NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Abiraterone for treating newly diagnosed metastatic hormone-naive prostate cancer [ID945]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Abiraterone for treating newly diagnosed metastatic hormone-naive prostate cancer [ID945]

Contents:

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

Pre-meeting briefing

Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer

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

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Prostate cancer disease background

- >46,700 people diagnosed with prostate cancer in UK (2014)
- ~18% new diagnoses present with metastases
- Newly diagnosed patients have poorer prognosis than primary progressive metastatic prostate cancer (people who present with localised disease but develop metastases later)
  - 30% 5-year survival
- ≥50% of patients experience pain, fatigue and drowsiness. Bone pain often the most distressing & dominant
- ≤75% of patients develop bone disease that can result in skeletal-related events (SREs) including spinal cord compression and pathological fracture (associated with loss of mobility/further impaired quality of life/significant healthcare costs)
- Urological complications often lead to abdominal pain, urinary retention and dysuria

Prostate cancer disease background

- Prostate cancer is an androgen dependent disease. Inhibition of testosterone (androgen deprivation therapy, ADT) is the key initial treatment strategy
- ADT consists of a luteinising hormone-releasing hormone (LHRH) agonist. Surgical castration (orchidectomy) and bicalutamide monotherapy are less commonly used options
- Most people respond to ADT → but vast majority develop progressive disease within 1 to 2 years
- Note on terminology:
  - Hormone sensitive metastatic prostate cancer (mHSPC): people with metastatic disease who have not yet received hormone therapy, or have received ADT but have not become resistant to it
  - Hormone naïve metastatic prostate cancer (mHNPC): people with metastatic disease who have not yet received hormone therapy
  - Castrate resistant metastatic prostate cancer (mCRPC, sometimes also referred to as hormone refractory prostate cancer (mHRPC): metastatic prostate cancer which has progressed and is resistant to ADT

Patient experience

Experience of current treatments

- although life expectancy with prostate cancer has improved, all treatments can decrease quality of life
- Problems with current treatments include fatigue, “chemo fog” (an inability to concentrate for long periods of time) and loss of libido
- Stressful for patients (+ carers) to know their treatment will eventually fail. Patients may worry about what may be the next treatment may be, its side effects and whether they can cope with it.

Patient experience/ thoughts on having option of abiraterone + androgen deprivation therapy (ADT)

- No curative treatments so all new life-extending treatment options welcomed.
- Particular unmet need for life-extending treatments for people who cannot have docetaxel +ADT, either because they are not fit enough to tolerate it, or docetaxel is contraindicated
- Patient on abiraterone reported: After almost 4 years of treatment I have very few problems. I am very active….. [and] busy around the house and garden. I don’t have, or need a carer.
- There is the worry that if all of the advanced treatments are given at the beginning of treatment there will be nothing left in reserve, but the benefits outweigh the disadvantages of this

Abiraterone (Zytiga, Janssen)

Mechanism	Selective androgen synthesis inhibitor that works by blocking cytochrome P450 17 alpha-hydroxylase. It blocks androgen production in the testes and adrenal glands, and in prostatic tumour tissue
Marketing authorisation	Indicated with prednisone or prednisolone for the treatment of newly diagnosed **high risk** metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) - *November 2017†*
Administration and dose	Oral single daily dose of 1,000 mg (2 x 500 mg tablets) Taken with prednisone or prednisolone 5 mg daily* Medical castration with luteinising hormone releasing hormone (LHRH) should be continued during treatment in patients not surgically castrated
Safety	Caution is required in treating patients whose condition may be compromised by increases in blood pressure, hypokalaemia or fluid retention

Abiraterone: licensed indications

Indication under appraisal (MA gained Nov 2017)

- the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT).
- In trials, high risk prognosis defined as having ≥2 of the following 3 risk factors:
  - (1) Gleason score of ≥8; (range 6 to 10. Cells taken from a biopsy are assessed for how quickly they are likely to grow)
  - (2) presence of 3 or more lesions on bone scan;
  - (3) presence of measurable visceral (excluding lymph node disease) metastasis

