, the approved indication)
Duration of follow-up	24 months
Source of funding	STEBA Biotech SA, Luxembourg

Table 7 presents the demographic and disease characteristics of the two treatment groups at baseline in the trial population ('ITT population') and in a subgroup of the population targeted by the indication ('indication population', representing 38% of the overall trial populations). The company's assessment was that the two treatment groups were well balanced in both randomised groups. The ERG has some reservations, as noted above.

Table 7 Baseline characteristics of participants in the RCT (CLIN 1001 PCM301) included in the company's review of clinical effectiveness (reproduced with modifications from Tables 9 and 10, Document B, and Table 1, Clarification Document)

Baseline characteristic	Indication population		ITT population	
	VTP (N=80)	AS (N=78)	VTP (N=206)	AS (N=207)
Age, years, mean (SD; range)	63.9 (6.27; 48-74)	62.3 (6.32; 46-73)	64.2 (6.70; 45-85)	62.9 (6.68; 44-79)
Race, n (%)				
Caucasian	78 (97.5)	78 (100)	202 (98.1)	206 (99.5)
Other	2 (2.5)	0	4 (1.9)	1 (0.5)
Body mass index, kg/m^2, mean (SD; range)	26.05 (3.328; 18.8-37.5)	26.47 (3.360; 19.3-40.6)	26.47 (3.337; 18.8-38.6)	27.34 (3.947; 18.8-44.8)
Time since diagnosis, months, mean (SD; range)	4.92 (4.656; 0.6-20.3)	4.81 (4.106; 0.2-18.9)	6.34 (8.536; 0.2-54.2)	6.02 (7.887; 0.2-47.4)
TNM staging, n (%)				
T1	66 (82.5)	71 (91.0)	178 (86.4)	180 (87.0)
T2a	14 (17.5)	7 (9.0)	28 (13.6)	27 (13.0)
PSA, ng/mL, mean (SD; range)	6.98 (1.796; 1.0-10.0)	7.12 (1.704; 3.1-10.0)	6.19 (2.114; 0.1-10.0)	5.91 (2.049; 0.5-10.0)
Estimated prostate volume, cm^3, mean (SD; range)	37.2 (9.67; 25-68)	37.6 (9.63; 25-66)	42.5 (12.49; 25-70)	42.5 (11.76; 25-70)
Disease status, n (%)				
Unilateral disease, low risk	80 (100)	78 (100)	87 (42.2)[a]	80 (38.6)[a]
Unilateral disease, very low risk	0	0	70 (34.0)	83 (40.0)
Bilateral disease	0	0	49 (23.8)	44 (21.3)
Total number of pre-treatment biopsy cores, mean (SD; range)	13.8 (3.64; 10-24)	14.3 (4.06; 10-26)	13.6 (3.31; 10-25)	13.6 (3.55; 10-26)
Total number of positive pre-treatment biopsy cores, mean (SD; range)	2.2 (0.74; 1-3)	2.1 (0.76; 1-3)	2.1 (0.68; 1-3)	2.0 (0.72; 1-3)
Number of positive cores, n (%)				
1	15 (18.8)	18 (23.1)	39 (18.9)	52 (25.1)
2	34 (42.5)	33 (42.3)	110 (53.4)	100 (48.3)
3	31 (38.8)	27 (34.6)	57 (27.7)	55 (26.6)
Total cancer core length, mm, mean (SD; range)	5.3 (2.64; 0-14)	3.8 (2.72; 0-12)	4.3 (2.31; 0-14)	3.8 (2.40; 0-11)

Note. [a]From Table 1, Clarification document; VTP: vascular-targeted photodynamic therapy; AS: active surveillance; SD: standard deviation; TNM: Tumour, node, metastasis; PSA: prostate specific antigen.

Outcome data from the trial were presented at the initial trial period of 24 months. The company submission also included preliminary data from the ongoing CLIN1001 PCM301-FU5 follow-up study (the follow-up evaluations at months 36 and 48) where available. However, the company stated that follow-up beyond two years was poor.

Table 8 presents a summary of clinical effectiveness results of the company's CLIN1001 PCM 301 trial.

Table 8 Efficacy outcomes from the RCT (CLIN1001 PCM301) included in the company's review of clinical effectiveness

Reported outcome	Indication population		ITT/ safety population[a]	
	VTP (N=80)	AS (N=78)	VTP (N=206/197)[a]	AS (N=207)
Absence of disease				
Negative biopsy at 24M in lobe diagnosed at baseline	52/80 (65.0%)	11/78 (14.1%)	NR	NR
Negative biopsy result at 24M	NR	NR	101/206 (49.0%)	28/207 (13.5%)
Crude risk ratio Negative biopsy at 24M (VTP vs AS)	(In lobe diagnosed at baseline) 4.61 (2.60-8.16) (p<0.001)[b]		3.67 (2.53-5.33) (p<0.0001)	
Disease progression				
No ipsilateral disease progression				
15M	75/79 (95%)	40/73 (55%)	NR	NR
[†]Relative risk (95%CI); p	1.73 (1.39, 2.14); p<0.0001			
27M	64/71 (90%)	28/67 (42%)	NR	NR
[†]Relative risk (95%CI); p	2.16 (1.60, 2.90); p<0.0001			
Progression at 24M	NR	NR	58/206 (28.2%)	120/207 (58.0%)
Hazard ratio (95% CI) for disease progression	NR	NR	0.34 (0.24-0.46) (p<0.0001)	
Initiation of radical therapy				
Cumulative % of radical therapies initiated (n analysed)				
0-12M	1% (n=80)	7% (n=78)	1% (n=206)	4% (n=207)
12-24M	8% (n=78)	39% (n=71)	7% (n=195)	33% (n=189)
24-36M	13% (n=68)	46% (n=43)	14% (n=177)	44% (n=117)
36-48M	28% (n=52)	57% (n=30)	24% (n=128)	53% (n= 76)
Hazard ratio (95% CI) for initiation of radical therapy	0.293 (0.163-0.527)		0.305 (0.207-0.450)	
Health-related quality of life				
IPSS score, mean (SD), n				

Reported outcome	Indication population		ITT/ safety population[a]	
	VTP (N=80)	AS (N=78)	VTP (N=206/197)[a]	AS (N=207)
Baseline	6.6 (5.42), n=80	6.2 (4.40), n=78	7.6 (6.09), n=179	6.6 (5.30), n=185
24M	6.0 (5.46), n=80	8.0 (5.80) , n=78	6.6 (5.47), n=165	8.2 (6.47), n=207
Mean change from baseline (SD)	-0.7 (5.36), n=80	1.8 (5.21), n=78	-1.0 (5.86), n=151	1.3 (5.80), n=138
Difference in adjusted change from baseline Mean (95% CI); p	-2.3 (-3.8, -0.8); p=0.004[c]		-1.2 (-2.2, -0.3); p=0.013[c]	
IIEF score, mean (SD), n				
Baseline	18.3 (10.07),	20.8 (9.83), n=78	18.6 (10.22), n=184	20.6 (9.92), n=188
24M	15.3 (10.07)	16.9 (9.67) , n=78	15.0 (10.70), n=159	16.8 (11.17), n=152
Mean change from baseline (SD)	-3.0 (8.53), n=79	-3.9 (8.47), n=78	-3.9 (9.25), n=150	-3.4 (9.73), n=140
Difference in adjusted change from baseline Mean (95% CI); p	0.0 (-2.5, 2.4); p=0.979[c]		-1.0 (-2.5, 0.6); p=0.233[c]	
EQ-5D VAS score, mean (SD)				
Baseline	83.2 (12.04)	80.2 (12.71)	82.5 (12.31) n=179	81.8 (12.09) n=184
24M	81.5 (14.09)	77.2 (14.88)	80.9 (14.28) n=166	79.2 (13.25) n=150
Change from baseline	-1.8 (11.3) n=60	-3.0 (16.02) n=47	-2.5 (12.50) n=151	-2.7 (12.87) n=136
Difference in adjusted change from baseline Mean (95% CI); p	2.5 (-2.4, 7.4); p=0.315[c]		0.7 (-2.1, 3.4); p=0.641[c]	

Note. [†]Computed by ERG. [a]All outcomes ITT population except for the health related quality of life outcomes, which is the safety population. [b]At clarification, the company provided the adjusted RR using the 12M biopsy results where the 24M biopsy result was missing. The RR (95%CI) was 4.63 (2.70-7.94); [c]Adjusted in ANCOVA model with treatment group as the fixed effect and baseline scores as covariates. Missing scores imputed using the Markov Chain Monte Carlo method. VTP: vascular-targeted photodynamic therapy; AS: active surveillance; IPSS: International Prostate Symptom Scores; IIEF: International Index of Erectile Function; EQ-5D VAS: EuroQoL 5D Visual analogue scale; M: month; NA: not applicable; NR: not reported;

Disease-free survival (co-primary endpoint A)

Disease-free survival was defined as absence of positive histology results (i.e. biopsy) at 24 months. In the indication population, the proportion of participants with a negative biopsy at 24 months in the lobe diagnosed at baseline was higher in the VTP group than in the AS group (65.0% vs. 14.1%, RR 4.61, 95% CI 2.60-8.16). At clarification, the company provided the adjusted risk ratio using the 12 months biopsy results where the 24 months biopsy result was missing. The risk ratio was comparable to the originally reported risk ratio (4.63, 95%CI 2.70-7.94). These results were broadly consistent with the ITT populations, where the proportions of negative biopsies were 49% and 13.5% in the VTP and AS groups, respectively (RR 3.67, 95% CI 2.53-5.33).

Progression of disease (co-primary endpoint B)

In the indication population, the proportion of participants with no disease progression at 15 months in the initially diagnosed lobe was higher in the VTP group as compared to the AS group (95% versus 55%). Results of absence of disease progression in the whole gland for the indication population were also reported by the company: 73% versus 36% for the VTP and AS groups, respectively, at 15 months, and 64% versus 25%, respectively, at 27 months. The results for the ITT population were broadly consistent, with fewer participants in the VTP group showing disease progression at 24 months compared with the AS group (28.2% versus 58.0%, HR 0.34, 95% CI 0.24-0.46).

Initiation of radical therapy

Results for the indication population show that patients who had VTP were less likely to undergo radical therapy by 48 months compared with those under AS (8% versus 39%, HR 0.293, 95% CI 0.163-0.527). In the ITT population, 7% of participants with VTP had initiated radical therapy by 48 months compared with 33% of AS participants.

Health-related quality of life

Health-related quality of life was largely determined by the company with the urinary incontinence and erectile dysfunction status, captured by the International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF), respectively. The IPSS scores (in which higher scores represent a poorer state) indicate a slight improvement after VTP, and worsening after AS, in urinary symptoms at 24 months, both in terms of the indication population and in the ITT population. The IEFF scores at 24 months showed little difference in erectile function between the randomised groups in either population. The EQ-5D scores for the VTP and AS groups in the safety population were similar at baseline and at 24 months, with a similar small decreases at 24 months from baseline. In the indication population, participants in the VTP group reported slightly higher scores at both baseline and 24 months, and the mean change from baseline was smaller, as compared to the AS group but this difference was not significant.

The company's safety population included all participants randomised to VTP who received any amount of VTP or initiated any study treatment-related procedure, and all participants randomised to receive active surveillance. At clarification, the company explained that adverse events reported as 'all AEs' relating to the VTP group included all AEs, regardless of

its association to the drug, device or procedure; in contrast, the AEs relating to ‘drug, device or VTP procedure’ included a narrower set of AEs, related only to the drug, device or procedure, as evaluated by the investigator.

Table 9 presents an overview of randomisation-emergent adverse events (AEs) by treatment group for the indication population and the safety population, respectively.

Table 9 Adverse event outcomes from CLIN1001 PCM301 (median follow-up 24 months)

Outcome	Indication population		Safety population	
	VTP (N=79)	AS (N=78)	VTP (N=197)	AS (N=207)
Mortality (ITT population)				
Prostate cancer-related mortality at 24M, n	NR	NR	0/194	0/194
Overview of AEs at 24M				
All AEs, n (%), total events	74/79 (93.7%), 344	39/78 (50.0%), 98	187/197 (94.9%), 939	114/207 (55.1%), 307
AEs related to drug, device or VTP procedure, n (%), total events	63/79 (79.7%), 194	NA	155/197 (78.7%), 551	NA
All SAEs: n (%), total events	21/79 (26.6%), 32	7/78 (9.0%), 7	60/197 (30.5%), 88	21/207 (10.1%), 25
SAEs related to drug, device or VTP procedure, n (%), total events	11/79 (13.9%), 14	NA	30/197 (15.2%), 39	NA
AEs leading to study discontinuation, n (%)	0/79 (0%)	0/78 (0%)	2/197 (1.0%)[a]	1/207 (0.5%)[b]
AEs leading to death, n (%)	0/79 (0%)	0/78 (0%)	1/197 (0.5%)[c]	0/207 (0%)
Any grade AEs of special interest in the context of early stage prostate cancer				
Erectile dysfunction, n (%)				
24M	28/79 (35%)	10/78 (13%)	74/197 (38%)	24/207 (12%)
36M	NR	NR	2/149 (1.3%)	9/129 (7.0%)
48M	NR	NR	6/147 (4.1%)	2/119 (1.7%)
Urinary incontinence, n (%)				
24M	8/79 (10%)	6/78 (8%)	19/197 (10%)	10/207 (5%)
36M	NR	NR	5/149 (3.4%)	4/129 (3.1%)
48M	NR	NR	4/147 (2.7%)	2/119 (1.7%)
Bowel dysfunction[d], n (%)				
24M	11/79 (13.9%)	0/78 (0)	15/197 (7.6%)	1/207 (<1%)
36M	NR	NR	NR	NR
48M	NR	NR	NR	NR

Note: [a]One myocardial infarction and one anaphylactic reaction; [b]One ureteric cancer; [c] One myocardial infarction; [d]Includes gastrointestinal hypermotility, gastrointestinal disorder, anal fistula, gastrooesophageal reflux disease, gastritis, abnormal faeces, rectal or anal haemorrhage, haematochezia, and frequent bowel movements;
AE: adverse event; AS: active surveillance; M: month; SAE: serious adverse event; NR: not reported; VTP: vascular-targeted photodynamic therapy

Mortality

Prostate-cancer related death was rare during the trial period of 24 months, occurring in none of 194 participants in the VTP group in the ITT population. No prostate cancer-related death was observed in the equivalent AS group. There was no prostate cancer-related death in the indication population during the trial period.

Death due to adverse event was reported in one of the 197 participants in the VTP group in the safety population; a 59 year old male died of a myocardial infarction 34 weeks & 2 days after VTP treatment. The death was assessed as unrelated to the drug, device or procedure by both investigator and sponsor. There were no deaths due to adverse events in the indication population during the trial period.

Adverse events: 24 Months

Overall, incidence of AEs was higher in the VTP group than in the AS group. In the safety population, 187 of 197 participants (94.9%) and 114 of 207 participants (55.1%) in the VTP and AS groups, respectively, experienced at least one AE (ERG calculated $p<0.0001$). Relatively higher rates of AEs in the VTP group than in the AS group were explained by events related to the study drug, device or procedure (155/197 in the VTP group). Serious adverse events were experienced by 30.5% of participants who received VTP compared with 10.1% in the AS group, in the safety population.

As expected, at 24 months, the numbers of participants with AEs of special interest in the context of early prostate cancer, notably, erectile dysfunction, urinary incontinence, and bowel dysfunction, were greater in the VTP group than the AS group (erectile dysfunction: 38% versus 12%; urinary incontinence: 10% versus 5%; bowel dysfunction: 7.6% versus <1%). However, the differences between the groups disappeared over time, albeit there remained a greater incidence of erectile dysfunction at 48 months in the VTP group as compared to the AS group (4.1% versus 1.7%). The company reported time with genitourinary toxicity ratios including both erectile dysfunction and urinary incontinence for the safety population of 0.93 (95% CI 0.47-1.03) over 24 months and 0.58 (95% CI 0.27-0.64) over 48 months. Results for the indication population were comparable, i.e. 0.85 (95% CI 0.37-1.18) and 0.62 (95% CI 0.23-0.83) over 24 and 48 months, respectively. The fact that the ratio of relative time with toxicity in the overall trial population is greater at 48 months as

compared to 24 months, is a result of the stable reduction in risk of RT between 24 and 48 months. [17]

The company stated that a limitation of the AE data was that the CLIN1001 PCM301 trial only captured AEs that occurred until the crossover to radical therapy. Adverse events occurring after radical therapy were, therefore, not reported consistently across all patients because initiation of radical therapy (considered a treatment failure) led to discontinuation of follow-up in some cases. At clarification, the company reported that 12/206 (5.8%) participants in the VTP group and 60/207 (29%) participants in the AS group received RT during the trial. Of these, 3/12 (25%) and 6/60 (10%) participants, respectively, were lost to follow-up.

The most common AEs (occurring in ≥5% of participants in either treatment group) are summarised in Table 10. The rates of AEs and SAEs in the indication population were comparable to the safety population.

Table 10 Randomisation-emergent adverse events (occurring in ≥5% of participants in at least one group) in the safety population of the CLIN101 PCM301 trial (median follow-up 24 months)

Adverse event, n (%)	VTP (N=197)	AS (N=207)
Gastrointestinal disorders	69 (35%)	18 (8.7%)
General disorders & administration site conditions	18 (9.1%)	12 (5.8%)
Infections and infestations	59 (29.9%)	37 (18%)
Injury, poisoning, and procedural complications	36 (18.3%)	9 (4.4%)
Investigations	13 (6.6%)	3 (1.5%)
Musculoskeletal and connective tissue disorders	30 (15.2%)	19 (9.3%)
Nervous system disorders	22 (11.2%)	10 (4.8%)
Psychiatric disorders	16 (8.1%)	7 (3.4%)
Renal and urinary disorders (including urinary incontinence)	133 (67.5%)	38 (18.7%)
Reproductive system and breast disorders (including erectile dysfunction)	121 (61.4%)	41 (20.1%)
Respiratory, thoracic, and mediastinal disorders	15 (7.6%)	7 (3.4%)
Skin and subcutaneous tissue disorders	13 (6.6%)	10 (4.9%)
Surgical and medical procedures	16 (8.1%)	6 (2.9%)
Vascular disorders	20 (10.2%)	10 (4.9%)

Note. Summarised from data in Table 3 of the company's clarification document. Data in Table 3 of Azzouzi 2017 and Table 28 of the company's CSR contain some slight variations, which the company attributes to transcription errors

Adverse events: 48 months

At month 48, in the safety population, 25 participants in the VTP group (17%) and 20 participants in the AS group (16.8%) had experienced at least one AE. The most common AE was erectile dysfunction, with 6 participants in the VTP group (4.1%) and two in the VTP group (1.7%). Compared with AS, the other most frequently experienced AEs in the VTP group were pollakiuria (2% versus 1.7% in the AS group), prostatitis (1.4% versus 0.8%), congenital, familial and genetic disorders (1.4% versus 0), hydrocele (1.4% versus 0) and urinary tract infection (1.4% versus 0).

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Methods

The CLIN1001 PCM301 trial recruited subjects with low-risk prostate cancer diagnosed by transrectal ultrasound (TRUS)-guided biopsy. Men assigned to the VTP arm underwent pre-treatment multiparametric MRI, which was reviewed to make recommendations on the number, length, and position of interstitial optical fibres using treatment guidance software.

In correspondence with the study investigators, Yan and colleagues[27] pointed out that the accuracy of tumour localisation in the CLIN1001 PCM301 trial did not meet the requirements for focal therapy. The study investigators agreed with this point[26] but noted that they used the diagnostic pathway that was standard at the time of recruitment to the trial although it has turned out to be inadequate. The study investigators also agreed that reduction in volume of treated tissue compared to non-treated tissue presented sampling challenges at biopsy that could increase the risk of false negatives. This would necessarily favour VTP over AS. However, they posit (as reasonable mitigation) that treated tissue was "*subject to standard sampling and, as a result, was exposed to an increased sampling density compared with non-treated tissue*".

The ERG notes that the conditions under which the CLIN1001 PCM301 trial was conducted would not be in line with current practice guidelines and that a study designed today would (in the investigators' own words) "*look very different*".[26] There is also no evidence available to support the investigators assertion that the risk of false negatives with regards biopsy sampling in the VTP arm of the trial has been sufficiently assuaged by any increase in sampling density.

4.2.2 Absence of definitive cancer

The VTP arm had significantly higher proportion of subjects with negative biopsy in the lobe diagnosed at baseline (RR=4.63; 95% CI 2.70-7.94) and negative biopsies in both lobes (RR=4.39; 95% CI 2.18-8.83) than the AS arm by 24 months. Longer term effectiveness data is not available for padeliporfin VTP.

4.2.3 Progression of disease

The CLIN1001 PCM301 trial demonstrates significantly lower disease progression of the VTP arm when compared to the AS arm in both the indication and ITT populations.

The ERG notes that disease progression in the whole gland of the active surveillance arm of the CLIN1001 PCM301 trial was 75% at month 27 in the indication population (Table 15 of company submission) and 58% at month 24 in the ITT population (Table 16 of company submission) in contrast to the less than 30% of those on active monitoring over 10 years of follow-up of the ProtecT trial.[10] This large difference is in spite of the fact that the ProtecT trial had a mixture of participants with low and intermediate risk disease and a few with high risk disease, while CLIN1001 PCM301 had only participants with very low and low risk disease. The PIVOT trial, which had a mixture of participants with low, intermediate, and high-risk disease, reported 68.4% disease progression among the observation arm of the trial after at least 8 years of follow-up (range: 8 – 15 years). [33]

The large proportion of the CLIN1001 PCM301 trial active surveillance arm that had disease progression in a relatively short period of time may skew any benefit in favour of VTP. This may be mitigated by the fact that the surveillance was biopsy-based in CLIN1001 PCM301 as against the PSA based surveillance of the ProtecT trial. However, the PIVOT trial monitoring was also biopsy-based.

The ERG could find no evidence that this was sufficient mitigation to explain the large differences in disease progression among the active surveillance arms of these trials.

The ERG also notes that 4 subjects in the indication population and 11 in the ITT population received treatment in a previously treated lobe after month 12. This is however not recommended as per the SmPC and EPAR.[17, 25]

4.2.4 Initiation of radical therapy

The CLIN1001 PCM301 trial demonstrates significantly reduced hazards of initiation of radical therapy in the VTP arm compared with the AS arm.

The ERG notes that the time-to-event used is time to 'notification' of initiation of radical therapy. It is not clear if this is an adequate surrogate for the time to initiation of radical therapy.

4.2.5 Health-related quality of life

The health-related quality of life outcomes analysis yielded mixed results. The IPSS demonstrated a slight but non-significant improvement in urinary symptoms of the VTP arm at month 24 from baseline in both the indication and safety populations while the AS arm showed slightly but significantly worsening urinary symptoms in these populations. Consequently, there was a significant difference favouring the VTP arm.

The IIEF measure demonstrated significant reduction in erectile function in both arms of the trial for both indication and safety populations but there was no difference in these reductions between arms.

There was no significant change in EQ-5D scores within the two trial arms of the indication population at month 24 and no difference between arms but in the safety population, there was a slight, though significant, decrease in EQ-5D scores in both trial arms. There was however no difference between arms.

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

The company did not carry out any meta-analysis for padeliporfin VTP as only one phase III trial was identified. The ERG did not identify any further trials that could have been used.

The company in its submission stated that it did not perform any indirect or mixed treatment comparisons as "*no appropriate network could be established due incongruence of key endpoints used in the cost-effectiveness model, e.g., time to radical therapy, between padeliporfin VTP/AS and radical therapies (i.e., RP, EBRT and brachytherapy)*".

The ERG is broadly in agreement that no indirect or mixed treatment comparisons could be done given the available evidence.

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

No indirect comparison was undertaken.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Relative risk of absence of progression of ipsilateral disease at month 15 and month 27 was computed for the indication population of the CLIN1001 PCM301 trial (see Table 8 above).

Test of difference in proportions of overall adverse events between VTP and AS arms of the safety population of the CLIN1001 PCM301 trial (see section 4.16, *Adverse events: 24 Months)*.

4.6 Conclusions of the clinical effectiveness section

The clinical effectiveness submitted was based on the CLIN1001 PCM301 trial. The results of this trial have demonstrated significantly better clinical outcomes for padeliporfin VTP compared with active surveillance over a relatively short period of time (2 years). The VTP arm of the trial had higher rates of absence of cancer and lower rates of disease progression at 24 months than the AS arm. There was also lower rates of initiation of radical therapy in the VTP arm compared to the AS arm. However, its effectiveness when compared with radical therapy (radical surgery or radiotherapy) is yet to be demonstrated.

The ERG notes that long term oncological outcomes for subjects treated with padeliporfin VTP is still unknown and it cannot be assumed that they will have similar outcomes with those choosing active surveillance or radical therapy (whose outcomes have been shown to be similar) from the outset.

The adverse events profile of padeliporfin VTP is expectedly significantly higher than that of active surveillance.

5 Cost effectiveness

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 State objectives of cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

The company conducted a systematic literature review to identify prior cost-effectiveness studies investigating padeliporfin VTP in low-risk localized prostate cancer in the UK context. Reports of cost effectiveness were sought by the company by searching MEDLINE, MEDLINE In-Process, EMBASE, NHS Economics Evaluation Database (NHS EED) and HTA Database (via Cochrane Library) in November 2017. The searches were not restricted by language or timeframe. The search strategies are documented in full in Appendix G of the company submission and are reproducible.

The MEDLINE and EMBASE searches combined three search facets using the Boolean operator AND: prostate cancer; padeliporfin; and economic evaluations while the search for NHS EED and HTA Database combined only prostate cancer and padeliporfin facets which was appropriate.

The search strategies were considered fit for purpose, including both relevant controlled vocabulary and text terms with appropriate used of the Boolean operators. For the economic evaluation facets in both MEDLINE and EMBASE, the company used the NHS EED economics filter.

A separate SLR was conducted for health-related quality of life studies to identify reports of HRQOL and utility data. The company searched MEDLINE, EMBASE and ScHARRHUD in November 2017. The searches were restricted to studies published between 2007-2017.The search strategies are documented in full in Appendix H of the submission and are reproducible.

The MEDLINE and EMBASE searches combined three search facets using the Boolean operator AND: prostate cancer; padeliporfin or active surveillance or radical therapy; and

side effects (specifically urinary incontinence, erectile dysfunction or radiation-induced enteropathy) or HROL terms. The ScHARRUD strategy searched any terms related to the scope – prostate cancer, padeliporfin, active surveillance, radical therapy or side effects which was appropriate.

The search strategies were considered fit for purpose, including both relevant controlled vocabulary and text terms with appropriate used of the Boolean operators.

No relevant cost-effectiveness studies for padeliporfin VTP were identified. However, the company selected three studies which were relevant to the economic analysis for the current UK setting with regard to the introduction of padeliporfin VTP in the treatment landscape. These included:

- A horizon scanning report by the National Institute for Health Research (NIHR) from January 2015, which anticipated the future introduction of padeliporfin VTP in the UK market.[28]
- A poster presentation by Olaye at. Al, 2010 on the costs of current treatments for prostate cancer.[29]
- A systematic review and health technology assessment of ablative therapies for people with localised prostate cancer by Ramsey et.al. 2015.[30]

The company considers Ramsey et al. 2015[30] to be the most relevant source of evidence for their technology appraisal as it is comprehensive and includes expert review of all variables in the model.

5.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate

The company's eligibility criteria for identifying relevant published cost-effectiveness studies are summarized in Table 29 of the Company submission, Appendix G. The SLR included cost-effectiveness studies considering patients with low-risk localized prostate cancer and treated with padeliporfin. No comparator, language or timeframe restrictions were imposed.

The eligibility criteria for including health-related quality of life studies are summarized in Table 36 of the company submission, Appendix H. The outcomes of interest included specific disease states, treatment types and side effects.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the most important cost effectiveness studies

The company's systematic literature review did not identify any relevant cost-effectiveness studies of padeliporfin VTP. However, the company indicated a horizon scanning report by the National Institute for Health Research (NIHR),[28] a poster by Olaye et al. 2010[29] and a systematic literature review and technology assessment of ablative therapies for people with localised prostate cancer by Ramsey et al.
2015[30] as relevant to the current UK setting. Utility and disutility model inputs as well as most cost inputs in the company's appraisal of padeliporfin VTP rely heavily on review and modelling by Ramsey's work.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details

The company submission concludes that due to the relatively recent regulatory approval of padeliporfin (TOOKAD®) VTP, it is not surprising that there are no relevant published cost-effectiveness studies that include VTP. The ERG agrees that studies identified in the SLR are not directly relevant to the decision problem of the current appraisal. A detailed critique of the submitted model and economic evaluation follow below.

5.2 Summary and critique of company's submitted economic evaluation by the ERG suggested research priorities

Table 11 NICE reference checklist

Attribute	**Reference case and TA methods guidance**	**Does the de novo economic evaluation match the reference case?**
Comparator(s)	Active surveillance Radical surgery Radical radiotherapy	Yes. For people who choose radical therapy the available options in the model are radical prostatectomy, external-beam radiotherapy (EBRT) and brachytherapy
Patient group	Adults with unilateral, low-risk localised prostate cancer	Yes
Perspective costs	Cost from an NHS and Personal Social Services (PSS) perspective	Partly. Personal Social Services to not appear to be included.
Perspective benefits	All direct health effects, whether for patients or, where relevant, carers	QALYs accruing to patients were calculated using health utilities from Ramsey et al, 2015,[30] and adjusted for rate and duration of adverse effects. Health effects for carers are not considered.
Form of economic evaluation	Cost-effectiveness analysis expressed in terms of incremental cost per quality adjusted life year	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being assessed	Yes. A life-time horizon of up to 40 years is modelled from a starting age of 63 in the base case analyses.
Synthesis of evidence on outcomes	Evidence synthesis should be based on a systematic review	Yes, but the company relied quite heavily on a previous review/model, published in

		2015, for a number of inputs. The appropriateness of the parameter estimates from this previous review were not always discussed in relation to the indication population for the current assessment.
Outcome measure	Quality-adjusted life years	Yes
Health states for QALY	Described using a standardized and validated instrument	The health status of patients at baseline was taken initially from Ramsey, 2015,[30] but subsequently from EQ-5D data collected in CLIN1001 PCM301 . Other utility values were derived from Ramsay et al. which included a review of studies that derived utility values using different methods (EQ-5D, HUI,SF-6D and direct preference elicitation methods)
Benefit valuation	Time-trade off or standard gamble	Although EQ-5D data were collected in the company's trial (CLIN1001 PCM301), they were not used in the model for estimating utility decrements. Instead, these were derived from a previous review by Ramsay et al, which included studies which relied on a variety of methods. The applied values generally relied on EQ-5D or direct TTO methods.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Partly. For example, the utility decrement for bowel dysfunction is based on a

		Japanese study which used the EQ-5D. The utility values for urinary incontinence and erectile dysfunction were from a study that elicited the values of US couples for these adverse effects of prostate cancer treatment.
Discount rate	An annual rate of 3.5% on both cost and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Probabilistic modelling	Probabilistic modelling	Yes. The company provided a probabilistic sensitivity analysis with 1000 iterations.
Sensitivity analysis		Yes, the company presented one-way sensitivity analysis and various scenario analyses. Most relevant parameters were included in the one-way sensitivity analysis.

5.2.1 Models structure

The company submission describes a partitioned survival analysis (PartSA) model where the cohorts are partitioned using 3 parametric survival curves: time to radical therapy (TTRT); time to metastasis (TTM); and disease specific survival which was also adjusted for general population mortality and is referred to as the overall survival (OS) curve from here on. The model compares 5 treatments for low risk localised prostate cancer: padeliporfin VTP, active surveillance (AS), external beam radiotherapy (EBRT), radical prostatectomy (RP) and brachytherapy (BT), first in a full incremental analysis and then in a pairwise comparison against padeliporfin VTP.

The model incorporates 4 mutually exclusive health states: “Pre-radical therapy”, “Post-radical therapy”, “Metastasis” and “Death” (Figure 2). The proportion of patients in each health state at each time point is derived by using the area under the curve (AUC) approach. Patients in the active surveillance or padeliporfin VTP arms of the model start in the “Pre-Radical Therapy” health state, and a proportion progress to the “Post-Radical Therapy” state over time. Patients in the immediate radical therapy arms of the model start in the “Post-Radical Therapy” health state.

With respect to data sources, the TTRT data for AS and padeliporfin VTP were taken from the CLIN1001 PCM301 trial. Given the immaturity of the metastatic progression and overall survival data from CLIN1001 PCM301 , data on freedom from disease progression (used to represent TTM in the company model) and disease specific survival (adjusted for general population mortality to reflect OS in the model) were digitally extracted from the published 10-year Kaplan-Meier curves from the ProtecT trial.[10] In the original model submitted by the company it was assumed that all treatments would have equivalent OS, but that AS and padeliporfin VTP would follow the higher disease progression rate observed in the AS arm of ProtecT. The company later revised this assumption, and modelled equivalent OS and TTM for all treatments. Parametric distributions were fitted to the selected curves for extrapolation to the life-time horizon.

The company submission states that the difference between the TTM and TTRT curves determine the proportion of AS and padeliporfin VTP patients in the post-RT health state, whilst the difference between the OS and the TTM curves determine the proportion of the cohorts in the metastasis health state. However, in the original model submitted by the company, general population mortality was factored into the overall survival curve but not the TTM curve (which was based on freedom from disease progression). This resulted in underestimation of the proportion of patients progressing to metastasis. In fact the TTM curve was replaced with the OS curve when OS fell below TTM (to avoid negative proportions in the metastasis state), and this was required across almost all time points in the radical therapy arms of the model. Thus no patients initially receiving radical therapy were progressing to metastasis. The company fixed this at clarification stage, but also implemented further changes and assumptions as discussed below (section 5.2.5 below).

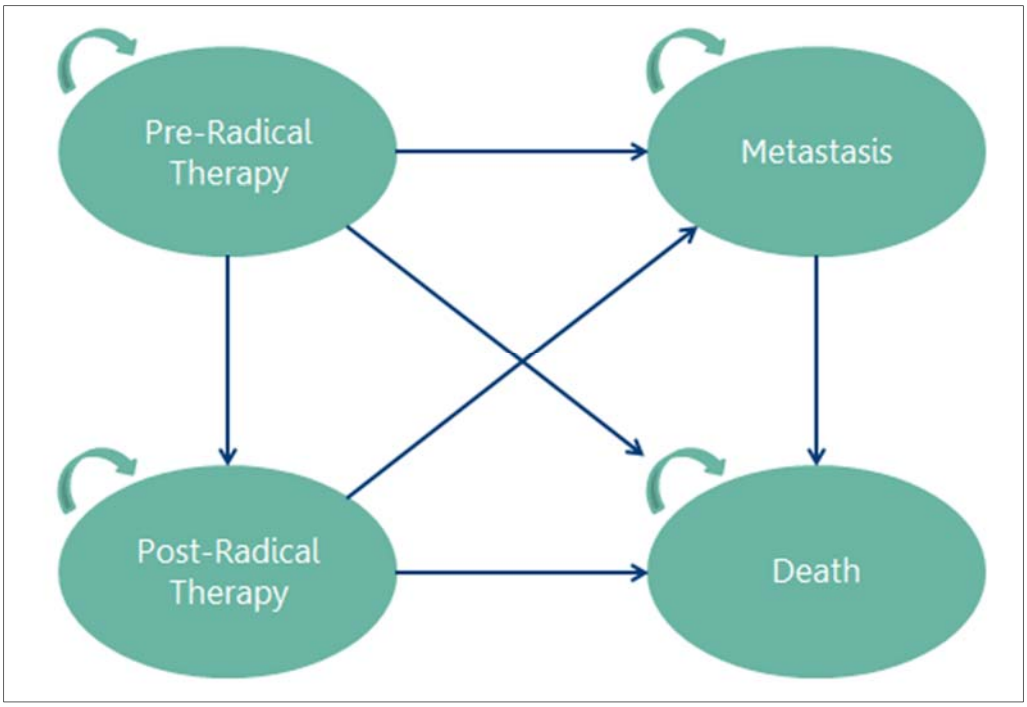

Figure 2 Model structure (Source: Figure 15, Company submission, document B)

Upon entering the post-RT health state patients are distributed by type of radical therapy received according to market share as follows: 51.3%, 24.4% and 24.4% for RP, EBRT and brachytherapy respectively. These percentages were derived by readjusting figures from Greenberg et al.[31] for the relevant population and available comparators. It was assumed for those commencing treatment on AS or padeliporfin VTP, that no one would receive radical therapy from age 75 years and above (11.9 years from baseline in the model). This assumption was based on the premise that radical therapies, which can take at least 10 years to show survival benefit, are typically not pursued by patients with remaining life expectancy of 10 years or less. This is the case for the average patient aged 75 years or above and appears to be a reasonable assumption, although there are no hard and fast rules regarding access to radical therapy by age.

Patients starting in the pre-RT or post-RT health states are assumed to have the same baseline utility value, which is only adjusted according to the prevalence and duration of three specific adverse events (erectile dysfunction, urinary incontinence and bowel dysfunction) in each arm of the model. Patients progressing to metastasis all receive the same relatively low health state-specific utility value, with no adjustments for adverse events.

Treatment-specific costs are applied in the pre and post-RT health states of the company model. All of these costs (except for padeliporfin VTP) are based on those applied in a previous modelling study of ablative therapies for localised prostate cancer, [30] inflated to 2017-18 prices. Patients receiving padeliporfin VTP incur treatment-related acquisition and administration costs in the first cycle, and cycle-specific monitoring costs thereafter. Patients in the AS arm receive the same monitoring cost structure as those in the VTP arm. Patients in the post-RT health state incur the costs of radical therapy and follow-up monitoring. A proportion of patients are also modelled to receive adjuvant therapies and/or salvage therapies following radical therapy. Adverse event monitoring costs are also applied to the proportion of patients experiencing each of the three key adverse events in each treatment arm of the model. Upon entering the metastasis state, patients incur a once-off cost to account for the expected costs of treatment and maintenance of metastatic disease. Finally, upon entry into the "Death" state, a once-off cost is applied to account for end of life care.

A 6-month cycle is applied in the company's model, and costs and QALYs are discounted at 3.5% as per NICE guidelines. The model is run over a life-time horizon of 40 years given a starting age of 63 years for the modelled cohort.

5.2.2 Population

The company base case analysis considers the population as "adults with unilateral, low-risk localised prostate cancer" as per the NICE final scope. To meet the requirements of their approved label, the company exclude from the population in their CLIN1001 PCM301 trial the very low risk patients and those with a bilateral disease. The license subgroup population referred to as "the indication population" is used for the derivation of key model parameters.