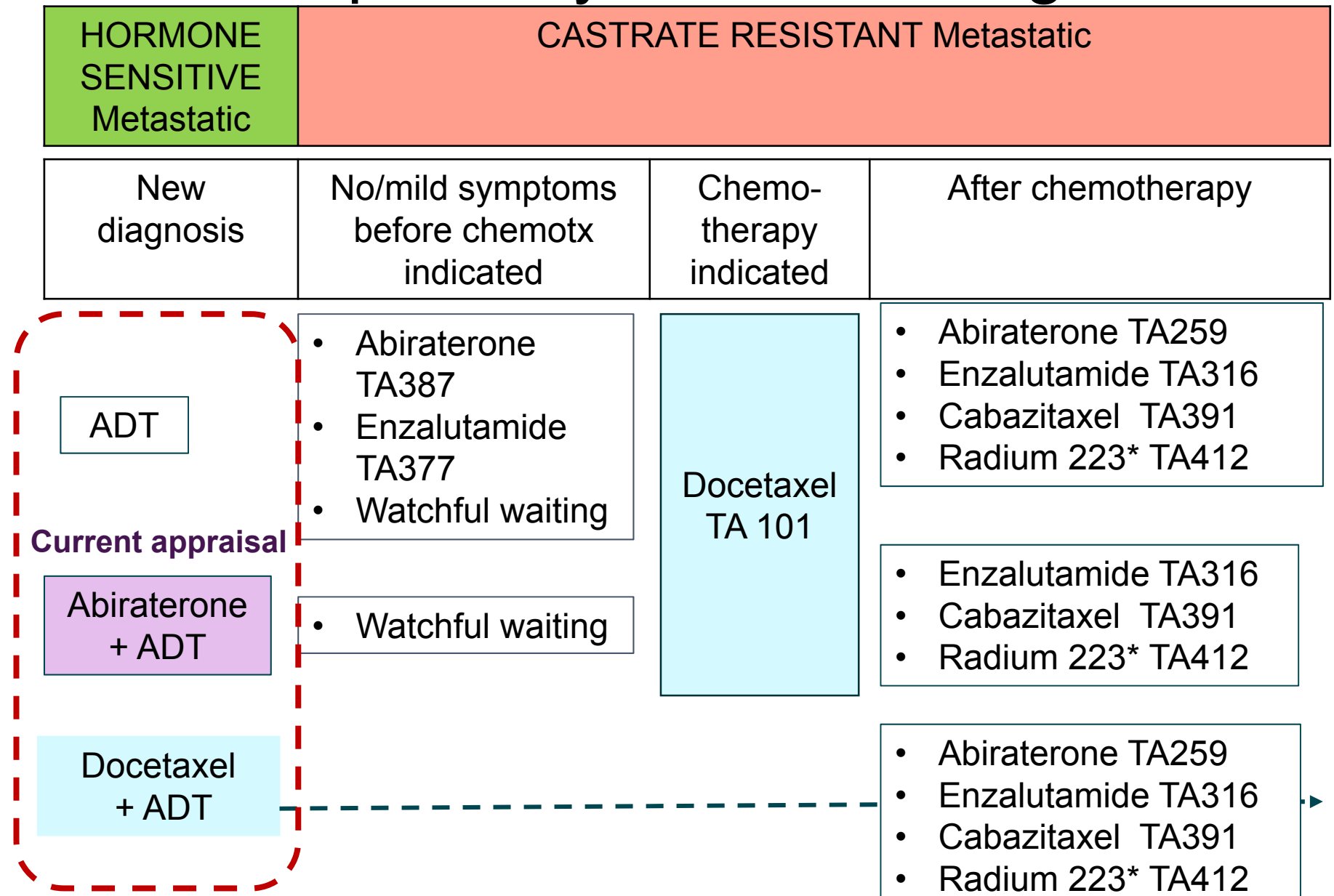
Indication appraised in TA387

- the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated

Indication appraised in TA259

- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

Treatment pathway NICE/NHSE guidance



ADT, androgen deprivation therapy; TA, technology appraisal; Chemotx, chemotherapy

Use of off-license docetaxel with ADT for hormone naïve prostate cancer

Marketing authorisation	Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with **hormone refractory metastatic prostate cancer** (when used for this indication people have up to 10 cycles of docetaxel)
NHS England (off-label use in combination with ADT)	
Clinical commissioning policy statement (2016)	NHS England will commission (**up to 6 cycles**) docetaxel for the treatment of **hormone naive metastatic prostate cancer**) if: • have newly diagnosed metastatic, prostate cancer; • are either commencing, or who have commenced within 12 weeks, long-term hormone therapy (Androgen Deprivation Therapy) for metastatic disease for the first time; and • have sufficient performance status to be treated with 6 cycles of docetaxel chemotherapy (dose same as label, prednisolone for first 3 weeks)

ADT, Androgen Deprivation therapy

Decision problem

ERG agrees with company's comparators

	Final scope issued by NICE	Decision problem addressed by company	Rationale if different from final NICE scope
Population	Adults with newly diagnosed high risk metastatic **hormone-naïve** prostate cancer (mHNPC)	Adults with newly diagnosed, high-risk, **hormone-sensitive** (mHSPC)	mHNPC = mHSPC because if a patients are newly diagnosed, they are hormone naïve
Intervention	AAP + ADT	AAP + ADT	
Comparators	1. ADT alone (including orchidectomy, luteinising hormone-releasing hormone [LHRH] agonist therapy or monotherapy with bicalutamide) 2. Docetaxel + ADT	1. ADT alone (including LHRH agonist therapy) 2. Docetaxel + ADT	Orchidectomy & bicalutamide monotherapy not included as types of ADT → Company's experts suggest they are rarely used in UK

Clinical trial evidence: overview

Abiraterone + prednisolone + ADT vs. ADT

- **Direct** comparison (newly diagnosed, high-risk mHSPC) with ADT
  - LATTITUDE: AAP (abiraterone + prednisolone) + ADT vs. ADT
  - STAMPEDE* (UK MRC trial, but included wider population than indicated for abiraterone + ADT because included people with localised disease)

Abiraterone + prednisolone + ADT vs. Docetaxel + ADT

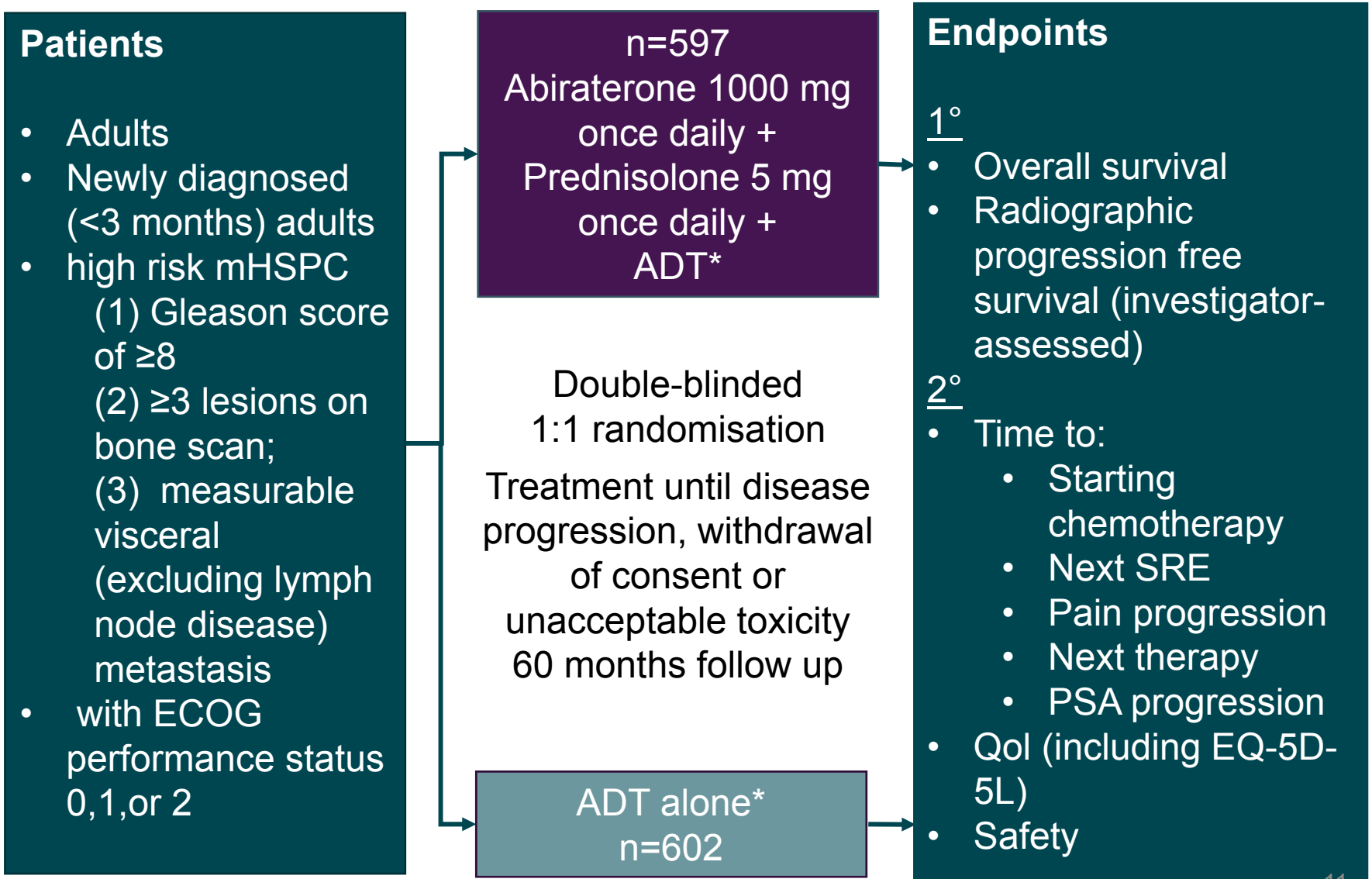
- **Direct** comparison
  - STAMPEDE
- **Indirect** comparison for comparison with Docetaxel + ADT
  - LATTITUDE: AAP + ADT vs. ADT
  - GETUG-AFU15 (Docetaxel + ADT vs ADT),
  - CHAARTED (Docetaxel + ADT vs. ADT)