Table 12 Characteristics of participants in the CLIN1001 PCM301 study across treatment groups (indication population) (Source: Table 9, Company submission, document B)

Baseline characteristic	VTP (N=80)	Active surveillance (N=78)
Age (years)*	63.9 (6.27; 48-74)	62.3 (6.32; 46-73)
Race, n (%)		
Caucasian	78 (97.5)	78 (100)
Black	1 (1.3)	0
Asian	0	0
Other	1 (1.3)	0
Body mass index (kg/m^2)	26.05 (3.328; 18.8-37.5)	26.47 (3.360; 19.3-40.6)
Time since diagnosis (months)†	4.92 (4.656; 0.6-20.3)	4.81 (4.106; 0.2-18.9)
TNM staging, n (%)		
T1a	0	0
T1c	66 (82.5)	71 (91.0)
T2a	14 (17.5)	7 (9.0)
PSA (ng/mL)	6.98 (1.796; 1.0-10.0)	7.12 (1.704; 3.1-10.0)
Estimated prostate volume (cm^3)‡	37.2 (9.67; 25-68)	37.6 (9.63; 25-66)
Disease status, n (%)		
Unilateral disease	80 (100)	78 (100)
Bilateral disease	0	0
Total number of pre-treatment biopsy cores	13.8 (3.64; 10-24)	14.3 (4.06; 10-26)
Total number of positive pre-treatment biopsy cores§	2.2 (0.74; 1-3)	2.1 (0.76; 1-3)
Number of positive cores, n (%)		
1	15 (18.8)	18 (23.1)
2	34 (42.5)	33 (42.3)
3	31 (38.8)	27 (34.6)
Total cancer core length (mm)	5.3 (2.64; 0¶-14)	3.8 (2.72; 0¶-12)

Data are mean (SD; range) unless otherwise specified

PSA: prostate-specific antigen; SD: standard deviation; TNM: tumour, nodes, metastasis

* $P = 0.126$ from Student t test

† 3 subjects diagnosed for more than 2 years before randomization were removed from the main analysis of the indication population – the mean time since diagnosis when including these patients was 5.99 months (SD=7.50).

‡ $P = 0.800$ from Student t test

§ $P = 0.477$ from Student t test

¶ Some of the subjects included on the basis of 2 biopsies at the beginning of the study had 1 of those 2 biopsies negative

Source: EMA Assessment Report TOOKAD®[43]

As indicated above, the population used for the derivation of the TTM and OS curves is the ProtecT trial population.[10] This population was not restricted to low-risk, localised prostate cancer. However, the company stated that 77% had a Gleason score of 6 and 76% had stage T1c disease. Over 20% in each arm of the trial had a Gleason score higher than 6 and/or had T2 disease.

Table 13 Baseline demographic and clinical characteristics by allocated treatment group in the ProtecT trial (Source: Table 41, Company submission, document B)

	Active monitoring (n=545)	Surgery (n=553)	Radiotherapy (n=545)
Mean age, years (SD)	62 (5)	62 (5)	62 (5)
Median PSA, ng/ml (IQR)	4.7 (3.7, 6.7)	4.9 (3.7, 6.7)	4.8 (3.7, 6.7)
PSA 10+ ng/ml (%)	57 (10)	57 (10)	58 (11)
Gleason score			
6	421 (77)	422 (76)	423 (78)
7	111 (20)	120 (22)	108 (20)
8-10	13 (2)	10 (2)	14 (3)
Missing	0	1	0
Clinical stage			
T1c	410 (75)	410 (74)	429 (79)
T2	135 (25)	143 (26)	116 (21)
For the large majority of men with PSA measures from the prostate check clinic to biopsy, the mean of these two has been taken SD, standard deviation; IQR, inter-quartile range; PSA, prostate-specific antigen			

5.2.3 Interventions and comparators

Intervention

The company submission describes padeliporfin VTP as monotherapy where the drug is injected and retained within the vascular system. It is activated with 753 nm wavelength laser light which triggers a series of pathophysiological events which lead to focal necrosis in a few days. It is administered as one single dose of 3.66 mg/kg and is restricted to hospital use only. The vascular - targeted photodynamic therapy procedure is performed under general anaesthesia after rectal preparation. The padeliporfin drug is administered by intravenous injection over 10 minutes immediately followed by laser illumination of the prostate gland for 22 minute and 15 seconds. The 753 nm laser light is delivered via interstitial optical fibres from a laser device at a power of 150 mW/cm of fibre, delivering an energy of 200 j/cm.

Comparators

The chosen comparators are in line with NICE final scope for adults with unilateral, low-risk localised prostate cancer. The company's base case compares padeliporfin VTP with the following 4 treatments: active surveillance, radical prostatectomy, external beam radiotherapy and brachytherapy. All the radical therapies included as comparators in the company's model are broadly defined procedures. Radical prostatectomy, EBRT and brachytherapy are a blend of practices rather than a single method since specific types are not defined in the decision problem. The company submission includes a 5-way analysis where treatments are compared incrementally to the next less costly non-dominated alternative, and a 2-way comparison between padeliporfin VTP and each other treatment option.

5.2.4 Perspective, time horizon and discounting

Health effects in the company model are assessed in terms of quality adjusted life years accruing to the patient. The perspective on costs is that of the NHS and personal social services.

The company model considers a life-time horizon of 40 years given that the average age of the population used in the modelling is 63 years. Both costs and health effects are discounted at 3.5% per annum, in line with NICE methods guide.

5.2.5 Treatment effectiveness and extrapolation

In the PartSA model submitted by the company, the main difference in treatment effect between padeliporfin VTP and active surveillance is measured by time to radical therapy in the two groups. CLIN1001 PCM301 demonstrated that progression to radical therapy was reduced in patients treated with padeliporfin VTP compared to those on active surveillance. The value proposition for padeliporfin VTP compared to AS is that fewer patients will experience the adverse events associated with transitioning to radical therapies, leading to HRQoL benefits overtime. The temporal trends in the prevalence of genitourinary toxicities between the groups in PCM301 appear to support this to some extent, with these adverse events being higher in the VTP group in the short term but higher in the active surveillance arm in the long-term (Figures 7 and 8 of the company submission, document B). The change in the International Prostate Symptom Scores for urinary symptoms also diverged over time in CLIN1001 PCM301 (Figure 9 of the company submission, document B), consistent with an emerging benefit for padeliporfin VTP. However, total adverse events were more frequent

in the VTP arm of CLIN1001 PCM301, and no differences in generic quality of life, assessed using the EQ-5D, emerged between the treatment groups over follow-up. The company note that "*although the safety profile appears to favour active surveillance, it is important to take into account that AEs occurring after radical therapy have not been reported consistently across all patients because radical therapy was considered a failure in the CLIN1001 PCM301 trial, which led to discontinuation of follow-up in some cases*".

Time to radical treatment (TTRT)

The proportion of patients in the pre-RT health state in each cycle of the model is determined by parametric survival curves fitted to the time to radical therapy (TTRT) observed for the indication population up to month 48 in CLIN1001 PCM301. The curve fitting approach followed NICE DSU guidance.[32] The proportional hazards assumption was rejected and so parametric curves were fitted to each arm. The observed TTRT and alternative fitted curves are provided in Figure 3 below. The preferred log-normal distribution was selected based on the sum of the AIC and BIC across the treatment arms (Table 14) and consideration of clinical plausibility. Whilst the gamma model resulted in the lowest sum of AIC and BIC, and also provided a good visual fit to the observed data, the company rejected it on the basis of questionable validity - since the standard errors for the parameter estimates were approximately 100 times greater than the means. They also noted a lack of clinical plausibility since the extrapolated curves crossed at around seven years. The ERG noted at clarification stage that the tails of the Kaplan-Meier curves for AS and padeliporfin VTP look like they may be starting to converge slightly, and so requested a scenario analysis which allowed the curves to converge using the fitted gamma distribution, but not cross.

The company provided the requested analysis in their response to clarification, but in combination with other changes to their base case model (discussed below). They also provided further arguments against the use of the gamma curve, emphasising the lack of plausibility regarding the "extreme" downward trajectory of the extrapolated curve from month 36, which would require acceleration of the of the hazard of disease to upgrade over time. They noted that based on expert review by a UK clinician, that this profile of progression is unlikely. They also noted that whilst the gamma distribution minimises the sum of AIC and BIC across the treatment groups, it is the second to last best fitting curve in the padeliporfin VTP arm based on the BIC. This is true, but the ERG also the Gompertz distribution minimises both the AIC and BIC in the padeliporfin VTP arm. This curve also

suggests a sharper downward trajectory in the extrapolation of TTRT in the padeliporfin VTP arm (Figure 2). In fact, there is very little to choose between the fitted curves based on the AIC and BIC in the padeliporfin VTP arm alone. It is the good fit of the lognormal in the AS group which is driving its selection as the preferred curve based on the sum of AIC and BIC. The ERG therefore suggest that the extrapolations are uncertain, and that it is important to consider the impact of all the alternative distributions.

Irrespective of which parametric curve is chosen for TTRT, it is only used to extrapolate up to the age of 75 in the model (11.9 years from baseline). This is because it is assumed that patients aged 75 years and above will not be eligible for radical therapy, based on remaining life expectancy being less than 10 years.

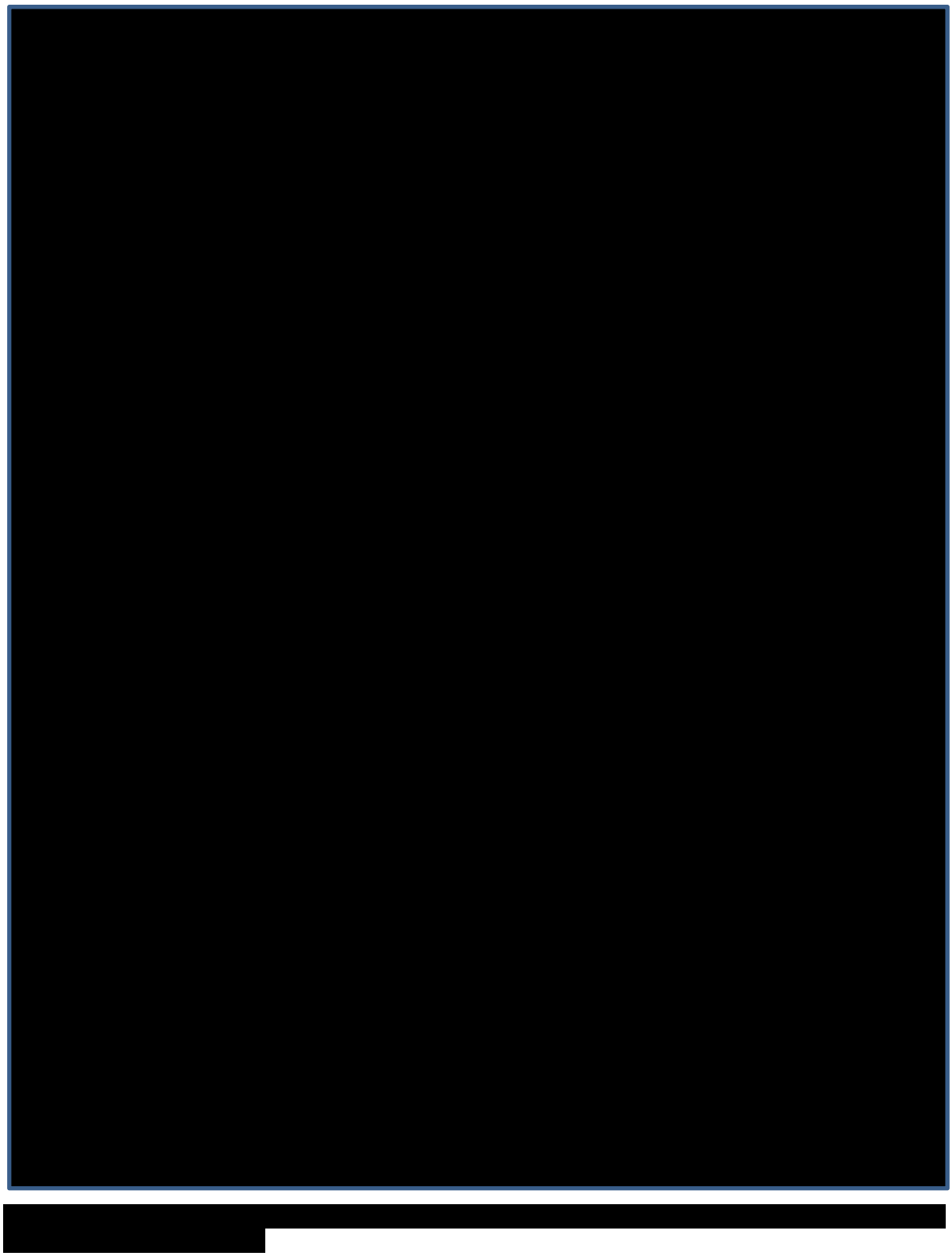

Figure 3 Extrapolation of time to radical therapy for padeliporfin VTP and active surveillance (Source: Figure 20, Company submission, document B)

Table 14 AIC and BIC statistics for time to radical therapy (Source: Table 40, company submission, document B)

Treatment	Distribution	AIC	BIC
VTP	Gompertz	194.76	199.52
	Weibull	194.94	199.70
	Log-logistic	195.27	200.03
	Lognormal	196.35	201.11
	Gamma	196.64	203.78
	Exponential	201.28	203.66
AS	Gamma	363.91	370.98
	Lognormal	372.06	376.77
	Log-logistic	375.94	380.65
	Weibull	380.96	385.68
	Gompertz	387.39	392.10
	Exponential	387.56	389.92
(Sum)	Gamma	560.55	574.76
	Lognormal	568.41	577.89
	Log-logistic	571.20	580.68
	Weibull	575.90	585.38
	Gompertz	582.14	591.62
	Exponential	588.84	593.58

VTP, vascular targeted photodynamic therapy; AS, active surveillance; AIC, Akaike information criterion; BIC, Bayesian information criterion

Source: Patient-level data of CLIN1001 PCM301 study

Another issue regarding time to radical therapy in CLIN1001 PCM301 is that the rate for AS is much higher than that observed in other trials and cohorts. In CLIN1001 PCM301 more than 50% of the AS group received radical therapy by 48 months, with the extrapolation (lognormal) projecting that approximately [redacted] of AS patients will undergo radical therapy by 10 years. This compares with just 55% of AS patients receiving RT by 10 years in the UK based ProtecT trial.[10] The company suggest that this is likely due to less frequent monitoring for progression and more stringent criteria for initiation of RT being applied in ProtecT. For

example, PSA testing was carried out every 3 months, and biopsies were routinely performed at month 12 and 24 and then every 24 months in CLIN1001 PCM301. Monitoring for progression in ProtecT relied largely on PSA testing every 3-12 months. The criteria for initiation of RT also took into account the findings of the monitoring biopsies and PSA results in CLIN1001 PCM301 , while in ProtecT it was based on a >50% increase in PSA (Tables 38 and 39 of the company submission provide details of the different surveillance schedules and the radical therapy initiation criteria).

Since the company originally used the AS arm of ProtecT to model freedom from disease progression for AS and padeliporfin VTP, the ERG requested a scenario that also used the ProtecT trial to model TTRT on AS, with TTRT on padeliporfin VTP expressed relative to this baseline. The company provided this analysis using the ratio of cycle-specific transition probabilities between padeliporfin VTP and AS from the CLIN1001 PCM301 trial. However, this analysis also incorporated other changes regarding disease progression on AS and padeliporfin VTP, discussed below, which perhaps make it less relevant and appropriate. The company also reemphasised that the following four criteria will have influenced the observed differences in TTRT on AS in the two trials: monitoring schedules, compliance with monitoring schedules, pre-planned criteria for consideration to initiate radical therapy and baseline risk of progression in the patient populations (Table 25, company response to clarification letter).

Freedom from disease progression and overall survival

In the first model submitted by the company, all the treatments were assumed to provide equivalent disease specific and overall survival, but padeliporfin VTP and AS were assumed to follow the same higher rate of disease progression (metastasis or disease specific mortality) compared to the radical therapies. However, the radical therapies incurred a higher rate of adverse events, resulting in lower HRQoL compared to AS and VTP prior to disease progression. Thus a trade-off existed between the risk of disease progression and adverse event rates in the comparison between padeliporfin VTP and the radical therapies.

Since there was very limited data available from CLIN1001 PCM301 on disease progression (to metastasis) and mortality, these outcomes were modelled based on data from the ProtecT trial. The ProtecT trial[10] published 10-year follow-up data in 2016. It showed no significant differences between radiotherapy, radical prostatectomy or active surveillance (AS) in terms

of disease specific mortality (death due to prostate cancer or its treatment), but it did find that active surveillance resulted in a higher rate of disease progression compared with the two radical therapies (see Figure 21 of the company's submission, document B). Disease progression was defined as "*death due to prostate cancer or its treatment; evidence of metastatic disease; long-term androgen deprivation therapy; clinical T3 or T4 disease; and ureteric obstruction, rectal fistula, or the need for a permanent catheter when those are not considered to be a complication of treatment in the ProtecT trial*" (company's submission, document B, page 105). Whilst this outcome includes multiple definitions of disease progression, it was used for the purpose of partitioning the cohort between the pre-progressed and metastasis health states in the company's model.

The Kaplan-Meier curves for disease progression following prostatectomy and radiotherapy overlapped in the ProtecT trial, and therefore only data from the radiotherapy arm was regenerated and was assumed to reflect freedom from disease progression for all the radical therapies in the company's model. Disease progression in the AS arm of ProtecT was used for AS and padeliporfin VTP in the model.

The company digitally extracted the data from the published ProtecT Kaplan-Meier curves, and fitted parametric survival functions to them. The best fitting distribution for the extracted disease progression data, based on the sum of AIC and BIC across treatment arms, was the lognormal. Similarly, the company extracted the prostate cancer-specific mortality data from the radiotherapy arm of ProtecT and selected an exponential distribution, which was used across all treatment arms in model.

It should be noted here that the ProtecT outcomes of prostate cancer-specific survival and freedom from disease progression are censored for other cause mortality, and so are not suitable for a partitioned survival model without adjustment for other cause mortality.[10,33] However, in the initial model submitted by the company, 'prostate cancer specific survival' was adjusted to include general population all-cause mortality, but the 'freedom from disease progression' curve was not. As a result the difference between the curves, used to represent the proportion of the cohort with progressed metastatic disease, was being grossly underestimated in the model. In fact, it was always negative in the radical therapy arms, and was being replaced with zero to overcome the inconstancy. Thus the model was assuming no

patients would progress to metastasis following radical therapies, and was grossly underestimating the observed proportion of patients progressing on AS in the ProtecT trial.

The ERG highlighted this discrepancy at clarification stage, and the company agreed in their response that the 'freedom from disease progression curve' had to be adjusted to include general population all-cause mortality. However, in doing so, they also changed their base case assumptions, and shifted to assuming that all the treatments would have equivalent efficacy in terms of time to metastasis in their chosen indication population. As justification, they referred to their response to one of the ERGs clarification questions (B2 of the clarification letter) regarding the comparability of the indication population from CLIN1001 PCM301 and population recruited to the ProtecT trial cohort.

The company noted that the inclusion of patients with intermediate and high risk disease in the ProtecT trial is likely to have had an impact on the higher rate of disease progression in the active surveillance arm of ProtecT.[10] The company response also noted the results from the PIVOT trial[33] which showed no significant difference in metastatic progression among patients with low risk disease assigned to RP or AS. The company further noted a trend for an increasing difference in the rates of metastatic progression between AS and RP in subgroups with intermediate and high risk disease in PIVOT, although none of these differences reached statistical significance (company response to clarification, question B2). The ERG would also note that the more intensive monitoring regimen and less stringent criteria for initiation of radical therapy in CLIN1001 PCM301, could also provide some justification for assuming that these patients will fare better in terms of disease progression than those who received AS in ProtecT. However, there are no observed long-term data to validate the assumptions for: a) equivalent metastatic progression between AS and padeliporfin VTP; or b) equivalent metastatic progression between AS or padeliporfin VTP and the radical therapies. Without long-term data, there may be some concern among clinicians and patients that the delayed time to radical therapy comes at the expense of poorer long-term outcomes.

Nevertheless, the company revised their base case in response to clarification, to assume equivalent time to metastasis across all five treatments in the model. By assuming an equal rate of disease progression, the model reduces the difference in treatment effect between padeliporfin VTP and the radical therapies down to the difference in the rate of the three main adverse events included in the model (urinary incontinence, erectile dysfunction, and bowel

dysfunction). Whilst 45.8% of patients on padeliporfin VTP experienced drug, device or procedure- related adverse events of moderate severity (Grade2) and 6.3% experienced severe AE (Grade 3), the company model does not include these (Table 25, p. 59 of the company submission, document B). The ERG queried this omission at clarification stage. In response, the company noted that the omitted events were transient and resolved quickly. They also noted that the economic model does not include other radical therapy specific adverse events such as haematuria, post-operative pain, and urinary tract infection, because these data are not readily available from the literature. Therefore, including the shorter-term procedure specific adverse events for padeliporfin VTP alone would bias the model. The Radical therapies are associated with much higher adverse event rates in the model than padeliporfin VTP (see section 5.2.6 below). This is what drives the QALY gain for padeliporfin VTP in the model, and also partially offsets [redacted].

5.2.6 Health related quality of life

The company model adopts a relatively simple approach to incorporating health state utility weights. The same baseline utility weight is applied for patients starting the model in the pre-radical therapy and post radical therapy states. Utility decrements are then applied to the proportion of patients experiencing each of the three main adverse events under the alternative treatments. Those progressing from pre-radical therapy to post-radical therapy are assigned the post-radical therapy adverse event rates from time of progression. Those progressing to "Metastasis" are assigned the lower health state utility weight assigned to this state. A key assumption is that progression from low to intermediate risk localised prostate cancer, among those starting in the pre-radical therapy state, is not associated with a reduction in quality of life independent of the effect of subsequent radical therapy on the prevalence of adverse events.

In the original company's submission, all treatment modalities were assumed to be equivalent in terms of overall survival, but AS and padelipofin VTP were assumed to have a higher rate of progression to metastasis than radical therapies based on data from ProtecT.[10] Therefore, in the company's original model the comparison of padelipofin VTP with radical therapies involved a trade-off between lower adverse event rates but a higher rate of progression to metastasis. However, as indicated above, the overall survival and metastasis free survival curves used to partition the cohort had not been consistently adjusted for other cause mortality in the original model. When asked to look at this during the clarification stage, the

company revised their case to assume equivalence of all treatment modalities in terms of both overall survival and progression to metastasis. Therefore, the company's revised model assumes that adverse event rates alone drive the difference in QALYs between the treatment arms.

Utility values applied in the model

The company rely heavily on the previously published model of ablative therapies by Ramsay et al.[30] for health state utilities and utility decrements associated with adverse events. Ramsay et al. searched available databases for published health state utility data, and applied a hierarchy of evidence approach for identifying the most appropriate utility values for use in their model. This placed an emphasis on values obtained using the EQ-5D. However, despite this, the authors reported that the available utility data for health states and events included in the model were poor, and so they had to rely on utility values from a number of difference studies which were elicited using a number of different methods. The company's submission provided very little discussion regarding the appropriateness of these values for the indication population in the current submission. The key values that the company sourced from Ramsay[30] are baseline utility (localised prostate cancer without adverse events), the utility value for metastatic disease, and utility decrements associated with the three main adverse events (urinary incontinence, erectile dysfunction, and bowel dysfunction). The values applied are presented in Table 15 below.

For baseline utility, the company initially applied a value of 0.88. The original source of this parameter is not entirely [30], but it corresponds closely with a pre-treatment EQ-5D value of 0.89 reported for a Dutch cohort (mean age 62.3) who received radical prostatectomy for localised prostate cancer.[34] Of note, the post radical prostatectomy EQ-5D values reported by Korfage remained relatively stable over time, increasing slightly at 6 and 12 months, before dropping slightly to 0.88 by 52 months. This was despite reported increases in erectile dysfunction and urinary incontinence associated with prostatectomy. This suggests that either the EQ-5D is insufficiently sensitive to capture the impact of these events on health related quality of life, or the events themselves have a limited impact on health related quality of life.

More important in the model are the utility decrements applied to the proportions of patients experiencing the main adverse events. The company submission states that these are also based on the values that Ramsay et al[30] identified from the literature. The utility decrement

for bowel dysfunction appears to have been adapted from a study by Hummel et al,[35] who in turn derived their estimate from Shimizu et al.[36] Shimizu et al reported EQ-5D data for a cohort of Japanese men with localise prostate cancer, and found that patients with bowel problems (defined as scores of 0-80 on a Japanese version of the UCLA Prostate Cancer Index (PCI) version 1.2 [37]) reported significantly lower EQ-5D values than men without bowel problems (0.84 versus 0.94). Hummel et al.[35] used these estimates to generate a relative multiplier of 0.8936 (=0.84/0.94), which they applied to age specific UK populations norms to generate expected utility scores for patients experiencing bowel dysfunction in their model of intensity-modulated radiotherapy for the treatment of prostate cancer. They illustrate this for 70 year old men with baseline utility of 0.813 (based in UK EQ-5D population norms), which generates and a value of 0.727 (=0.813 x 0.8936) for those with bowel dysfunction. This multiplicative approach is in line with NICE DSU guidance on the application of utility values in economic models.[38] However, instead of applying the utility multiplier in their model, the company have calculated an absolute decrement of 0.16 for bowel dysfunction, by subtracting 0.72 from 0.88 (=0.16). This overestimates the original decrement associated with bowel dysfunction reported by Shimizu et al. (0.10).

For the utility decrements associated with UI and ED, the ERG traced the original source of these to a study by Volk et al.[39] This study reported TTO values for prostate cancer treatment outcomes (described using health state caveats), elicited directly from couples (individually and conjointly). The male participants were 45-70 years old and had no history of prostate cancer. Volk reported mean TTO values (from the perspective of male partners) of 0.84 for partial impotence and 0.83 for mild to moderate incontinence. These values appear to have been used in the study by Ramsay et al.[30] and the company have estimated decrements associated with these complications by subtracting them from the baseline utility value applied in their model (0.88). This yields the applied decrement of 0.04 for ED and 0.05 for UI respectively.

The ERG cross checked the company applied utility decrements for UI and ED against differences in EQ-5D scores by urinary function and sexual function reported by Shimizu (the original source of the bowel dysfunction decrement described above).[36] Shimizu reported no significant difference in EQ-5D by sexual function, measured by the Japanese version of the UCLA Prostate Cancer Index (PCI), but found that those in the lowest functioning category had an EQ-5D sore that was 0.03 lower than those in the best functioning category

(0.90 versus 0.93). Those in the middle and lowest category of urinary function had EQ-5D scores that were 0.06 and 0.1 lower than those in the best function category respectively (0.88 and 0.84 versus 0.94), and this difference was significant. Therefore, according to the EQ-5D data reported by Shimizu et al,[36] the decrements applied for ED and UI appear to be broadly reasonable, but it should be noted that the company have applied these as constant decrements rather than age adjusted multipliers which may have been preferable.

Table 15 Summary of utility values for cost-effectiveness analysis (Source: Table 47 of company's submission, document B)

State	Utility value: mean (SE)	95% CI	Reference in submission	Justification
Localised PCa				
Localised PCa without AEs	0.88 (0.088)	0.708, 1.052	**Error! Reference source not found.** (p 116 of CS)	Based on CLIN1001 PCM301 data (i.e. similar utility in VTP and AS groups) and Ramsay et al 2015[30] analysis (i.e. similar utility in focal therapy, brachytherapy, EBRT and surveillance)
Metastasis				
Metastasis	0.58 (0.058)	0.708, 1.052	**Error! Reference source not found.** (p 119 of CS)	HRQoL once patients have metastatic disease unlikely to differ based on prior treatment
Adverse effects				
Urinary incontinence	-0.05 (0.005)	-0.060, -0.040	**Error! Reference source not found.** (p 116 of CS)	Well-documented that active treatment of prostate gland leads to urinary, erectile and bowel dysfunction in many patients, which leads to deterioration in HRQoL
Erectile dysfunction	-0.04 (0.004)	-0.048, -0.032		
Bowel dysfunction	-0.16 (0.016)	-0.191, -0.129		

SE, standard error; CI, confidence interval; PCa, prostate cancer; AEs, adverse events; CS, company submission; VTP, vascular targeted photodynamic therapy; AS, active surveillance; EBRT, external beam radiation therapy; HRQoL, health-related quality of life

Source: Ramsay et al 2015

Given the uncertainty in the utility decrements applied to adverse events in the company model, the ERG assess the impact of reducing the decrement associated with bowel dysfunction to from 0.16 to 0.1. Further, since the company are in possession of EQ-5D data collected from patients enrolled in their trial (CLIN1001 PCM301), the ERG asked the

company to clarify the rationale for not using this data in the model and to explore the impact of using it to derive utility decrements associated with the main adverse events. The company noted correctly that they had already explored the impact of deriving baseline utility from their own EQ-5D data. They further noted that they did not use it to explore the impact of adverse events on utility because of limited availability of points where EQ-5D had been collected prior to and after relevant adverse events (Table 16). However, the company did provide analysis showing EQ-5D scores prior to and after adverse events in response to clarification, and these showed little or no change (Table 17). Given the limited number of observations and lack of face validity, the ERG agree that these data should be treated with caution.

Table 16 Number of events: ED, UI, or BD, Grade ≥ 2 (by duration type) with adjacent EQ-5D assessments (ITT population) (Source: Table 42 of company's response to clarification)

Adverse event	Transient	Permanent
Grade ≥ 2 ED	16	21
Grade ≥ 2 UI	6	6
Grade ≥ 2 BD	4	1
ED, erectile dysfunction; UI, urinary incontinence; BD, bowel dysfunction		

Table 17 Utility values based on EQ-5D data for adverse events (Source: Table 43 of company's response to clarification)

	Utility values			Mean duration between EQ-5D and AE dates	
Adverse event	EQ-5D assessment prior to AE	EQ-5D assessment post-AE	Difference	Prior EQ-5D and AE (months)	Post-EQ-5D and AE (months)
Grade ≥ 2 ED	0.962	0.975	0.013	3.8	8.4
Grade ≥ 2 UI	0.954	0.954	0.000	4.8	7.5
Grade ≥ 2 BD	0.958	0.958	0.000	3.1	9.7
AE, adverse event; ED, erectile dysfunction; UI, urinary incontinence; BD, bowel dysfunction					

Frequency of adverse events

The frequency of adverse events following the alternative treatments is also of importance for the company's economic case. The company have used their own observed rates from CLIN1001 PCM301 for padeliporfin VTP and active surveillance (AS). For the radical therapies, the company have relied on the rates calculated previously by Ramsay et al.[30] These are presented in Table 18 below, and were derived from studies included in a systematic review of ablative therapies for localised prostate cancer. This included evidence from RCTs, non-randomised comparative studies (NRCSs) (if no RCT evidence was identified), and from single-arm cohort studies (case series) (greater than 10 participants) for the ablative procedures. It was reported by Ramsay et al.[30] that the rates of adverse events applied in their model were based on the median of the rates from all available sources reporting adverse events before 6 months, and the mean of the annualised rates from all available sources reporting adverse events beyond 6 months. Given the numbers of studies involved, it is not possible to trace the exact calculation, and the approach could be considered a form of naïve indirect comparison. Further, the comparison between the rates for AS and padeliporfin VTP from CLIN1001 PCM301 and the rates reported for radical therapies by Ramsay et al. is a naïve indirect comparison,[30] which does not control for factors that may influence the observed rates such as age, baseline prevalence, and grade and stage of disease, year of study.

Table 18 Short- vs long-term adverse event probabilities (Source: Table 44 of the company's submission, document B)

Treatment	Duration	Urinary incontinence	Erectile dysfunction	Bowel dysfunction
VTP	Short-term	0.013	0.175	0.050
	Long-term	0.000	0.100	0.013
Active surveillance	Short-term	0.013	0.013	0.000
	Long-term	0.000	0.013	0.000
Radical prostatectomy	Short-term	0.248	0.645	0.040
	Long-term	0.278	0.706	0128
EBRT	Short-term	0.092	0.486	0.152
	Long-term	0.111	0.406	0.181
Brachytherapy	Short-term	0.332	0.268	0.055
	Long-term	0.363	0.262	0.116
VTP, vascular targeted photodynamic therapy; EBRT, external beam radiation therapy Sources: CLIN1001 PCM301 trial; Ramsay et al 2015[37]				

Given the uncertainties regarding the comparability of the adverse rates applied for alternative treatments in the model, the ERG cross checked the applied rates against those reported in the ProtecT trial,[10] a key source of UK randomised data comparing AS with radical therapies. The ProtecT trial compared patient reported urinary function, sexual function and bowel function between those randomised to AS, radical prostatectomy, or radiotherapy. The investigators found that radiotherapy had a small effect on urinary incontinence, with the use of absorbent pads increasing from 0 to 5% by 6 months, before varying between 3% and 4% over longer-term follow-up (up to 72 months). No increase in the use of pads was observed at 6 months among those who received active monitoring without subsequent radical therapy, but the rate in this group did increase to between 0.4% and 1.9% over longer-term follow-up. In the radical prostatectomy group, the rate of urinary incontinence (use of pads) increased substantially, from 1% at baseline to 46% at 6 months (a 45% increase), before dropping off slightly to between 17% and 26% over longer term follow-up.

For erectile dysfunction (erections not firm enough for intercourse), there was an increase from baseline among men continuing to receive active monitoring, from 35% to 43% at 6 months, and to between 47% to 62% over longer term follow-up. In the radiotherapy arm, the increase in erectile dysfunction was from 32% at baseline to 77% at 6 months and to between 62% and 73% over longer term follow-up. Radical prostatectomy performed worse on this measure, with an increase from 34% at baseline to 88% at six months, and to between 79% and 85% over longer term follow-up.

Finally, there were no changes in bowel dysfunction from baseline in those assigned to AS or radical prostatectomy in ProtecT,[10] with the percentages with faecal incontinence, loose stools and bloody stools all falling slightly over time. In the radiotherapy group, scores on these outcomes fared worse. Faecal incontinence increased from 0.4% at baseline to 5.2% at six months, before dropping to between 2.3% and 4.3% over longer term follow-up. The incidence of loose stools (about half of the time or more frequently) increased from 15.6% at baseline to 25.1% at six months, before dropping to between 15.5% and 21.5% over longer term follow-up. Bloody stools (about half the time or more frequently) increased from 1.6% at baseline to 3.8% at six months, and increased further to between 3.8% and 8.4% over longer term follow-up. Based on the above data, the ERG believe that some of the adverse event rates applied in the company's model for the radical therapies are questionable.

Therefore the ERG explored the impact of basing the prevalence of adverse events for radical prostatectomy and radiotherapy on the observed percentage point differences (adjusted for baseline) compared to AS in the ProtecT trial. Table 19 below provides the alternative values. The three forms of bowel dysfunction reported in ProtecT are applied additively for EBRT. For the prevalence values beyond 6 months, we took the average of the values reported over the longer-term follow-up in ProtecT (12 to 72 months). The Brachytherapy data remain unchanged since no data are available from ProtecT. [40]

Table 19 ERG alternative short- vs long-term adverse event probabilities based on difference in change from baseline observed in the ProtecT trial.[40]

Treatment	Duration	Urinary incontinence	Erectile dysfunction	Bowel dysfunction
VTP	Short-term	0.013	0.175	0.05
	Long-term	0	0.1	0.013
Active surveillance	Short-term	0.013	0.013	0
	Long-term	0	0.013	0
Radical prostatectomy	Short-term	0.453	0.472	0
	Long-term	0.170	0.311	0
EBRT	Short-term	0.063	0.379	0.165
	Long-term	0.025	0.203	0.100
Brachytherapy	Short-term	0.332	0.268	0.055
	Long-term	0.363	0.262	0.116

VTP, vascular targeted photodynamic therapy; EBRT, external beam radiation therapy
Sources: Donovan et al. 2016;[40] CLIN1001 PCM301 trial;[26] Ramsay et al 2015[30]

Notes: * Prevalence rates for RP and EBRT are calculated by adding the percentage point differences in change from baseline compared to AS in ProtecT

5.2.7 Resources and costs

Reports of UK costs and resource use were identified by the company by searching MEDLINE, MEDLINE In-Process, EMBASE, NHS Economics Evaluation Database (NHS EED) and HTA Database (via Cochrane Library) in October 2017. The searches were restricted to publications from 2012 onwards to ensure currency but were not restricted by language. The search strategies are documented in full in Appendix I and are reproducible. The MEDLINE and EMBASE searches combined three search facets using the Boolean operator AND: prostate cancer; economic or resource use; and the UK while the search for NHS EED and HTA Database comprised only prostate cancer terms which was appropriate. The search strategies were considered fit for purpose, including both relevant controlled vocabulary and text terms with appropriate used of the Boolean operators. For the economics

facets in both MEDLINE and EMBASE, the company used the NHS EED economics filter supplemented by resource use terms while UK costs used a published filter.[41]

The company model includes costs associated with the initial treatments or active surveillance, monitoring post treatment, management of adverse events, adjuvant therapies and salvage therapies (post radical treatment), treatment of metastatic disease and end of life palliative care. Patients on active surveillance or padeliporfin VTP who progress to radical therapy incur the full cost associated with radical therapy and adjuvant and salvage therapies upon entry into the state. The proportional distribution of radical therapies that patients receive upon transition is assumed to be the same post AS and padeliporfin VTP. Current market shares for the radical therapies following AS or padeliporfin VTP were estimated to be 51.3%, 24.4% and 24.4% for radical prostatectomy, EBRT and brachytherapy respectively. These were calculated from data reported by Greenberg et al on the primary treatment of non-metastatic prostate cancer in a UK cohort. The relative distribution of radical therapies applied is also generally in line with the distribution of radical therapies that patients received upon progression from AS in the ProtecT trial. [40]

Intervention and comparator costs

The intervention cost for padeliporfin VTP includes the acquisition cost for the padeliporfin drug, optical fibres, catheters and rectal probe. The costs applied for these items are reproduced in Table 20. The company's submission states that the "*recommended dosage of padeliporfin is 3.66 mg/kg.[25] As a vial of padeliporfin contains 183 mg, each vial is suitable for 50 kg. For patients weighing >50 kg and ≤100 kg, two vials of padeliporfin are required. For patients weighing >100 kg and ≤150 kg, three vials of padeliporfin are required".* The submission also states that each vial is for single use. In CLIN1001 PCM301 , 96% of patients weighed >100kg and remainder weighed >100kg and ≤ 150kg. These proportions are applied in the company's model for the computation of padeliporfin drug costs. The other numbers of units per procedure in Table 20 were also based on data from CLIN1001 PCM301 .

Table 20 Acquisition cost of padeliporfin VTP (Source: Table 48 of the company's submission, document B)

Material description	Cost/procedure (£)	# units/procedure	Cost/unit (£)
Padeliporfin (183 mg vial)	7,672.95	2.04	3,761.25
Optical fibres	3,282.24	12.9	254.44
Catheters	713.53	12.9	55.31
Rectal probe	331.88	1	331.88
Catheters	110.63	2	55.31
Total	**12,111.23**		
VTP, vascular targeted photodynamic therapy			

In terms of administration costs for padeliporfin VTP, the company state that they are offering to lease the generator for [redacted] per procedure. The cost of administration also includes the cost of physical exams, use of an operating room (theatre), an anaesthetist, an uro-oncologist surgeon, a nurse and an electrocardiogram. The costs applied for these items are reproduced in Table 21 below.