Supporting direct randomised comparison data from STAMPEDE*

- AAP + ADT vs. ADT
- STAMPEDE metastatic disease subgroup
- Sensitivity analyses around indirect comparison)

LATITUDE: overview

abiraterone + ADT vs. ADT



*LHRH or bilateral orchidectomy

LATITUDE: statistical analysis plan

- Pre-randomisation stratification by presence/absence visceral disease and performance status (0,1 or 2)
- Intention to treat (ITT) used for all analyses (excluding 10 patients removed from ITT population because of Good Clinical Practice non-compliance at 1 study site)
- Safety population: all randomised patients who received study drug, except those from non-compliant site
- Statistical significance for co-primary endpoint 0.05: OS (0.049) and rPFS (0.001)
- Planned statistical analyses:

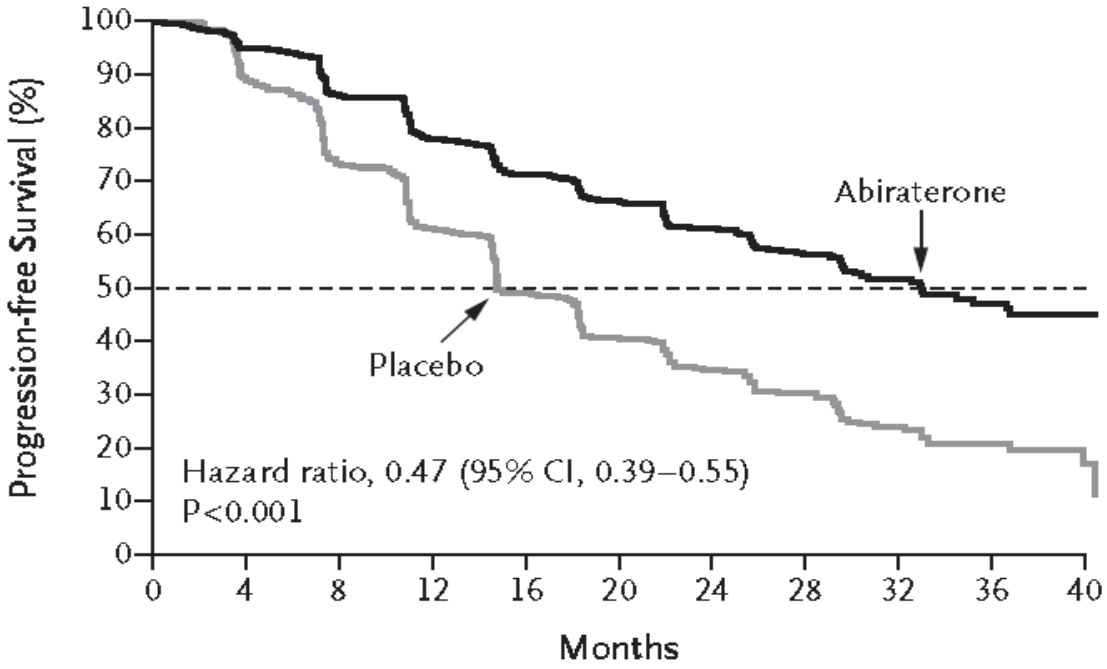
Interim analysis	Number (%) of required events (deaths) for statistical power	Date met	In company model
Interim 1	426 (50%)	31st Oct 2016 (30.4 months follow up)	Yes
Study ended early; unblinded + crossover permitted 12th Jan 2017			
Interim 2	554 (65%)	2nd Oct 2017 (41.4 months follow up)	No
Final	852 (100%)	Not met	No