Table 21 Unit costs associated with intervention and comparators in the economic model (Source: Table 49, company's submission, document B –modified by the ERG to reflect the companies revised base case)

Items	Cost (SE), £	Reference in company's submission
Padeliporfin VTP treatment costs		
Acquisition cost	12,111.23 (1,211,1)	Table 48 of the company's submission
Administration cost	[redacted]	Intervention and comparators' costs and resource use (p 122 of the company's submission)
Laser generator	[redacted]	
Physical exams	50.97	
Operating room	1,010.05	
Anaesthesiologist	119.94	
Uro-oncologist surgeon	166.50	
Nurse	9.88	
Electrocardiogram	275.74	
Active surveillance and padeliporfin VTP post-treatment monitoring costs		
First year	510.95 (85.8)	Table 50 in the company's submission
Second year	425.31 (78.3)	
Third year	195.39 (32.6)	
Fourth year	425.31 (78.3)	
Fifth year	195.39 (32.6)	
Annually thereafter	22.89 (2.9)	
Radical prostatectomy	4,446.71 (444.7)	Intervention and comparators' costs and resource use (p 122 of the company's submission)
EBRT	2,898.32 (369.7)	
Brachytherapy	7806.32 (1207.5)	
SD, standard deviation; VTP, vascular targeted photodynamic therapy; EBRT, external beam radiation therapy		

In their original submission the company based the cost of physical exams on the cost of three GP appointments and the cost of a nurse consultation based on a GP practice nurse visit. In response to clarification, the company updated these to reflect secondary care costs. The ERG queried the use of primary care costs for this purpose, and the company updated these using secondary care costs in a revised base case analysis. This makes little difference to the results as the cost of the required secondary care consultant time is lower than the cost of three separate GP visits. The cost of theatre time in the company model is based on the weighted average of the daycase NHS reference cost for HRG codes LB06H, LB06J, LB06K, LB06L, and LB05M: Kidney, Urinary Tract or Prostate Neoplasms, with Interventions, with CC Score 9+; with CC Score 6-8; with CC Score 4-5; with CC Score 2-3; and with CC Score 0-1. This may be sufficient if the daycase setting, and average theatre time and staff mix for

these HRG codes are generalisable to the padeliporfin VTP procedure, but this is not clearly justified in the company's submission. Over and above the HRG based costs of delivering the procedure, the company have also applied the cost of an outpatient appointment with a uro-oncologist surgeon, and an anaesthetics outpatient appointment. Finally, the cost of two electrocardiograms are included based on the NHS reference cost for EY51Z [Electrocardiogram Monitoring or Stress Testing]. Overall, the estimated total cost of the procedure comes to [redacted] in the company's revised case following clarification.

The rational for each of the administration cost items is not particularly clear in the company's submission, making it difficult to comment on the appropriateness of the final cost estimate. However, the ERG note from the trial publication that all patients randomised to padeliporfin VTP underwent pre-treatment mutli-parametric MRI, which was reviewed with the biopsy results by a team of radiologists and urologists who determined the number and positioning of the interstitial optical fibres using treatment guidance software. It is not obvious that the MRI costs had been included. Furthermore, the trial publication states that the padeliporfin VTP procedure was carried out during a 2 hour theatre allocation with a planned overnight stay. This calls into question the validity of using the daycase reference cost for the procedure. The ERG therefore explore the impact of incorporating multi-parametric MRI costs, and also assess the impact of applying HRG based reference costs for elective short stay rather than daycase.

The company based the costs of active surveillance and the comparator radical therapies on those applied in the model by Ramsay et al[30] (inflated to 2017/208 prices) – see Table 21 above. These costs were based on detailed bottom up calculations, and appear generally appropriate for use in the company's model. The company also assessed the impact of basing the radical prostatectomy and EBRT costs on NHS reference costs in scenario analysis. The applied reference costs were higher than the base case costs in both instances. The resource use and costs for active surveillance and monitoring post padeliporfin VTP (same requirement as active surveillance), are summarised by year in Table 22. In terms of post radical therapy surveillance, lower resource requirements and costs were applied (Table 23).

Table 22 Annual resource use and costs of AS, and for monitoring patients post padeliporfan VTP (Source: Tables 50 and 54, company's submission, document B)

Year	Resource inputs	Annual cost (SE)
1	• 4 nurse-led outpatient appointments • 4 PSA tests • 1 digital rectal exam (DRE) • 1 multidisciplinary team (MDT) meeting	510.95 (85.8)
2	• 1 transrectal ultrasound (TRUS)-guided biopsy • 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	425.31 (78.3)
3	• 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	195.39 (32.6)
4	• 1 TRUS-guided biopsy • 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	425.31 (78.3)
5	• 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	195.39 (32.6)
Annually thereafter	• 1 practice nurse appointment • 1 PSA test • 1 DRE	22.89 (2.9)
PSA, prostate-specific antigen; DRE, digital rectal exam; MDT, multidisciplinary team; TRUS, transrectal ultrasound guided Source: Ramsay et al 2015, inflated to 2017/2018 price levels[30]		

Table 23 Annual surveillance resource use and costs post radical therapy (Source: Tables 53 and 54, company's submission, document B)

Year	Resource inputs	Annual cost £ (SE)
1	• 4 nurse-led outpatient appointments • 4 PSA tests • 1 DRE	393.28 (50.2)
2-5	• 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	196.64 (25.1)
Annually thereafter	• 1 practice nurse appointment • 1 PSA test	22.89 (2.9)
PSA, prostate-specific antigen; DRE, digital rectal exam Source: Ramsay et al 2015; inflated to 2017/2018 price levels		

Adjuvant therapy and salvage therapy costs

The company have also applied costs of adjuvant and salvage treatments to proportions of patients following radical prostatectomy, EBRT and brachytherapy (detailed in Tables 51 and 52 of the company submission). These proportions and unit costs are again based on the modelling by Ramsay et al.[30] However, the inclusion of some of the adjuvant treatments is questionable based on NICE guidance covering the indication population.[20] For example, the company model assumes that 22% and 36% of patients who undergo radical prostatectomy receive adjuvant hormone therapy and adjuvant EBRT respectively. The NICE guideline does not actively recommend these treatments in low risk men. Further, in the context of primary treatment with radiotherapy, the guideline only states to "*offer men with intermediate- and high-risk localised prostate cancer a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone"*.

In terms of salvage therapies, the company apply annual probabilities of progression to the proportion of patients who have radical therapies, and then multiply further by the proportion of progressions that are local, and the proportion of local progressions that are treated with salvage therapy. The cost of diagnosing local progression and the cost of salvage therapies is applied to the proportion of patients estimated to receive this in each cycle of the model (see Table 52 of the company submission for details). Cumulatively, the model predicts that 15.5% of those who have primary RP, 6.2% of those who have primary EBRT, and 12.4% of

those who have primary brachytherapy, also receive salvage therapies. The ERG have some concerns about the appropriateness of these rates for low risk indication population. All of the data used to inform the probabilities come from Ramsay et al. which was informed by a literature review.[30] The generalisability of the probabilities to the company's indication population is uncertain.

Adverse event costs

The company's model also includes costs associated with the management of three main adverse events: UI, ED and BD. The costs and assumptions are reproduced below in Table 24. The company's submission states that one-off costs involved in fitting an AUS device (for UI) or a penile prosthesis (for ED), are only applied once to the proportion of patients who experience long-term dysfunction. However, the cost of a penile prosthesis was not applied in the company model as the probability of this type of treatment was set to zero rather than the stated 0.024 in Table 24 below. Therefore the overall probability of treatment for ED in the model is 0.556 rather than 0.57. Ongoing clinical or self-management costs are applied on a cycle by cycle basis. A mean annual monitoring cost and a mean treatment cost of 425.75 and £2718.45 are applied in the model to the proportions experiencing bowel dysfunction. However, it was not stated in the company submission what the monitoring and treatment entails. Consulting the company's stated source (Ramsay et al.), there was an error in the referencing of the primary study which made it difficult to trace the original source. However, from contacting the authors it appears to have derived from the modelling study by Hummel et al[35] (see Table 30, page 46 in the published monograph), inflated to the current cost year. Hummel et al state: *"It has been assumed that all patients with grade 2 and 3 toxicities will be monitored in a hospital outpatient setting, with the frequency depending on severity (see Table 30). There is no standard treatment for late GI toxicity. Most are likely to be investigated with flexible sigmoidoscopy, and possibly biopsy. The majority will be treated with low-cost items such as laxatives, the cost of which have not been considered. Some patients with more severe cases may need procedures such as laser treatment. The average monitoring and treatment costs for the treatment of all late GI toxic effects has been calculated by estimating the proportion of patients with grade 3 toxic effects."* (Source, Hummel et al. 2010, page 45).[42]

It is clear from reading the report by Hummel et al.[42] that the calculated monitoring cost (£425.75 based on 3-6 outpatient appointments per year) is suitable for application on an

annual basis. However, the treatment costs are reported as the mean cost per patient, not per patient year. Therefore, the ERG believe it may be more suitable to apply this cost on a once-off basis to the proportion of the patients experiencing long-term BD, and not on an annual basis as the company have done.

Table 24 List of adverse reactions and summary of costs in the economic model (Source: Tables 53 and 54, company's submission, document B)

Adverse events	Management / treatment strategy	Cost (SD), £	Short-term frequency	Long-term frequency	Reference in company's submission
Urinary incontinence	Self-management	304.54 (30.5) per year	0.948	0.948	Adverse reaction unit costs and resource use (p 130)
	AUS device*	10,220.32 (1022.0)	0.000	0.052	
	Implantation	4,538.26	-	-	
	Device	5,682.07	-	-	
Erectile dysfunction	No treatment	-	0.430	0.430	
	Treatment	-	0.570	0.570	
	Sildenafil, 100 mg	5.88 (0.6) per week	0.822 of treated	0.822 of treated	
	Alprostadil, 20 µg	11.94 (1.2) per week	0.154 of treated	0.154 of treated	
	Penile prosthesis*	8,416.81 (841.7)	0.000	0.024	
	Implantation	2,613.43	-	-	
	Device	5,803.38	-	-	
Bowel dysfunction	Annual monitoring cost	425.75 (42.6) per year	1.000	1.000	
	Mean treatment cost	2,718.45 (271.8)	0.000	1.000	

SD, standard deviation; AUS, artificial urinary sphincter
*Non-recurring cost
Source: Ramsay et al. 2015[30]

Metastasis and end of life costs

The company's submission describes how the expected cost of diagnosing and treating metastatic progression was estimated and applied as a once-off cost to the proportion of the cohort entering the metastasis state in each cycle of the model. The costs assumed that diagnosis would require the additional cost of a bone scan (£755) and that 50% of patients would receive a first-line docetaxel based chemotherapy regimen, with 70% of these going on to receive a second line treatment with an aberaterone based regimen. Finally, the costs

included three weeks of cypoterone acetate (Androcur®, Bayer) and two course (each 3 months) of goserelin (Zoladex® LA, AstraZeneca) administered by a practice nurse in a primary care setting. It should be noted that the company's revised base case assumes no difference in metastatic progression between the treatment arms, and so the metastasis treatment costs on their own have no bearing on the cost-effectiveness results.

Similarly, end of life costs are applied to the proportion of the cohort that die in each cycle of the model. These costs, which account for palliative treatments and care, are also taken from Ramsay et al.,[30] the original source being Collins et al.[43] It is potentially problematic that these costs appear to be applied to all deaths rather than just prostate cancer specific deaths. However, since the company model assumes no difference in prostate cancer or other cause mortality between the treatment arms, these costs have no impact on cost-effectiveness.

5.2.8 Cost effectiveness results

The company's original base case

The company incremental base case results and a pairwise comparisons against padeliporfin VTP from the initially submitted model are presented in Tables 25 and 26 below. The full incremental analysis (Table 25) indicates that EBRT, RP and BT are dominated by AS, making AS the relevant reference treatment for expressing the ICER for padeliporfin VTP. This comes to £43,960. In the pairwise comparisons, the ICERs for padeliporfin VTP range from £17,408 against RP, to the £43,960 against AS (Table 26). The ICERs for padeliporfin VTP versus EBRT and BT lie between these values.

The company's base case results also include a comparison between a world where padeliporfin VTP is available as a treatment option and a world where it is not (Table 27). This analysis weights the comparator treatments according to current market shares for patients with low risk localised prostate cancer, and makes assumptions about anticipated changes in market shares if padeliporfin VTP is introduced. Importantly, it assumes that [redacted] (See Table 61 of the company's submission).

Table 25 Base case results: fully incremental analysis (Source: Table 59, company's submission, document B)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Active surveillance	16,609	13.673	11.413	-	-	-	-	-
EBRT	16,999	13.673	11.340	390	0.000	-0.073	Dominated by AS	Dominated by AS
Radical prostatectomy	18,752	13.673	11.185	2,143	0.000	-0.227	Dominated by AS	Dominated by EBRT
Brachytherapy	19,871	13.673	11.393	3,262	0.000	-0.020	Dominated by AS	5,392
VTP	26,714	13.673	11.643	10,105	0.000	0.230	43,960	27,390
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy; VTP, vascular-targeted photodynamic therapy								

Table 26 Base case results: pairwise comparisons against padeliporfin VTP (Source: Table 60, company's submission, Document B)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
VTP	26,714	13.673	11.643	-	-	-	-
Active surveillance	16,609	13.673	11.413	-10,105	0.000	-0.230	43,960
Radical prostatectomy	18,752	13.673	11.185	-7,962	0.000	-0.457	17,408
EBRT	16,999	13.673	11.340	-9,715	0.000	-0.303	32,082
Brachytherapy	19,871	13.673	11.393	-6,843	0.000	-0.250	27,390
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy; VTP, vascular-targeted photodynamic therapy							

Table 27 Base case results: without vs with padeliporfin VTP (Source: Table 62, company's submission, document B)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without padeliporfin VTP	17,579	13.673	11.345	-	-	-	-
World with padeliporfin VTP	19,856	13.673	11.461	2,277	0.000	0.116	19,549
VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year							

The above results are based on the company's initial assumption of equivalent TTM for AS and padeliporfin VTP, extracted from the AS arm of the ProtecT trial.[10] These TTM curves (based on freedom from disease progression) were not adjusted appropriately for general population mortality and comparison with the estimated OS curve. Therefore, they were not suitable for partitioning the cohorts between the pre and post metastasis states in the model.

When the ERG queried the suitability of the approach at the clarification stage, the company agreed that the "freedom from disease progression" curve needed to be adjusted to include general population all-cause mortality. In response to the clarifications letter, the company revised their based case to include an adjustment to the "freedom from disease progression" curves, but they also incorporated a new assumption of equivalence between all treatments with respect to metastatic progression (discussed under 5.2.5 above). The list of changes made by the company in their revised base case are as follow:

- Inclusion of costs for second VTP treatment,
- Adjustment of the TTM curve for AS and VTP to take into account the differences in populations between CLIN1001 PCM301 indication population (low-risk only) and ProtecT population (very low-risk, low-risk, and intermediate-risk) – this equates to assuming equivalence in TTM between all treatments, using the "freedom from disease progression" curve for EBRT from the ProtecT trial to model progression[10]
- Use of baseline utility values derived from EQ-5D data from CLIN1001 PCM301 ,
- Using secondary care costs for physical examinations and nurse consultations in the VTP administration costs, and
- Incorporating adjustment of TTM for general mortality

The company's revised base case

Based on their revised model, the company provided a full incremental analysis (Table 28), a pairwise comparison of padeliporfin VTP against each comparator (Table 29), and a further comparison between a world with and world without padeliporfin VTP (Table 30).

With the combined changes, EBRT, RP and BT remain dominated by AS, and padeliporfin VTP has an ICER of £49,415 versus AS. The pairwise ICERs for padeliporfin VTP versus each of the radical therapies is improved (Table 29), with these all falling below £30,000 per QALY gained. The key driver of this improvement over the original base case is the assumption of equivalent metastatic progression across all therapies.

Table 28 Revised base case results: fully incremental analysis (Source: Table 14, company's response to clarification questions)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus AS (£/QALY)	ICER incremental (£/QALY)
AS	16,650	13.673	12.269	-	-	-	-	-
EBRT	17,522	13.673	12.113	872	0.000	-0.156	Dominated by AS	Dominated by AS
RP	19,334	13.673	11.970	2,684	0.000	-0.299	Dominated by AS	Dominated by AS
BT	20,554	13.673	12.162	3,904	0.000	-0.107	Dominated by AS	Dominated by AS
VTP	27,652	13.673	12.492	11,002	0.000	0.223	49,415	49,415

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; BT, brachytherapy; VTP, vascular-targeted photodynamic therapy

Table 29 Revised base case: pairwise comparison against VTP (Source: Table 15, company's response to clarification questions)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus VTP (£/QALY)
VTP	27,652	13.673	12.492	-	-	-	-
AS	16,650	13.673	12.269	-11,002	0.000	-0.223	49,415
RP	19,334	13.673	11.970	-8,318	0.000	-0.522	15,946
EBRT	17,522	13.673	12.113	-10,130	0.000	-0.379	26,728
BT	20,554	13.673	12.162	-7,097	0.000	-0.330	21,533

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VTP, vascular-targeted photodynamic therapy; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

Table 30 Revised base case: world without vs with VTP (Source: Table 16, Company response to clarification questions)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
World without VTP*	17,889	13.673	12.163	-	-	-	-
World with VTP†	20,263	13.673	12.301	2,373	0.000	0.137	17,287

VTP, vascular targeted photodynamic therapy; LYG, life year gained; QALY, quality-adjusted life year

* Current market share values for AS, RP, EBRT and BT are 51%, 25%, 12% and 12%, respectively

† Future market share values for AS, RP, EBRT, BT and VTP are [redacted], [redacted], [redacted], [redacted] and [redacted], respectively

The company's submission provided further disaggregation of the initial base case results in the Appendices (J1.2) but these were not provided for the revised base case. However, they were available in the Excel model. The incremental QALY gain associated with padeliporfin VTP against all other treatments was driven by the higher proportion of patients remaining in the Pre-RT health state which is associated with lower rates of adverse events than the post-RT health state. [redacted]

5.2.9 Sensitivity analyses

Company's revised probabilistic sensitivity analysis

Whilst the company presented a revised base case in response to the clarification letter, they did not present updated probabilistic results. The ERG reproduced these using the company's revised model. The results are presented in Tables 31 to 34 and Figures 4-7 below. They show the probabilistic ICER for padeliporfin VTP against each treatment alternative, and the corresponding cost-effectiveness acceptability curve. The company did not produce a full incremental analysis for the probabilistic results. The pairwise ICERs are similar to the pairwise deterministic equivalents.

Table 31 PSA results: padeliporfin vs active surveillance

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Padeliporfin VTP	27,864	13.658	12.437	-	-	-	-
AS	16,592	13.654	12.228	11,272	0.004	0.210	53,733
VTP, vascular targeted photodynamic therapy; AS, active surveillance; LYG, life year gained; QALY, quality adjusted life year gained.							