Baseline Characteristics

	AAP + ADT (N=597)	ADT Alone (N=602)
Age, median years (range)	68 (38–89)	67 (33–92)
ECOG Performance status, n (%)	0: 326 (54.6) 1: 245 (41.0) 2: 26 (4.4)	0: 331 (55.0) 1: 255 (42.4) 2: 16 (2.7)
Gleason score at initial diagnosis, n (%)	<7: 4 (0.7) 7: 9 (2) ≥8: 584 (98)	<7: 1 (0.2) 7: 15 (2) ≥8: 586 (97)
≥3 bone metastases at screening, n (%)	586 (98.2)	585 (97.2)
High-risk at screening, n (%)	597 (100)	601 (100)
Extent of disease, n (%)	596 (100)	600 (100)
Bone	580 (97)	585 (98)
Liver	32 (5)	30 (5)
Lungs	73 (12)	72 (12)
Node	283 (47)	287 (48)
Prostate mass	151 (25)	154 (26)
Viscera	18 (3)	13 (2)
Soft Tissue	9 (2)	15 (3)
Other	2 (0.3)	0

LATITUDE: investigator-assessed radiographic progression free survival (rPFS)

- AAP + ADT delayed disease progression compared with ADT alone
- Median rPFS 33.0 months with AAP + ADT and 14.8 months with ADT
- Hazard ratio, 0.47 (95% CI 0.39 to 0.55)



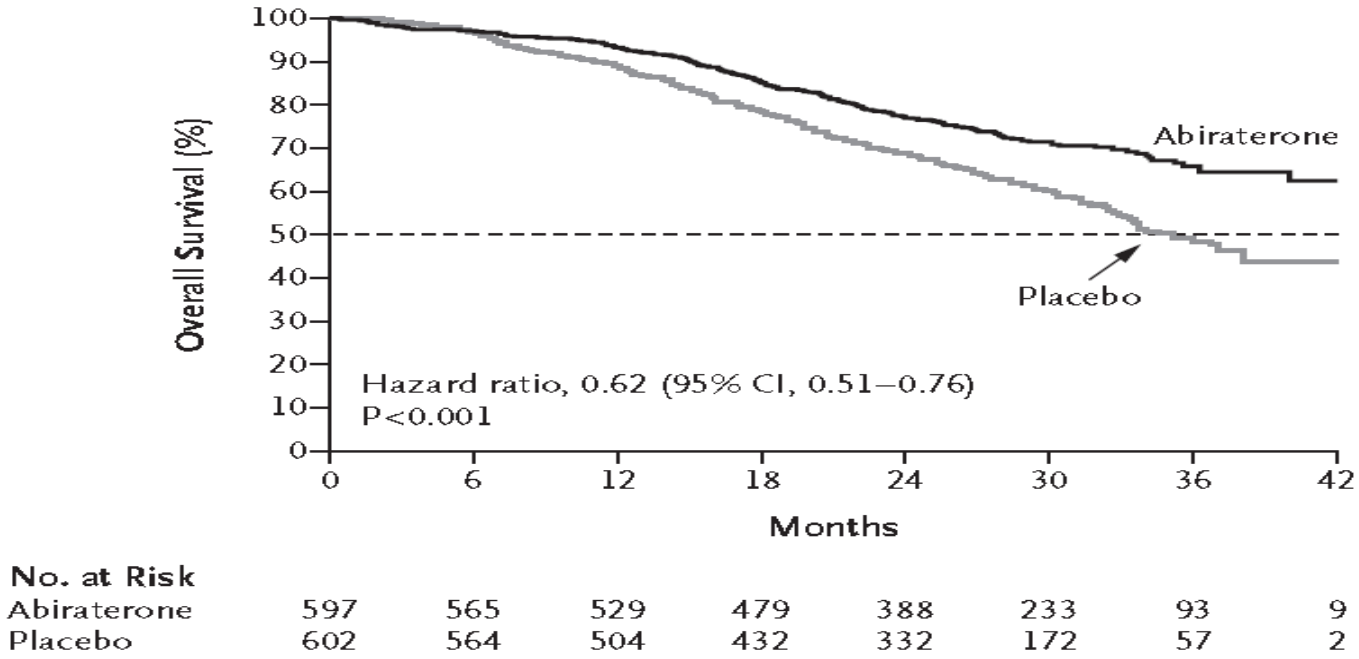
No. at Risk											
Abiraterone	597	533	464	400	353	316	251	177	102	51	21
Placebo	602	488	367	289	214	168	127	81	41	17	7

Reference: Fizazi et al. 2017 NEJM 377:352-360

LATITUDE: Overall survival

- At interim analysis 1 (30.4 months follow up)

	ADT	AAP + ADT
Deaths n (%)	237 (39%)	169 (28%)
Median survival months (95% CI)	34.7 (33.0, not reached)	Not reached
Hazard ratio	0.62, 95% CI 0.51 to 0.76 p<0.001	



Reference: Fizazi et al. 2017 NEJM 377:352-360

LATITUDE: adjustment for subsequent treatments

- More people on ADT (40.9%) had subsequent treatments than AAP + ADT (20.9%)
- Company used the Inverse Probability Censoring Weighted (IPCW) analyses to adjust for subsequent treatment
  - adjusted hazard ratio for overall survival 0.48 (95% CI 0.36 to 0.63)
- Company "Due to small sample sizes across sequences of interest, limited follow-up and an imbalance in patient characteristics across switchers versus non-switchers in the current dataset, these analyses are **not robust enough to present or take forward to subsequent modelling at this time**, but were all in favour of AAP + ADT"

	AAP + ADT (n=597)	ADT alone (n=602)
Patients with life-extending subsequent therapy, n (%):	125 (20.9)	246 (40.9)
Docetaxel	106 (17.8)	187 (31.1)
Enzalutamide	30 (5.0)	76 (12.6)
Cabazitaxel	11 (1.8)	30 (5.0)
Radium-233	11 (1.8)	27 (4.5)
AAP	10 (1.7)	53 (8.8)