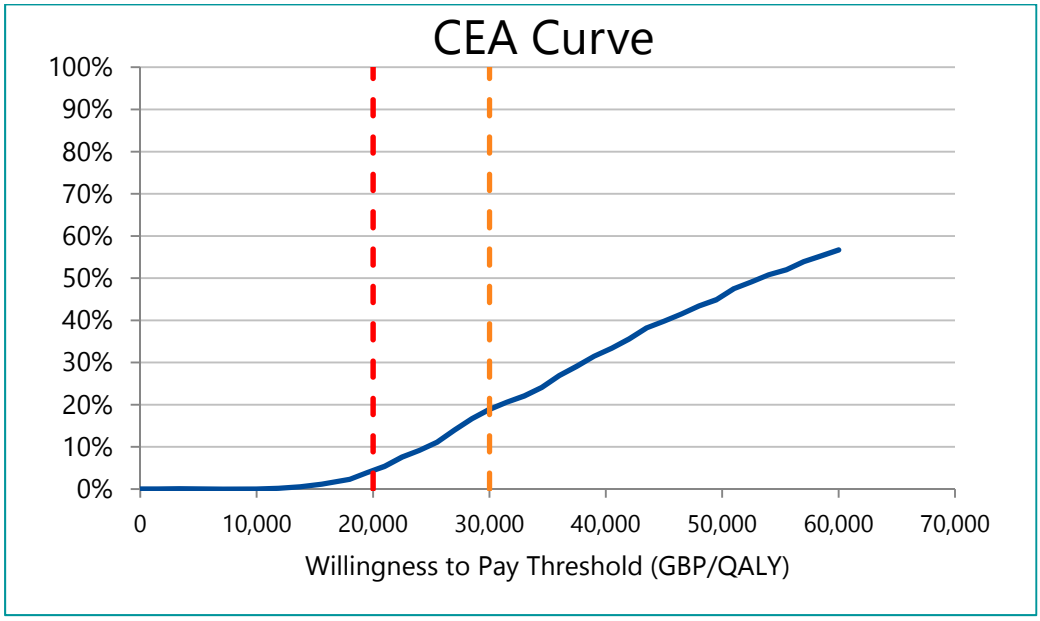

Figure 4 PSA results: padeliporfin VTP vs active surveillance

Table 32 PSA results: padeliporfin VTP vs radical prostatectomy

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Padeliporfin VTP	27,776	13.657	12.360	-	-	-	-
RP	19,316	13.660	11.849	8,460	-0.002	0.511	16,552
VTP, vascular targeted photodynamic therapy; RP, radical prostatectomy; LYG, life year gained; QALY, quality adjusted life year gained.							

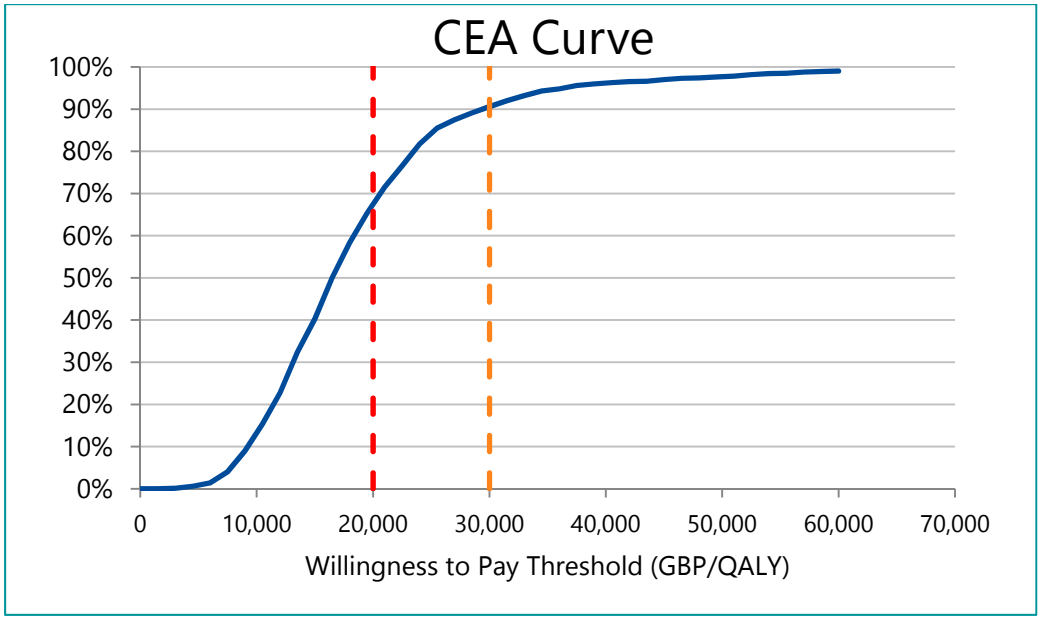

Figure 5 PSA results: padeliporfin VTP vs radical prostatectomy

Table 33 PSA results: padeliporfin VTP vs EBRT

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Padeliporfin VTP	27,943	13.655	12.430	-	-	-	-
EBRT	17,513	13.657	12.065	10,430	-0.002	0.365	28,576
VTP, vascular targeted photodynamic therapy; EBRT, external beam radiotherapy; LYG, life year gained; QALY, quality adjusted life year gained.							

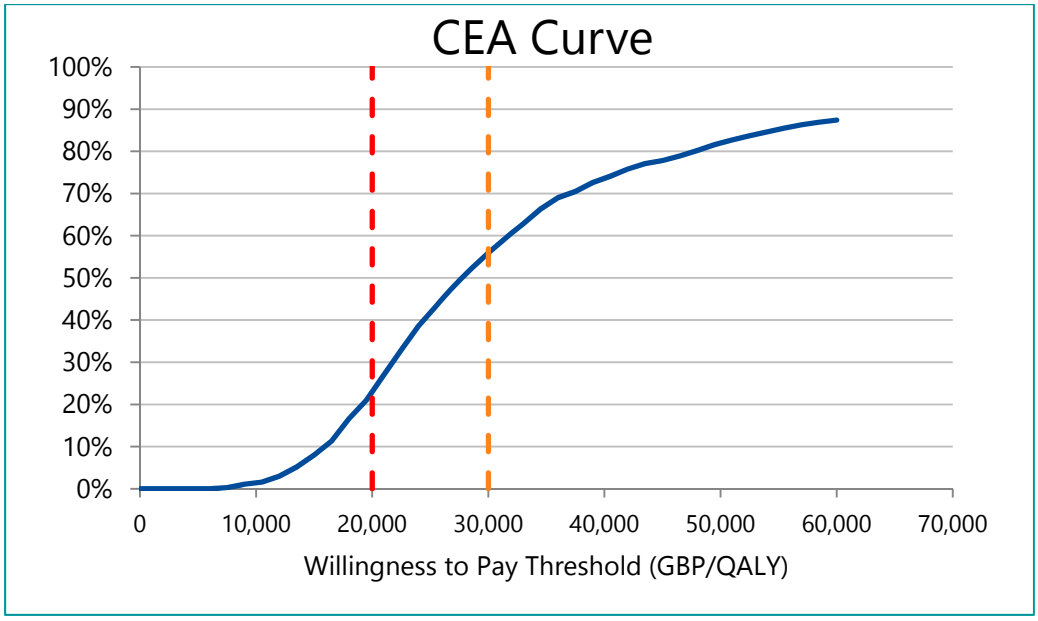

Figure 6 PSA results: padeliporfin vs radical EBRT

Table 34 PSA results: padeliporfin VTP vs brachytherapy

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Padeliporfin VTP	27,777	13.656	12.405	-	-	-	-
BT	20,575	13.659	12.091	7,201	-0.003	0.313	23,002
VTP, vascular targeted photodynamic therapy; BT, brachytherapy; LYG, life year gained; QALY, quality adjusted life year gained.							

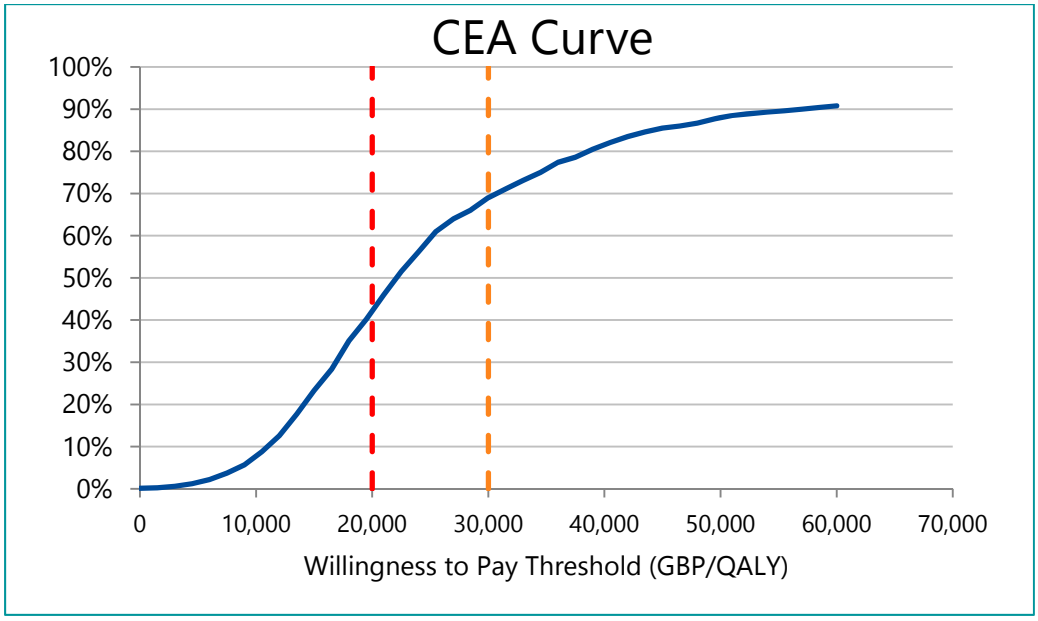

Figure 7 PSA results: padeliporfin vs brachytherapy

Company's revised scenario analysis

The company also generated a range of deterministic scenario analyses with their revised model. The results of these scenarios are presented in Tables 35-38 below, showing the pairwise comparison of padeliporfin VTP against each comparator in turn. Out of the scenarios assessed by the company, the results for each comparison are most sensitive to the choice of parametric distribution for TTRT.

The company also provided a number of further scenario analyses in response to the ERGs clarification questions. These generally showed the impact of individual or combined changes incorporated in the company's new base case, from the reference point of the original base case (see company response to the clarification letter for details). Since the company have now revised their base case, they are not presented here. However, the ERG have re-implemented three of them on the fully revised model, and incorporated the results in Tables 35 to 38:

1. Modelling TTRT on AS on observed TTRT for AS in the ProtecT trial, and expressing TTRT on padeliporfin VTP relative to this alternative baseline; Note, the ERG believe this analysis to be less relevant given the new assumption regarding equivalent metastatic progression between RT , AS and VTP. It was originally requested to match the company's original assumptions that TTM for AS and VTP would follow the "freedom from disease progression" curve observed for AS in ProtecT.

2. Applying the gamma function to TTRT and allowing the TTRT curves for padeliporfin VTP and AS to converge but not cross.
3. Applying utility decrements for adverse events, derived from CLIN1001 PCM301 EQ-5D data

In the pairwise comparison of padeliporfin VTP against Active surveillance, modelling AS TTRT based on the ProtecT trial data, or using the generalized gamma to model AS TTRT on the company's own CLIN1001 PCM301 trial data, significantly increased the ICER compared to the revised base case (Table 35). In the pairwise comparison against radical treatments (Tables 36-38), expressing TTRT on padeliporfin VTP relative to AS TTRT in ProtecT, significantly improved the ICERs. Padeliporfin VTP was dominated by all comparators when using disutility values derived from the EQ-5D data from the CLIN1001 PCM301 trial.

Table 35 Scenario analysis: padeliporfin VTP vs active surveillance

Scenario		Total cost		Total QALY		ICER
		VTP	AS	VTP	AS	
Base case		27,652	16,650	12.49	12.27	49,415
Time horizon	20 years	26,376	14,944	11.25	11.06	61,808
	30 years	27,453	16,450	12.40	12.18	49,420
Cycle length	3 months	27,690	16,629	12.64	12.41	49,076
TTRT curves	Log-logistic	28,991	16,518	12.43	12.28	80,580
	Weibull	30,905	17,384	12.34	12.23	125,830
	Exponential	26,103	15,841	12.56	12.31	41,617
AS TTRT curve based on ProtecT (Weibull)*	VTP TTRT relative to AS TTRT	23,864	11,217	12.652	12.561	139,042
Using generalized gamma to model TTRT*	Allowing TTRT curves for AS and VTP to converge	29,452	14,427	12.404	12.385	803,382
Localised PCa without AEs utility value	0.96	27,652	16,650	12.49	12.27	49,415
AE disutility value	UI: -0.14	27,652	16,650	12.41	12.07	32,346
	ED: -0.10	27,652	16,650	12.32	11.99	33,720
	UI: -0.14 ED: -0.10	27,652	16,650	12.23	11.79	24,793
	CLIN1001 PCM301 EQ-5D data*	27,652	16,650	12.792	12.815	VTP dominated
Radical therapy distribution after VTP or AS	RP: 83% EBRT: 9% BT: 9%	27,665	16,700	12.48	12.23	44,990
Cost	RP: £5,418	27,928	17,074	12.49	12.27	48,749
	RP: £7,362	28,481	17,923	12.49	12.27	47,419
	RP: £13,193	30,139	20,470	12.49	12.27	43,428
	RP: £6,344	28,191	17,479	12.49	12.27	48,116
	EBRT: £3,952	27,794	16,869	12.49	12.27	49,072
	EBRT: £5,292	27,975	17,146	12.49	12.27	48,637

*Scenarios implemented by the ERG; VTP, vascular targeted photodynamic therapy; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; TTRT, time to radical therapy; AE, adverse event; UI, urinary incontinence; ED, erectile dysfunction; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

Table 36 Scenario analysis: padeliporfin VTP vs radical prostatectomy

Scenario		Total cost		Total QALY		ICER
		VTP	RP	VTP	RP	
Base case		27,652	19,334	12.49	11.97	15,946
Time horizon	20 years	26,376	17,412	11.25	10.79	19,480
	30 years	27,453	19,090	12.40	11.89	16,168
Cycle length	3 months	27,690	19,259	12.64	12.10	15,718
TTRT and TTM curves	Log-logistic	29,042	19,384	12.40	11.94	21,101
	Weibull	30,961	19,398	12.30	11.93	31,753
	Exponential	25,968	19,226	12.58	11.99	11,394
AS TTRT curve based on ProtecT (Weibull)*	VTP TTRT relative to AS TTRT	23,864	19,334	12.652	11.970	6,642
Using generalized gamma to model TTRT*	Allowing TTRT curves for AS and VTP to converge	29,452	19,334	12.404	11.970	23,356
OS curve	Lognormal	27,539	19,216	12.41	11.89	15,955
Localised PCa without AEs utility value	0.96	27,652	19,334	12.49	11.97	15,946
AE disutility value	UI: -0.14	27,652	19,334	12.41	11.65	11,047
	ED: -0.10	27,652	19,334	12.32	11.44	9,421
	UI: -0.14 ED: -0.10	27,652	19,334	12.23	11.12	7,465
	CLIN1001 PCM301 EQ-5D data*	27,652	19,334	12.792	12.871	VTP dominated
Radical therapy distribution after VTP or AS	RP: 83% EBRT: 9% BT: 9%	27,665	19,334	12.48	11.97	16,439
Cost	RP: £5,418	27,928	20,300	12.49	11.97	14,623
	RP: £7,362	28,481	22,233	12.49	11.97	11,977
	RP: £13,193	30,139	28,031	12.49	11.97	4,041
	RP: £6,344	28,191	21,221	12.49	11.97	13,363
	EBRT: £3,952	27,794	19,334	12.49	11.97	16,219
	EBRT: £5,292	27,975	19,334	12.49	11.97	16,565

*Scenarios implemented by the ERG; VTP, vascular targeted photodynamic therapy; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; TTRT, time to radical therapy; AE, adverse event; UI, urinary incontinence; ED, erectile dysfunction; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

Table 37 Scenario analysis: padeliporfin VTP vs EBRT

Scenario		Total cost		Total QALY		ICER
		VTP	EBRT	VTP	EBRT	
Base case		27,652	17,522	12.49	12.11	26,728
Time horizon	20 years	26,376	15,583	11.25	10.92	32,604
	30 years	27,453	17,277	12.40	12.03	27,096
Cycle length	3 months	27,690	17,552	12.64	12.25	26,060
TTRT and TTM curves	Log-logistic	29,042	17,568	12.40	12.08	36,287
	Weibull	30,961	17,580	12.30	12.07	60,001
	Exponential	25,968	17,426	12.58	12.13	19,050
AS TTRT curve based on ProtecT (Weibull)*	VTP TTRT relative to AS TTRT	23,864	17,522	12.652	12.113	11,757
Using generalized gamma to model TTRT*	Allowing TTRT curves for AS and VTP to converge	29,452	17,522	12.404	12.113	41,054
OS curve	Lognormal	27,539	17,409	12.41	12.03	26,727
Localised PCa without AEs utility value	0.96	27,652	17,522	12.49	12.11	26,728
AE disutility value	UI: -0.14	27,652	17,522	12.41	11.99	24,095
	ED: -0.10	27,652	17,522	12.32	11.80	19,614
	UI: -0.14 ED: -0.10	27,652	17,522	12.23	11.68	18,158
	CLIN1001 PCM301 EQ-5D data*	27,652	17,522	12.792	12.822	VTP dominated
Radical therapy distribution after VTP or AS	RP: 83% EBRT: 9% BT: 9%	27,665	17,522	12.48	12.11	27,853
Cost	RP: £5,418	27,928	17,522	12.49	12.11	27,457
	RP: £7,362	28,481	17,522	12.49	12.11	28,915
	RP: £13,193	30,139	17,522	12.49	12.11	33,289
	RP: £6,344	28,191	17,522	12.49	12.11	28,151
	EBRT: £3,952	27,794	18,570	12.49	12.11	24,338
	EBRT: £5,292	27,975	19,902	12.49	12.11	21,300

*Scenarios implemented by the ERG; VTP, vascular targeted photodynamic therapy; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; TTRT, time to radical therapy; AE, adverse event; UI, urinary incontinence; ED, erectile dysfunction; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

Table 38 Scenario analysis: padeliporfin VTP vs Brachytherapy

Scenario		Total cost		Total QALY		ICER
		VTP	BT	VTP	BT	
Base case		27,652	20,554	12.49	12.16	21,533
Time horizon	20 years	26,376	18,758	11.25	10.96	26,667
	30 years	27,453	20,319	12.40	12.08	21,856
Cycle length	3 months	27,690	20,478	12.64	12.30	21,325
TTRT and TTM curves	Log-logistic	29,042	20,612	12.40	12.13	31,561
	Weibull	30,961	20,629	12.30	12.12	59,368
	Exponential	25,968	20,431	12.58	12.18	13,885
AS TTRT curve based on ProtecT (Weibull)*	VTP TTRT relative to AS TTRT	23,864	20,554	12.652	12.162	6,754
Using generalized gamma to model TTRT*	Allowing TTRT curves for AS and VTP to converge	29,452	20,554	12.404	12.162	36,891
OS curve	Lognormal	27,539	20,438	12.41	12.08	21,545
Localised PCa without AEs utility value	0.96	27,652	20,554	12.49	12.16	21,533
AE disutility value	UI: -0.14	27,652	20,554	12.41	11.75	10,789
	ED: -0.10	27,652	20,554	12.32	11.96	19,971
	UI: -0.14 ED: -0.10	27,652	20,554	12.23	11.55	10,382
	CLIN1001 PCM301 EQ-5D data*	27,652	20,554	12.792	12.798	VTP dominated
Radical therapy distribution after VTP or AS	RP: 83% EBRT: 9% BT: 9%	27,665	20,554	12.48	12.16	22,591
Cost	RP: £5,418	27,928	20,554	12.49	12.16	22,372
	RP: £7,362	28,481	20,554	12.49	12.16	24,049
	RP: £13,193	30,139	20,554	12.49	12.16	29,079
	RP: £6,344	28,191	20,554	12.49	12.16	23,171
	EBRT: £3,952	27,794	20,554	12.49	12.16	21,965
	EBRT: £5,292	27,975	20,554	12.49	12.16	22,514

*Scenarios implemented by the ERG; VTP, vascular targeted photodynamic therapy; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; TTRT, time to radical therapy; AE, adverse event; UI, urinary incontinence; ED, erectile dysfunction; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy

5.2.10 Model validation and face validity check

The ERG checked the cohort flow, and the cost and QALY calculations in the economic model. As discussed earlier, there was an issue with the initially submitted model relating to inconsistent adjustment of the disease specific survival curve and the freedom from disease progression curve, which were used to partition the cohort between the pre-metastasis and post metastasis health states. This resulted in underestimation of progression to metastasis compared with the observed data from stated source (the ProtecT trial). However, the company corrected this at the post clarification stage. Following the correction, the 10-year model based estimate of the cumulative proportion of patients making the transition to metastasis was 6.3% across all treatment arms. This compares with ~7.7% (42/545) who had evidence of disease progression (excluding prostate cancer deaths) in the EBRT arm of ProtecT. The company's method for estimating the proportion of patients experiencing metastasis in each cycle of the model, is to take the difference in the proportion of the cohort with metastasis in the current cycle compared with the previous cycle, unless this generates a negative value in which case zero is assumed. This may slightly underestimate the proportion making the transition to metastasis for the purpose of applying the cost of treating metastatic disease. However, since equivalent progression to metastasis is assumed across treatment modalities, this will have very little bearing on the cost-effectiveness results.

A further potential issue was identified with respect to the way the TTRT curve used to partition the cohort between the pre- and post-radical therapy states. The ERG assume that the TTRT curves from CLIN1001 PCM301 were censored for deaths, and so represent the risk of progression to radical therapy conditional on survival. Yet, the TTRT curves were not adjusted for general population mortality in the company model the way that the prostate cancer specific survival curve and the freedom from disease progression curves were. Instead, the proportion remaining in the pre-progressed state was set equal to the unadjusted TTRT curve, and this was only adjusted downward to equal the adjusted freedom from disease (metastasis free) progression curve when it fell lower than the unadjusted TTRT curve. The ERG have some concerns that this may overestimate the proportion of patients remaining the in the Pre-RT health state. Therefore, the ERG assessed the impact of adjusting TTRT for general population mortality in the company model, and using the difference between the two curves to estimate the proportion in the post-RT health state. For this analysis, the ERG also had to revise the formulas for estimating the proportion of the cohort receiving radical therapy in each cycle of the model. This was calculated by applying the estimated time

dependent transition probability derived from the fitted TTRT curve, to proportion of patients remaining at risk at the end of the previous cycle. Whilst adding the in the competing risk of general population mortality in the Pre-RT health state slightly reduced the percentage of patients transitioning to RT, it also reduced the proportion of patients remaining the pre-RT health state.

A further issue was identified in the mode calculations with respect to the proportion of patients modelled to transition to each radical treatment upon progression to radical therapy from the pre-RT health state. The cumulative proportion of patients incurring costs for any type of RT (across all model cycles) was estimated to be 65.7% in the padeliporfin VTP arm and 94.3% in the AS arm of the company's base case model. However, as a result of the model calculations, the sum of cycle specific proportions progression to radical prostatectomy, EBRT and brachytherapy came to only 40.8% and 71.6% in the padeliporfin VTP and AS arms respectively. These proportions for the individual types of radical therapy were only used in the model to calculate the proportion of patients transitioning to salvage therapies following radical treatment, and so do not have a large impact on the ICERs. Nevertheless, the ERG assessed the impact of recalculating these so the sum of the individual proportions equaled the overall proportion progressing to any radical therapy in each cycle of the model.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 Exploratory analysis on the company's originally submitted model

The ERG conducted several analyses to explore the impact of altering a number of the company's assumptions. Since the company's originally submitted model assumed that AS and padeliporfin VTP would follow the freedom from disease progression curve observed for AS in the ProtecT trial,[10] we first of all assessed the impact of implementing the company's post-clarification adjustment of the curve for general population mortality in this model, without implementing the other post clarification changes to the company's base case (Table 39 and 40). Under this scenario, the ICER for padeliporfin VTP versus AS remains relatively stable, increasing from £43,960 to £48,346. However, the ICERs for padeliporfin VTP versus the radical therapies are affected more dramatically. Against RP, the ICER increases from £17,408 to £60,707. Against the EBRT and BT, padeliporfin becomes dominated (less effective and more costly). Thus, it is clear that the economic case for padeliporfin VTP is

dependent on it having a lower metastatic disease progression rate than that observed for AS in the ProtecT trial, which was significantly higher than the rate observed for radical therapy (RP and EBRT).

Table 39 Company's original model adjusted for general population all-cause mortality: fully incremental analysis

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER * (£/QALY)
AS	17,444	13.673	10.873	-	-	-	-
EBRT	17,522	13.673	11.089	78	0.000	0.216	361
RP	19,334	13.673	10.947	1,812	0.000	-0.142	Dominated by EBRT
Brachytherapy	20,554	13.673	11.139	3,032	0.000	0.050	60,640
VTP	27,621	13.673	11.083	7,067	0.000	-0.056	Dominated by Brachytherapy
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; EBRT, external beam radiation therapy; RP, radical prostatectomy; VTP, vascular-targeted photodynamic therapy							

*ICER against the next less expensive non-dominated alternative

Table 40 Company's original model adjusted for general population all-cause mortality: pairwise comparison against VTP

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) (vs VTP)	Incremental QALY (vs VTP)	ICER vs VTP (£/QALY)
VTP	27,621	11.083	-	-	-
AS	17,444	10.873	-10,177	-0.210	48,346
RP	19,334	10.947	-8,287	-0.136	60,707
EBRT	17,522	11.089	-10,099	0.006	VTP dominated
BT	20,554	11.139	-7,067	0.056	VTP dominated
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; VTP, vascular-targeted photodynamic therapy					

5.3.2 Exploratory analysis on the company's revised model

All further exploratory analysis conducted by the ERG focused on the company's post-clarification revised economic model. The ERG explored the impact of testing the following further assumptions:

1. Assessing the impact of recalculating the percentage of patients receiving RP, EBRT and BT following AS or padeliporfin VTP in each cycle of the model (see section 5.2.10 for justification)
2. Adjusting the TTRT curves on AS and padeliporfin VTP for general population mortality (see section 5.2.10 for justification)
3. Reducing the utility decrement associated with BD from 0.16 to 0.1, the observed decrement in utility between those with and those without bowel dysfunction in the original source publication.[36]
4. Removing the costs of adjuvant therapies following radical therapy.
5. Setting the prevalence of bowel dysfunction in the radical prostatectomy arm equal to the prevalence in the AS arm of the model, based on comparative data from the ProtecT trial[40] (see section 5.2.6 for justification)
6. Setting the prevalence of bowel dysfunction in the radical prostatectomy arm equal to the prevalence in the padeliporfin VTP arm of the model, to avoid potentially biasing against padeliporfin VTP (see section 5.2.6 for justification).
7. Basing the prevalence of ED, UI and BD in the RP and EBRT arms of the model on the observed differences in prevalence compared to AS in the ProtecT trial (see section 5.2.6 for justification).
8. Including costs for multi-parametric MRI prior to padeliporfin VTP administration and active surveillance; £343.42 [20]
9. Including the cost of an overnight stay (£275.59) in the padeliporfin VTP procedure costs
10. Applying the cost of treating BD on a once-off basis to the proportion of patients experiencing long-term BD beyond 6 months)

The results of these analyses are summarised in Table 41 (full incremental analysis), Table 42 (pairwise comparisons), and Table 43 (world with and world without padeliporfin VTP).

In six of the ten primary ERG scenarios assessed (1, 2, 3, 4, 8 and 9), all the radical therapies remained dominated by AS, and in all of these scenarios the ICER for padeliporfin VTP versus AS remained above the £30,000 per QALY gained.

Setting the bowel dysfunction prevalence of radical prostatectomy first equal to that of AS (Scenario 3) and then VTP (Scenario 4), resulted in RP being the lowest cost treatment option. In these two scenarios AS was cost-effective compared to RP (ICERs £3,897 and £1,085, respectively) and dominated EBRT and Brachytherapy. The ICER for VTP versus AS remained above £30,000 in these two scenarios.

Radical prostatectomy was also the least costly treatment option when the prevalence of UI, ED and BD, for RP and EBRT, were based to the observed differences in patient reported prevalence compared to AS in the ProtecT trial (Scenario 5). In this scenario both EBRT and Brachytherapy were dominated by RP, and the ICER for AS versus RP was £35,340. The ICER for VTP versus AS was £146,408. The ICERs were particularly sensitive to this change, with only the pairwise ICER for padeliporfin VTP versus BT falling below £30,000 per QALY gained, but this is partly due to the fact that the adverse event rates for BT were not updated in this scenario.

In the pairwise comparisons against the radical therapies, the ICER for padeliporfin VTP remained below £30,000 against all the radical therapies in scenarios 1, 4, 8 and 9. The ICER for VTP versus RP was most sensitive to changes in the prevalence of bowel dysfunction and the other adverse events following RP (Scenarios 5, 6 and 7). The pairwise ICER for padeliporfin VTP versus EBRT was sensitive to the ERG adjustment to the VTP TTRT curve for general population mortality (Scenario 2), reducing the utility decrement associated with bowel dysfunction (scenario 3), adjusting the prevalence of EBRT adverse events (scenario 7), and the once-off application of treatment costs for bowel dysfunction (scenario 10).

Two further combined scenarios were assessed. Scenario 11 incorporated the reduced utility decrement of -0.1 (rather than -0.16) for bowel dysfunction (scenario 3); the removal of adjuvant therapy costs (scenario 4); post-RP bowel dysfunction prevalence equal to bowel dysfunction prevalence on AS (scenario 5); the addition of a hospital bed day to the administration cost of padeliporfin VTP (scenario 9); and the once-off application of bowel dysfunction treatment costs (scenario 10). In this scenario we also applied the HRG based reference costs for RP and EBRT, for consistency with previous NICE models in the area of prostate cancer.[20] Scenario 12 is the same as scenario 11 except that bowel dysfunction following RP was set equal to the post padeliporfin VTP bowel dysfunction prevalence. In

both these scenarios, all the pairwise ICERs for VTP were above £30,000 per QALY gained (Table 42).

Considering the states of the world analysis (Table 43), the ICER for a world with padeliporfin versus a world without ranged from £17,465 to £51,157 across the scenarios 1-10. In the combined scenarios 11 and 12, the ICER was £33,763 and £32,661 respectively.

Table 41 ERG scenario analysis: full incremental analyses

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER * (£/QALY)
Scenario 1 recalculating the percentage of patients receiving RP, EBRT and BT following AS or padeliporfin VTP in each cycle of the model							
AS	16,729	13.673	12.269	-	-	-	-
EBRT	17,522	13.673	12.113	793	0	-0.156	Dominated by AS
RP	19,334	13.673	11.970	2,605	0	-0.299	Dominated by AS
Brachytherapy	20,554	13.673	12.162	3,825	0	-0.107	Dominated by AS
VTP	27,733	13.673	12.492	11,004	0	0.223	49,424
Scenario 2 Adjusting the TTRT curves on AS and padeliporfin VTP for general population mortality							
AS	16,583	13.673	12.257	-	-	-	-
EBRT	17,522	13.673	12.113	939	0	-0.143	Dominated by AS
RP	19,334	13.673	11.970	2,752	0	-0.286	Dominated by AS
Brachytherapy	20,554	13.673	12.162	3,972	0	-0.094	Dominated by AS
VTP	27,931	13.673	12.452	11,349	0	0.196	57,931
Scenario 3 Company's new model using bowel disutility value equal to -0.1 (Shimizu et al)							
AS	16,650	13.673	12.340	-	-	-	-
EBRT	17,522	13.673	12.250	872	0	-0.090	Dominated by AS
RP	19,334	13.673	12.065	2,684	0	-0.275	Dominated by AS
Brachytherapy	20,554	13.673	12.249	3,904	0	-0.091	Dominated by AS
VTP	27,652	13.673	12.530	11,002	0	0.190	58,047
Scenario 4 Removing costs of adjuvant EBRT and HR therapies in the company's new model							
AS	16,029	13.673	12.269	-	-	-	-
EBRT	17,085	13.673	12.113	1,056	0	-0.156	Dominated by AS
RP	18,242	13.673	11.970	2,212	0	-0.299	Dominated by AS

Brachytherapy	20,315	13.673	12.162	4,286	0	-0.107	Dominated by AS
VTP	27,248	13.673	12.492	11,218	0	0.223	50,387
Scenario 5 Setting bowel dysfunction prevalence of RP equal to AS in the company's new model (ProtecT trial)							
RP	14,373	13.673	12.223	-	-	-	-
AS	14,901	13.673	12.358	528	0	0.136	3,897
EBRT	17,522	13.673	12.113	2,620	0	-0.245	Dominated by AS
Brachytherapy	20,554	13.673	12.162	5,653	0	-0.196	Dominated by AS
VTP	26,929	13.673	12.529	12,027	0	0.170	70,562
Scenario 6 Setting bowel dysfunction prevalence of RP equal to VTP in the company's new model							
RP	14,930	13.673	12.195	-	-	-	-
AS	15,097	13.673	12.348	167	0	0.154	1,085
EBRT	17,522	13.673	12.113	2,425	0	-0.235	Dominated by AS
Brachytherapy	20,554	13.673	12.162	5,458	0	-0.186	Dominated by AS
VTP	27,012	13.673	12.525	11,916	0	0.176	67,651
Scenario 7 Setting the prevalence rates for UI, ED and BD, for RP and EBRT, based on the observed differences compared to AS in the ProtecT trial [40]							
RP	12,996	13.673	12.479	-	-	-	-
EBRT	13,590	13.673	12.424	594	0	-0.056	Dominated by RP
AS	13,758	13.673	12.501	762	0	0.022	35,340
Brachytherapy	20,554	13.673	12.162	6,797	0	-0.338	Dominated by RP&AS
VTP	26,455	13.673	12.588	12,697	0	0.087	146,498
Scenario 8 Adding one-off cost of a pre-treatment multiparametric MRI scan to the cost of Active surveillance and VTP (includes total cost of mpMRI and additional cost of using fusion image registration)							
AS	16,975	13.673	12.269	-	-	-	-
EBRT	17,522	13.673	12.113	546	0	-0.156	Dominated by AS
RP	19,334	13.673	11.970	2,359	0	-0.299	Dominated by AS
Brachytherapy	20,554	13.673	12.162	3,579	0	-0.107	Dominated by AS
VTP	28,016	13.673	12.492	11,040	0	0.223	49,588
Scenario 9 Adding a weighted average cost of an inpatient excess bed day (£275.59) to the treatment cost of padeliporfin VTP in the company's new model							
EBRT	16,650	13.673	12.269	-	-	-	-
AS	17,522	13.673	12.113	872	0	-0.156	Dominated by AS
RP	19,334	13.673	11.970	2,684	0	-0.299	Dominated by AS
Brachytherapy	20,554	13.673	12.162	3,904	0	-0.107	Dominated by AS
VTP	27,944	13.673	12.492	11,294	0	0.223	50,730
Scenario 10 Applying the treatment cost of bowel dysfunction as a one-off long term cost							
EBRT	11,817	13.673	12.113	-	-	-	-

AS	13,696	13.673	12.269	1,879	0	0.156	12,019
RP	15,391	13.673	11.970	1,695	0	-0.299	Dominated by AS
Brachytherapy	16,956	13.673	12.162	3,259	0	-0.107	Dominated by AS
VTP	26,115	13.673	12.492	12,419	0	0.223	55,782
Scenario 11 Applying scenarios 3, 4, 5, 9 and 10 simultaneously and using a weighted average of HRG cost for RP and EBRT							
EBRT	12,428	13.673	12.250	-	-	-	-
AS	13,767	13.673	12.396	1,339	0	0.146	9,176
RP	15,167	13.673	12.223	1,400	0	-0.173	Dominated by AS
Brachytherapy	16,717	13.673	12.249	2,949	0	-0.147	Dominated by AS
VTP	26,525	13.673	12.553	12,758	0	0.157	81,304
Scenario 12 Applying scenarios 3, 4, 6, 9 and 10 simultaneously and using a weighted average of HRG cost for RP and EBRT							
EBRT	12,428	13.673	12.250	-	-	-	-
AS	13,805	13.673	12.389	1,377	0	0.140	9,882
RP	15,277	13.673	12.205	1,471	0	-0.184	Dominated by AS
Brachytherapy	16,717	13.673	12.249	2,911	0	-0.141	Dominated by AS
VTP	26,542	13.673	12.550	12,737	0	0.160	79,376
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; VTP, vascular-targeted photodynamic therapy							

*ICER against the next less expensive non-dominated alternative

Table 42 ERG scenario analysis: pairwise comparison against padeliporfin VTP

Technologies	Total cost (£)	Total QALYs	Incremental costs (£) (vs VTP)	Incremental QALY (vs VTP)	ICER vs VTP (£/QALY)
Scenario 1 recalculating the percentage of patients receiving RP, EBRT and BT following AS or padeliporfin VTP in each cycle of the model					
VTP	27,733	12.492	-	-	-
AS	16,729	12.269	-11,004	-0.223	49,424
RP	19,334	11.970	-8,399	-0.522	16,101
EBRT	17,522	12.113	-10,211	-0.379	26,942
Brachytherapy	20,554	12.162	-7,178	-0.330	21,780
Scenario 2 Adjusting the TTRT curves on AS and padeliporfin VTP for general population mortality					
VTP	27,931	12.452	-	-	-
AS	16,583	12.257	-11,349	-0.196	57,931
RP	19,334	11.970	-8,597	-0.482	17,837
EBRT	17,522	12.113	-10,409	-0.339	30,673
Brachytherapy	20,554	12.162	-7,377	-0.290	25,441
Scenario 3 Company's new model using bowel disutility value equal to -0.1 (Shimizu et al)					
VTP	27,652	12.530	-	-	-
AS	16,650	12.340	-11,002	-0.190	58,047
RP	19,334	12.065	-8,318	-0.465	17,906
EBRT	17,522	12.250	-10,130	-0.280	36,195
Brachytherapy	20,554	12.249	-7,097	-0.281	25,273
Scenario 4 Removing costs of adjuvant EBRT and HR therapies in the company's new model					
VTP	27,248	12.492	-	-	-
AS	16,029	12.269	11,218	-0.223	50,387
RP	18,242	11.970	9,006	-0.522	17,265
EBRT	17,085	12.113	10,162	-0.379	26,813
BT	20,315	12.162	6,932	-0.330	21,033
Scenario 5 Setting bowel dysfunction prevalence of RP equal to AS in the company's new model (ProtecT trial)					
VTP	26,929	12.529	-	-	-
AS	14,901	12.358	12,027	-0.170	70,562
RP	14,373	12.223	12,555	-0.306	41,036
EBRT	17,522	12.113	9,407	-0.416	22,623
BT	20,554	12.162	6,374	-0.366	17,397
Scenario 6 Setting bowel dysfunction prevalence of RP equal to VTP in the company's new model					
VTP	27,012	12.525	-	-	-
AS	15,097	12.348	-11,916	-0.176	67,651
RP	14,930	12.195	-12,083	-0.330	36,612
EBRT	17,522	12.113	-9,490	-0.412	23,061
BT	20,554	12.162	-6,458	-0.362	17,833
Scenario 7 Setting the prevalence rates for UI, ED and BD, for RP and EBRT, based on the observed differences compared with AS in the ProtecT trial [40]					
VTP	26,455	12.588	-	-	-
AS	13,758	12.501	-12,697	-0.087	146,498
RP	12,996	12.479	-13,459	-0.108	124,345
EBRT	13,590	12.424	-12,865	-0.164	78,568
BT	20,554	12.162	-5,900	-0.425	13,881
Scenario 8 Adding one-off cost of a pre-treatment multiparametric MRI scan to the cost of Active surveillance and VTP (includes total cost of mpMRI and additional cost of using fusion image registration)					
VTP	28,016	12.492	-	-	-
AS	16,975	12.269	-11,040	-0.223	49,588
RP	19,334	11.970	-8,681	-0.522	16,643