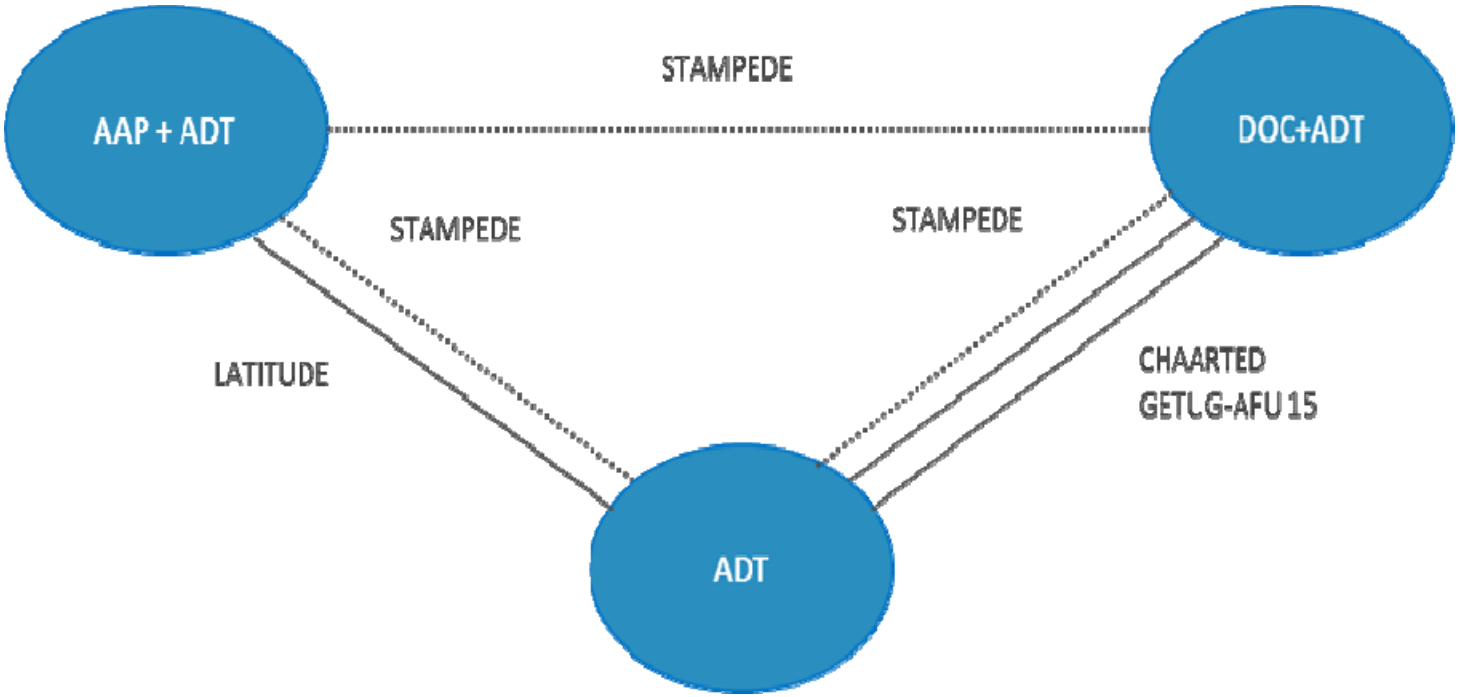
Second interim analysis
unadjusted for crossover

*** of patients had crossed over from ADT to AAP +ADT (median time on AAP + ADT after ADT was *** months). The presented results are unadjusted for crossover.

	Interim analysis 1		Interim analysis 2	
	ADT	AAP + ADT	ADT	AAP + ADT
Median follow up (months)		30.4		41.36
Number of deaths	237 (39%)	169 (28%)	***	***
Median overall survival, months (95% CI)	34.7 (33.0 to NR)	NR	*** ***	*** ***
Hazard ratio (95% CI)	0.62, 95% CI 0.51 to 0.76 p<0.001			*** ***

NR, not reached

Trials included in the network meta-analysis



ERG agree that STAMPEDE does not provide sufficiently comparable data for the considered patient population to be included in the indirect treatment comparison

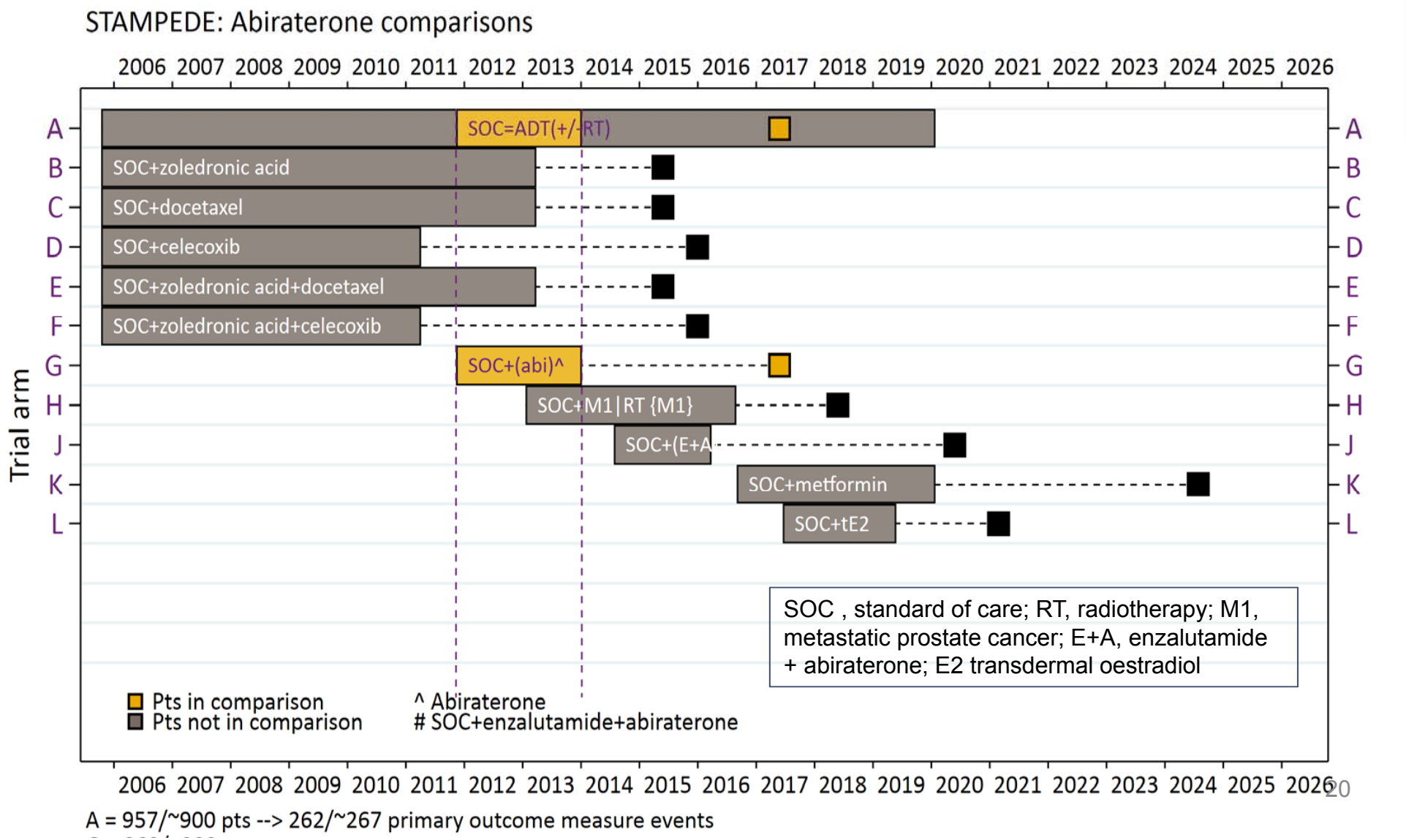
However, STAMPEDE investigators have performed a direct randomised comparison of abiraterone (+ prednisone + ADT) to docetaxel (+ ADT)