EBRT	17,522	12.113	-10,494	-0.379	27,688
BT	20,554	12.162	-7,461	-0.330	22,637
Scenario 9 Adding a weighted average cost of an inpatient excess bed day (£275.59) to the treatment cost of padeliporfin VTP in the company's new model					
VTP	27,944	12.492	-	-	-
AS	16,650	12.269	-11,294	-0.223	50,730
RP	19,334	11.970	-8,610	-0.522	16,507
EBRT	17,522	12.113	-10,423	-0.379	27,500
BT	20,554	12.162	-7,390	-0.330	22,422
Scenario 10 Applying the treatment cost of bowel dysfunction as a one-off long term cost					
VTP	26,115	12.492	-	-	-
AS	13,696	12.269	-12,419	-0.223	55,782
RP	15,391	11.970	-10,725	-0.522	20,560
EBRT	11,817	12.113	-14,299	-0.379	37,727
BT	16,956	12.162	-9,160	-0.330	27,792
Scenario 11 Applying scenarios 3, 4, 5, 9 and 10 simultaneously and using a weighted average of HRG cost for RP and EBRT					
VTP	£26,525	12.553	-	-	-
AS	£13,767	12.396	-£12,758	-0.157	81,304
RP	£15,167	12.223	-£11,358	-0.330	34,444
EBRT	£12,428	12.250	-£14,097	-0.303	46,544
Brachytherapy	£16,717	12.249	-£9,808	-0.304	32,284
Scenario 12 Applying scenarios 3, 4, 6, 9 and 10 simultaneously and using a weighted average of HRG cost for RP and EBRT					
VTP	£26,542	12.550	-	-	-
AS	£13,805	12.389	-£12,737	-0.160	79,376
RP	£15,277	12.205	-£11,266	-0.345	32,676
EBRT	£12,428	12.250	-£14,114	-0.300	47,016
Brachytherapy	£16,717	12.249	-£9,826	-0.301	32,628
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; AS, active surveillance; RP,radical prostatectomy; EBRT, external beam radiation therapy; VTP, vascular-targeted photodynamic therapy					

Table 43 ERG scenario analysis: world with versus a world without padeliporfin VTP

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 1 recalculating the percentage of patients receiving RP, EBRT and BT following AS or padeliporfin VTP in each cycle of the model					
World without padeliporfin VTP	17,930	12.163	-	-	-
World with padeliporfin VTP	20,327	12.301	2,398	0.137	17,465
Scenario 2 Adjusting the TTRT curves on AS and padeliporfin VTP for general population mortality					
World without padeliporfin VTP	17,855	12.157	-	-	-
World with padeliporfin VTP	20,312	12.282	2,457	0.125	19,596
Scenario 3 Company's new model using bowel disutility value equal to -0.1 (Shimizu et al)					
World without padeliporfin VTP	17,889	12.250	-	-	-
World with padeliporfin VTP	20,263	12.371	2,373	0.121	19,616
Scenario 4 Removing costs of adjuvant EBRT and HR therapies in the company's new model					
World without padeliporfin VTP	17,218	12.163	-	-	-
World with padeliporfin VTP	19,712	12.301	2,494	0.137	18,170
Scenario 5 Setting bowel dysfunction prevalence of RP equal to AS in the company's new model (ProtecT trial)					
World without padeliporfin VTP	15,752	12.272	-	-	-
World with padeliporfin VTP	18,901	12.370	3,148	0.098	32,183
Scenario 6 Setting bowel dysfunction prevalence of RP equal to VTP in the company's new model					
World without padeliporfin VTP	16,000	12.259	-	-	-
World with padeliporfin VTP	19,059	12.362	3,059	0.102	29,885
Scenario 7 Setting the prevalence rates for UI, ED and BD, for RP and EBRT, based on the observed differences compared with AS in the ProtecT trial [40]					
World without padeliporfin VTP	14,355	12.446	-	-	-
World with padeliporfin VTP	17,637	12.510	3,282	0.064	51,157
Scenario 8 Adding one-off cost of a pre-treatment multiparametric MRI scan to the cost of Active surveillance and VTP (includes total cost of mpMRI and additional cost of using fusion image registration)					
World without padeliporfin VTP	18,056	12.163	-	-	-
World with padeliporfin VTP	20,538	12.301	2,482	0.137	18,082
Scenario 9 Adding a weighted average cost of an inpatient excess bed day (£275.59) to the treatment cost of padeliporfin VTP					
World without padeliporfin VTP	17,889	12.163	-	-	-

World with padeliporfin VTP	20,350	12.301	2,461	0.137	17,927
Scenario 10 Applying the treatment cost of bowel dysfunction as a one-off long term cost					
World without padeliporfin VTP	14,284	12.163	-	-	-
World with padeliporfin VTP	17,345	12.301	3,061	0.137	22,297
Scenario 11 Applying scenarios 3, 4, 5, 9 and 10 simultaneously and using a weighted average of HRG cost for RP and EBRT					
World without padeliporfin VTP	14,309	12.318			
World with padeliporfin VTP	17,561	12.414	3,252	0.096	33,763
Scenario 12 Applying scenarios 3, 4, 6, 9 and 10 simultaneously and using a weighted average of HRG cost for RP and EBRT					
World without padeliporfin VTP	14,356	12.310			
World with padeliporfin VTP	17,592	12.409	3,236	0.099	32,661

5.4 Conclusion of the cost effectiveness section

The company's originally submitted model used the 10-year "freedom from disease progression" curve from the active surveillance arm of the ProtecT trial to model progression to metastasis for both AS and padeliporfin VTP. Metastatic progression for the radical therapies was based on the lower disease progression rate observed for EBRT in ProtecT. Thus, there was a trade-off between a superior adverse event profile and a higher risk of progression to metastasis in the comparison between padeliporfin VTP and the radical therapies in the company's originally submitted model. However, there was an inconsistency in the way that the unadjusted "freedom from disease progression" curve was being combined with the estimated overall survival curve to partition the cohort between the metastasis and pre-metastatic health states in the model. The company therefore provided a revised model in response to the clarification letter, in which they corrected this issue. However, they also revised their assumptions to assume that all treatment options would follow the same rate of disease progression (to metastasis) as observed for the radical therapies in the ProtecT trial. This is an important issue for consideration, because applying the company's correction to the partitioning calculations alone in the original model results in in padeliporfin VTP having an unfavourable ICER against all the comparators.

With the revised model assuming equivalent metastatic disease progression and mortality for all treatment modalities, the economic case is dependent on these assumptions. In comparison with AS and all the alternative radical therapies, the incremental benefit for padeliporfin VTP

is generated through reducing the time spent in the post-radical therapy state, which has a higher adverse event burden compared to the pre-radical therapy state in both the AS and padeliporfin VTP arms of the model.

In the revised company base case, and almost all revised scenario analyses assessed, the ICER for padeliporfin VTP versus active surveillance remains above £30,000 per QALY gained. Thus the cost-effectiveness case rests on the more favourable ICERs for padeliporfin VTP versus the radical therapies. In the company revised base case, the ICER for padeliporfin VTP remains below £30,000 against all the radical therapies (Table29). The ICERs also remains below £30,000 against the radical therapies in the vast majority of scenario analyses implemented by the company (Tables 36-38). However, they are sensitive to the choice of parametric distribution and the assumptions used to model time to radical therapy following padeliporfin VTP, and the source of the utility decrements applied to the adverse events (see Tables 36-38).

In addition to the sensitivity analysis conducted by the company, the ERG carried out a number of additional scenario analyses to explore the impact of changing a number of uncertain input parameter values and assumptions (Tables 41-43). In addition to the choice of parametric function for TTRT, the ERG believe the most important uncertainties relate to:

3. The comparative prevalence of the key adverse events (UI, ED and BD) following the alternative treatment modalities; and
4. The health state utility and cost-impact of bowel dysfunction

When several justified changes are applied simultaneously to the company's revised base case, the ICER for VTP increases above £30,000 per QALY gained against all comparators.

6 Overall conclusions

The company's submission considered padeliporfin (TOOKAD®, Steba Biotech) for adults with unilateral, low-risk, localised prostate cancer. The company also included analyses for padeliporfin in adults with unilateral, low-risk prostate cancer, excluding very low risk disease, which was consistent with the approved indication.

6.1 Clinical effectiveness evidence

The company's clinical effectiveness evidence consists mainly of one phase III RCT, the CLIN1001 PCM301 trial, which compared padeliporfin VTP with active surveillance. The co-primary endpoints were absence of definitive cancer at 24 months and treatment failure (defined as progression of cancer from low to moderate risk or higher over 24-month follow-up). In the indication population (i.e. people with unilateral low risk [but not very low risk] disease), 65% of the VTP group and 14.1% of the AS group had a negative biopsy in the ipsilateral lobe at 24 months (risk ratio 4.61, 95%CI 2.60-8.16). In the overall ITT population, 49% of the VTP group and 13.5% of the AS group had a negative biopsy result at 24 months (risk ratio 3.67, 95%CI 2.53-5.33). Absence of disease progression was shown in 90% vs 42% of the VTP and AS groups, respectively, of the indication population at 27 months. In the ITT population, disease progression was reported in 28.2% and 58%, respectively (hazard ratio 0.34, 95%CI 0.24-0.46). Adverse events and serious adverse events were more common in the VTP group (94.9%, 30.5%) than the AS group (55.1%, 10.1%) of the ITT population, with similar proportions in the indication population. There were no prostate cancer-related deaths at 24 months.

The company's cost-effectiveness evidence is based on a four state partitioned survival model. The ICER for padeliporfin VTP remained above £30,000 per QALY in almost all scenarios assessed. The company's economic case therefore rests on the more favourable ICERs for padeliporfin VTP versus the radical therapies. These ICERs in turn rely on an assumption of equal efficacy in terms of overall survival and metastatic disease progression between padeliporfin VTP and all the radical therapies. If these assumptions are accepted, the ICERs for padeliporfin versus the radical therapies remain sensitive to: the choice of parametric curve for modelling time to radical therapy following padeliporfin VTP treatment; the comparative prevalence of

the key adverse events (UI, ED and BD) following the alternative treatment modalities; and the health state utility and cost-impact of the adverse events (particularly bowel dysfunction).

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Padeliporfin for treating localised prostate cancer

ADDENDUM to the ERG report

Additional economic analyses comparing padeliporfin VTP against radical therapies

Produced by Aberdeen HTA Group

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Version 1

Following a request by NICE prior to the first appraisal committee meeting for this topic, this addendum provides further full incremental cost-effectiveness analyses comparing padeliporfin VTP against the radical therapies (radical prostatectomy, external beam radiotherapy (EBRT) and brachytherapy (BT)). The committee may find these results useful if they believe that active surveillance should be excluded as a comparator. The following analyses are presented in the tables below:

1. The company's original based case (Table 1), as an alternative to Table 25 in the original ERG report
2. The company revised base case (Table 2), as an alternative to Table 28 in the original ERG report.
3. The company's original base case but with time to metastasis adjusted for general population mortality (Table 3) – as an alternative to Table 39 in the ERG report.
4. The ERGs further exploratory analysis (Table 4); as an alternative to Table 41 in the ERG report.

To provide further information to the committee, the ERG have also added two combined scenarios in Table 4. These replicate the original combined scenarios 11 and 12, but also add in the adjustment of time to radical therapy for general population mortality. The ERG believe the adjusted curve may be more appropriate for partitioning the padeliporfin VTP cohort between the pre-radical therapy and post-radical therapy states. In addition, these additional scenarios (13 and 14 in Table 4) incorporate the fix to ensure that the sum of the proportions for the different types of radical therapy occurring in each cycle of the model (following progression from the pre-radical therapy state), is equal to the overall proportion of patients progressing to radical therapy in each cycle of the model.

Table 1 Company's original base case results: fully incremental analysis of VTP against radical therapies (excluding active surveillance)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER * (£/QALY)
EBRT	16,999	13.673	11.340	-	-	-	-
RP	18,752	13.673	11.185	1,754	0	-0.155	Dominated by EBRT
Brachytherapy	19,871	13.673	11.393	2,873	0	0.053	Extended dominated
VTP	26,714	13.673	11.643	9,715	0	0.303	32,082

Table 2 Company's revised base case results: fully incremental analysis of VTP against radical therapies (excluding active surveillance)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER * (£/QALY)
EBRT	17,522	13.673	12.113	-	-	-	-
RP	19,334	13.673	11.970	1,812	0	-0.143	Dominated by EBRT
Brachytherapy	20,554	13.673	12.162	3,033	0	0.049	Extended dominated
VTP	27,652	13.673	12.492	10,130	0	0.379	26,728

Table 3 Company's original model adjusted for general population all-cause mortality: fully incremental analysis of VTP against radical therapies (excluding active surveillance)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER * (£/QALY)
EBRT	17,522	13.673	11.089	-	-	-	-
RP	19,334	13.673	10.947	1,812	0	-0.143	Dominated by EBRT
Brachytherapy	20,554	13.673	11.139	3,033	0	0.049	61,372
VTP	27,621	13.673	11.083	7,067	0	-0.056	Dominated by Brachytherapy

Table 4 ERG scenario analysis: fully incremental analyses of VTP against radical therapies (excludes active surveillance)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER * (£/QALY)
Company revised base case							
EBRT	17,522	13.673	12.113	-	-	-	-
RP	19,334	13.673	11.970	1,812	0	-0.143	Dominated by EBRT
Brachytherapy	20,554	13.673	12.162	3,033	0	0.049	Extended dominated
VTP	27,652	13.673	12.492	10,130	0	0.379	26,728
Scenario 1 Recalculating the percentage of patients receiving RP, EBRT and BT following AS or VTP in each cycle of the model							
EBRT	17,522	13.673	12.113	-	-	-	-
RP	19,334	13.673	11.970	1,812	0	-0.143	Dominated by EBRT
Brachytherapy	20,554	13.673	12.162	3,033	0	0.049	Extended dominated
VTP	27,733	13.673	12.492	10,211	0	0.379	26,942
Scenario 2 Adjusting the TTRT curves on AS and padeliporfin VTP for general population mortality							
EBRT	17,522	13.673	12.113	-	-	-	-
RP	19,334	13.673	11.970	1,812	0	-0.143	Dominated by EBRT
Brachytherapy	20,554	13.673	12.162	3,033	0	0.049	Extended dominated
VTP	27,931	13.673	12.452	10,409	0	0.339	30,673
Scenario 3 Company's new model using bowel disutility value equal to -0.1 (Shimizu et. al.)							
EBRT	17,522	13.673	12.250	-	-	-	-
RP	19,334	13.673	12.065	1,812	0	-0.185	Dominated by EBRT
Brachytherapy	20,554	13.673	12.249	3,033	0	-0.001	Dominated by EBRT
VTP	27,652	13.673	12.530	10,130	0	0.280	36,195
Scenario 4 Removing costs of adjuvant EBRT and HR therapies in the company's new model							
EBRT	17,085	13.673	12.113	-	-	-	-
RP	18,242	13.673	11.970	1,156	0	-0.143	Dominated by EBRT
Brachytherapy	20,315	13.673	12.162	3,230	0	0.049	Extended dominated

VTP	27,248	13.673	12.492	10,162	0	0.379	26,813
Scenario 5 Setting bowel dysfunction prevalence of RP equal to AS in the company's new model (ProtecT trial)							
RP	14,373	13.673	12.223	-	-	-	-
EBRT	17,522	13.673	12.113	3,149	0	-0.110	Dominated by RP
Brachytherapy	20,554	13.673	12.162	6,181	0	-0.060	Dominated by RP
VTP	26,929	13.673	12.529	12,555	0	0.306	41,036
Scenario 6 Setting bowel dysfunction prevalence of RP equal to VTP in the company's new model							
RP	14,930	13.673	12.195	-	-	-	-
EBRT	17,522	13.673	12.113	2,592	0	-0.082	Dominated by RP
Brachytherapy	20,554	13.673	12.162	5,625	0	-0.032	Dominated by RP
VTP	27,012	13.673	12.525	12,083	0	0.330	36,612
Scenario 7 Setting the prevalence rates for UI, ED and BD, for RP and EBRT, based on the observed differences compared to AS in the ProtecT trial							
RP	12,996	13.673	12.479	-	-	-	-
EBRT	13,590	13.673	12.424	594	0	-0.056	Dominated by RP
Brachytherapy	20,554	13.673	12.162	7,559	0	-0.317	Dominated by RP
VTP	26,455	13.673	12.588	13,459	0	0.108	124,345
Scenario 8 Adding one-off cost of a pre-treatment multiparametric MRI scan to the cost of AS and VTP (includes total cost of mpMRI and additional cost of using fusion image registration)							
EBRT	17,522	13.673	12.113	-	-	-	-
RP	19,334	13.673	11.970	1,812	0	-0.143	Dominated by EBRT
Brachytherapy	20,554	13.673	12.162	3,033	0	0.049	Extended dominated
VTP	28,016	13.673	12.492	10,494	0	0.379	27,688
Scenario 9 Adding a weighted average cost of an inpatient excess bed day (£275.59) to the treatment cost of padeliporfin VTP in the company's new model							
EBRT	17,522	13.673	12.113	-	-	-	-
RP	19,334	13.673	11.970	1,812	0	-0.143	Dominated by EBRT
Brachytherapy	20,554	13.673	12.162	3,033	0	0.049	Extended dominated
VTP	27,944	13.673	12.492	10,423	0	0.379	27,500
Scenario 10 Applying the treatment cost of bowel dysfunction as a one-off long term cost							
EBRT	11,817	13.673	12.113	-	-	-	-

RP	15,391	13.673	11.970	3,574	0	-0.143	Dominated by EBRT
Brachytherapy	16,956	13.673	12.162	5,139	0	0.049	Extended dominated
VTP	26,115	13.673	12.492	14,299	0	0.379	37,727
Scenario 11 Applying scenarios 3,4,5,9 and 10 simultaneously and using a weighted average of HRG cost for RP and EBRT							
EBRT	12,428	13.673	12.250	-	-	-	-
RP	15,167	13.673	12.223	2,739	0	-0.027	Dominated by EBRT
Brachytherapy	16,717	13.673	12.249	4,288	0	-0.001	Dominated by EBRT
VTP	26,525	13.673	12.553	14,097	0	0.303	46,544
Scenario 12 Applying scenarios 3,4,6,9 and 10 simultaneously and using a weighted average of HRG cost for RP and EBRT							
EBRT	12,428	13.673	12.250	-	-	-	-
RP	15,277	13.673	12.205	2,848	0	-0.045	Dominated by EBRT
Brachytherapy	16,717	13.673	12.249	4,288	0	-0.001	Dominated by EBRT
VTP	26,542	13.673	12.550	14,114	0	0.300	47,016
Scenario 13 Applying scenarios 1,2,3,4,5,9 and 10 simultaneously and using a weighted average of HRG cost for RP and EBRT							
EBRT	12,428	13.673	12.250	-	-	-	-
RP	15,167	13.673	12.223	2,739	0	-0.027	Dominated by EBRT
Brachytherapy	16,717	13.673	12.249	4,288	0	-0.001	Dominated by EBRT
VTP	26,565	13.673	12.524	14,137	0	0.274	51,543
Scenario 14 Applying scenarios 1,2,3,4,6,9 and 10 simultaneously and using a weighted average of HRG cost for RP and EBRT							
EBRT	12,428	13.673	12.250	-	-	-	-
RP	15,277	13.673	12.205	2,848	0	-0.045	Dominated by EBRT
Brachytherapy	16,717	13.673	12.249	4,288	0	-0.001	Dominated by EBRT
VTP	26,586	13.673	12.521	14,158	0	0.271	52,235
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; AS, active surveillance; RP, radical prostatectomy; EBRT, external beam radiation therapy; VTP, vascular-targeted photodynamic therapy							

*ICER against the next less expensive non-dominated alternative