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; DOC, docetaxel.
Notes: [a], Continuous lines in this network represent the trials contributing to the primary analyses and is meant to depict the greatest number of trials that can be included in the analyses. One trial (STAMPEDE) was not considered in the base case ITC due to differences in patient population. Dotted lines represent the trials contributing to the sensitivity analyses.

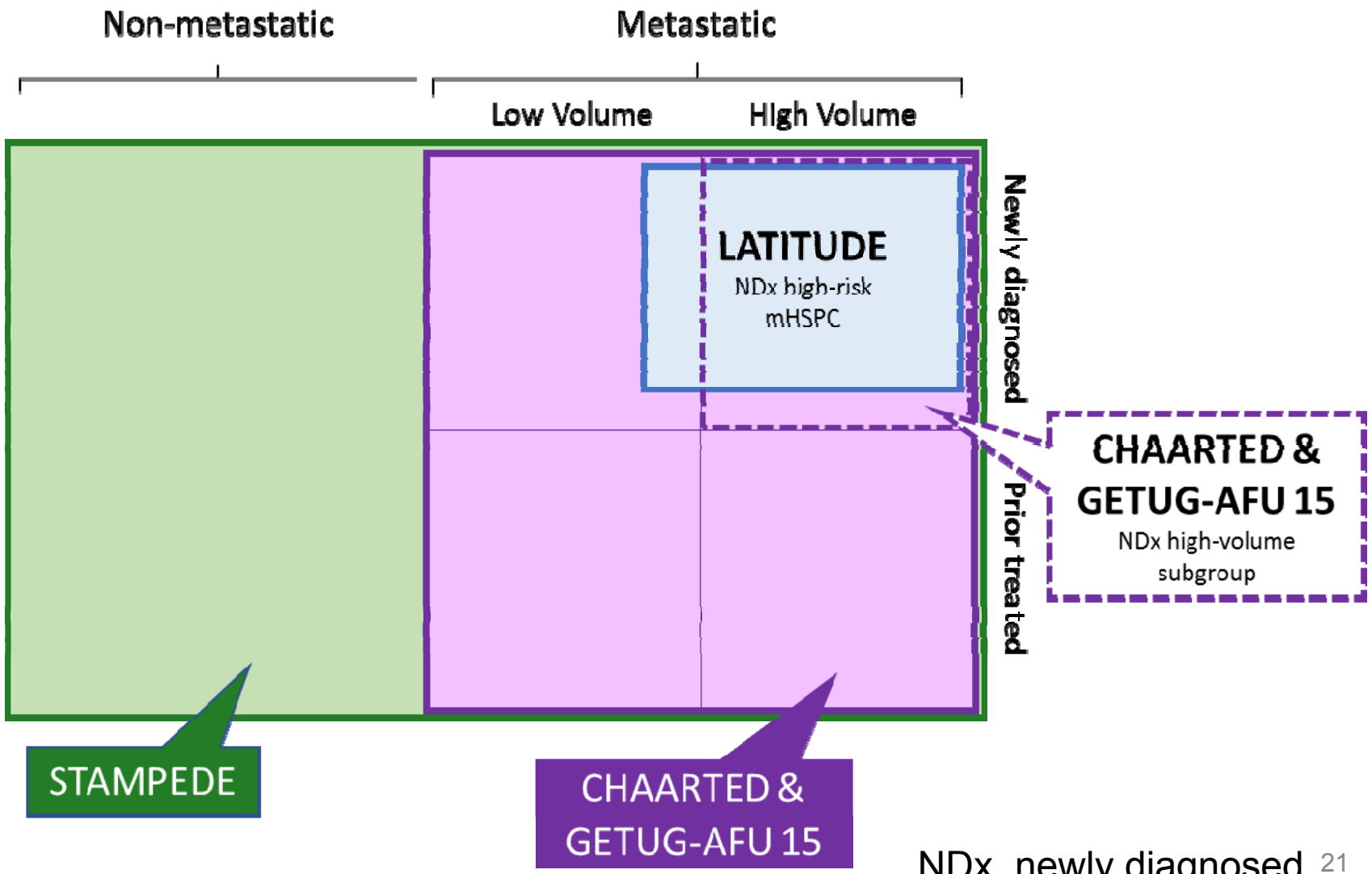
Description of trials included in the network meta-analysis (NMA)

	Population	Subgroup in NMA base case	Intervention	Comparator
LATTITUDE Median follow up 30.4 months	• mHSPC • Newly diagnosed • High risk	ITT (whole population)	Abiraterone (AAP) + ADT	ADT
CHAARTED Median follow up 53.7 months	• mHSPC • Newly diagnosed or primary progressive	Newly diagnosed and high-volume	Docetaxel + ADT	
GETUG-AFU 15 Median follow up 83.9 months				
STAMPEDE *(included in sensitivity analysis)* Median follow up: 43 months (metastatic subgroup)	Localised, locally advanced or mHSPC	Metastatic subgroup (in sensitivity analysis) STAMPEDE did not report results for any high risk/volume subgroup	• Docetaxel + ADT • AAP + ADT • (other study arms not relevant to decision problem- see notes)	

STAMPEDE: comparison of abiraterone + ADT with ADT

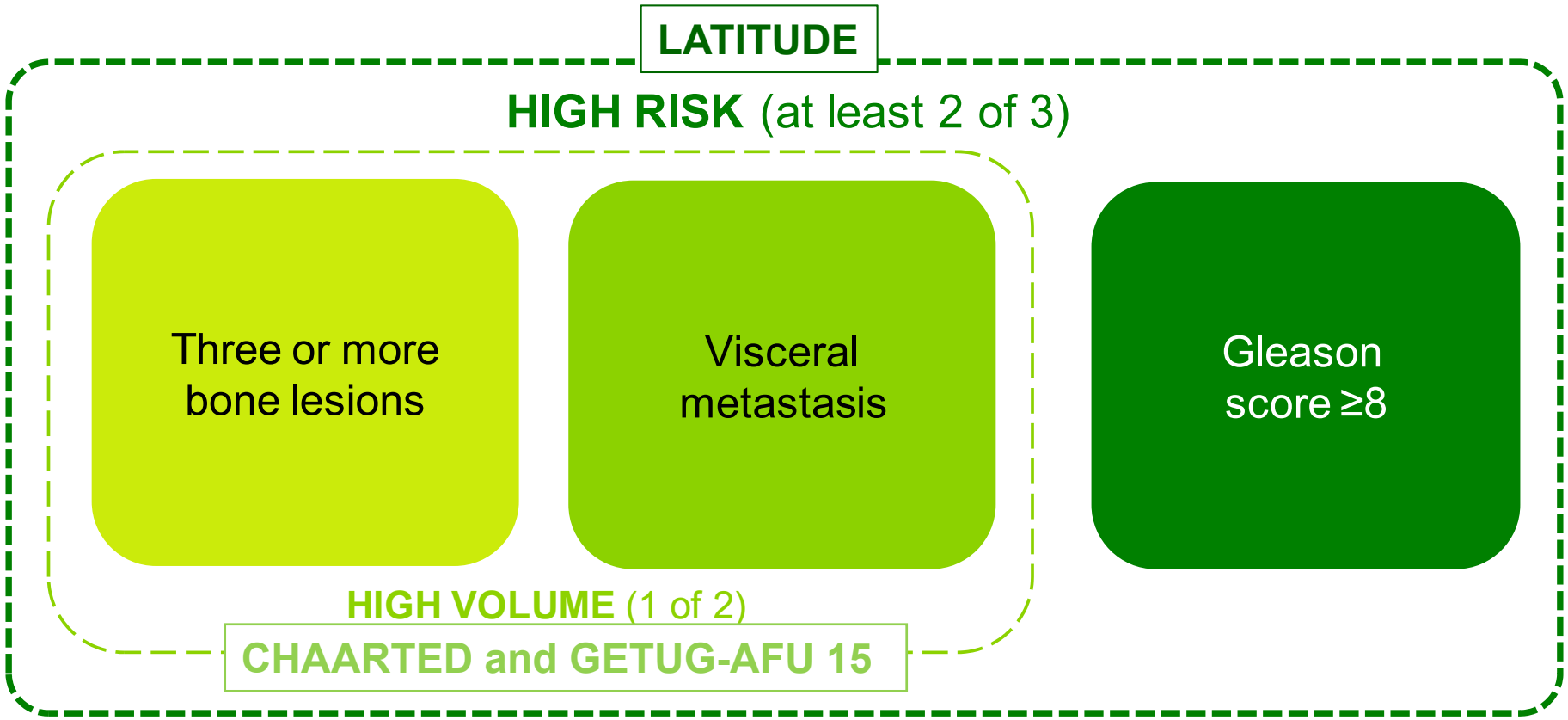


Summary: differences in populations included in clinical trials in the NMA



NDx, newly diagnosed

Definition of high risk (and high volume disease



Further differences between trials included in network meta-analysis

	Issue	Company: potential impact
Treatment and dosing*	Variability in definition of ADT and dose scheduling of docetaxel	Minimal
Subsequent therapies	Differences in proportion of people having subsequent treatments • LATITUDE (AAP + ADT: 32%; ADT 53.5%) • GETUG-AFU 15 not reported • CHAARTED (Doc + ADT 59.9%; ADT 73%) • STAMPEDE: AAP + ADT 79%; ADT 89%	Could bias NMA results, but not possible to adjust as insufficient data on subgroups of interest
Trial outcomes	No single measure of disease progression • LATITUDE: rPFS based on RECIST 1.1 and PCWG2 • GETUG-AFU 15 based on rPFS RECIST 1.0 and PCWG2 • (STAMPEDE, CHAARTED no rPFS outcomes)	Only overall survival endpoint iscomparable across 4 trials

ADT, Androgen deprivation therapy; AAP abiraterone + prednisolone; Doc, docetaxel; RECIST, Response Evaluation Criteria in Solid Tumours; PCWG2, Prostate Cancer Working Group 2; rPFS, radiographic Progression Free Survival

Baseline characteristics across trials

red boxes show notable differences to LATITUDE

	LATITUDE	GETUG-AFU 15	CHAARTED	STAMPEDE
Number of patients with mHSPC	1,198	385	790	1,817[a]
Patients with newly diagnosed mHSPC	100%	71%	75%	100%
Patients with high-volume disease[b]	79.7% (955/1,198)	52% (202/385)[c]	65% (514/790)	Not Reported
Median age, years (range)	67 (33–92)	64 (57–70)	64 (36–91)	65 (42–84)
Gleason score of 8–10, %	98%	56%	61%	70%
Performance status of 0–1, %	97.5%[56]	Not Reported	98%	99%
Median PSA level before ADT	• AAP + ADT: 25.4 • ADT: 23.1	• Doc + ADT: 26.7 • ADT: 25.8	• Doc + ADT: 50.9 • 52.1	AAP + ADT: 51 ADT: 56

[a] metastatic subgroup; [b], High-volume disease defined as visceral metastases and/or ≥4 bone metastases with at least one metastasis beyond the pelvis or vertebral column; [c], High-volume disease was retrospectively defined in the GETUG-AFU 15 trial following the CHAARTED definition (visceral metastases and/or ≥4 bone metastases with at least one metastasis beyond the pelvis or vertebral column)

Network meta-analysis: results

Similar overall survival and progression free survival with AAP + ADT vs. docetaxel + ADT

Outcome for Base Case	AAP + ADT vs. ADT	ADT vs. docetaxel + ADT		AAP + ADT vs. docetaxel + ADT	
	LATITUDE	CHAARTED	GETUG-AFU 15	ITC	
	ITT	**NDx HV**	**NDx HV**	**HR (95% CrI)**	**P_{AA-Doc}**
OS	0.62	0.63	0.78	0.92	71.8%
HR (95% CI)	(0.51, 0.76)	(0.49, 0.81)	(0.54, 1.12)	(0.69, 1.23)	
rPFS[a]	0.47	-	HV^+: 0.61	0.76	92.9%
HR (95% CI)	(0.39, 0.55)		(0.44, 0.83)	(0.53, 1.10)	
Sensitivity analysis: same data from LATITUDE, CHAARTED and GETUG-AFU 15 and data from metastatic subgroup of STAMPEDE shown in rows below					
Overall survival	Included data from STAMPEDE for AAP + ADT vs. ADT; ADT vs. docetaxel + ADT; AAP + ADT vs. docetaxel + ADT			*** ***	***
PFS	Included data from STAMPEDE for AAP + ADT vs. ADT; ADT vs. docetaxel + ADT (+ HV subgroup from LATITUDE)			***	***

AAP, abiraterone; ADT, androgen deprivation therapy; ITT, intention to treat; NDx new diagnosis; HV, high volume; HR, hazard ratio; CI, confidence interval; CrI, credible interval; **P_{AA-Doc} ,** Bayesian pairwise probability of abiraterone + ADT being more effective than docetaxel + ADT

PFS: estimates from LATITUDE and metastatic subgroup from STAMPEDE

Study	LATITUDE [ITT]		STAMPEDE Metastatic subgroup		STAMPEDE Metastatic subgroup	
Treatment	AAP + ADT	ADT	AAP + ADT	ADT	AAP + ADT	Docetaxel + ADT
Metastatic (n)	597	602	500	502	227	115
Median follow-up	30.4 months		40 months		48 months	
	Radiographic PFS		**PFS [b]**			
Events (%)	239 (40.0)	354 (58.8)	173 (34.6)	301 (60.0)	94 (41.4)	62 (53.9)
Median [95% CI]	33 [29.57-NE]	14.8 [14.69-18.27]	-	-	-	-
HR	0.47 [0.39-0.55]		0.43 [0.36-0.52]		0.69 [0.50-0.95]	
p-value	<0.0001		-		0.02	
			Failure-free survival			
HR [95% CI]			0.31 [0.26 -0.37]		0.56 [0.42 -0.75	
p-value			<0.001			

Definitions of progression outcomes in STAMPEDE. Failure free survival: radiologic, clinical, PSA progression or death from prostate cancer. PFS[b] defined as radiologic or clinical progression or death from prostate cancer

Overall survival results from LATITUDE compared with STAMPEDE

For abiraterone vs. docetaxel, STAMPEDE directly randomised results differ from company's indirect comparison

Study	LATITUDE [ITT]		STAMPEDE Metastatic subgroup		STAMPEDE Metastatic subgroup	
Treatment	AAP + ADT	ADT	AAP + ADT	ADT	AAP + ADT	Docetaxel + ADT
Median follow-up	30.4 months		40 months		48 months	
Overall Survival						
Events (%)	169 (28.3)	237 (39.4)	150 (30.0)	218 (43.4)	89 (39.2)	38 (33.0)
Median	NE	34.7	-	-	-	-
[95% CI]	NR-NR	33.05-NR	-	-	-	-
HR	0.62		0.61		1.13	
[95% CI]	0.51-0.76		0.49-0.75		0.77-1.66	
p-value	<0.0001		0.195×10^{-7}		0.53	

NE, not estimated; NR, not reported; - not presented in company submission

LATITUDE: Adverse events

	LATITUDE	
	AAP + ADT (n=597)	ADT alone (n=602)
Any TEAE, n (%)	558 (93.5)	557 (92.5)
Drug-related	336 (56.3)	269 (44.7)
Any serious TEAE, n (%)	165 (27.6)	146 (24.3)
Drug-related	29 (4.9)	12 (2.0)
Grade 3–4 TEAE, n (%)	374 (62.6)	287 (47.7)
Drug-related	162 (27.1)	67 (11.1)
Discontinuation due to TEAE, n (%)	73 (12.0)	61 (10.1)
Drug-related	21 (3.5)	11 (1.8)
Death due to TEAE, n (%)	28 (4.7)	24 (4.0)
Drug-related	3 (0.5)	3 (0.5)

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; TEAE, treatment-emergent adverse event.
Source: Fizazi et al. 2017[7]; European Public Assessment Report.[57]

EPAR, “the safety profile of AAP is well characterised. In this new setting, no new unexpected events have been reported.” In addition, whilst it “cannot be excluded that a lower dose of prednisone did not impact the incidence of hypertension in (LATITUDE), AEs (including hypertension) were generally manageable and the benefits outweigh the risks for the claimed indication.”

LATITUDE: types of adverse event

	AAP + ADT	ADT
Most frequently reported TEAE (≥ 20% of patients in either arm)		
Hypertension	37%	22%
hypokalaemia	20%	4%
Back pain	18%	20%
Commonly reported serious adverse events (≥ 1% of patients in either arm)		
pneumonia	1.8%	0.3%
Spinal cord compression	1.7%	1.8%
Urinary retention	1.5%	1.7%
Most commonly reported AEs leading to treatment discontinuation (≥ 1% in either arm		
Spinal cord compression	0.8%	1.0%
Bone pain		

- Dose reductions reported for *** of patients treated with AAP + ADT and *** of patients treated with ADT alone
- Dose interruptions reported for *** and *** of patients, respectively.
- Discontinuations for hypokalaemia, hypertension and cardiac disorders rare.

STAMPEDE: adverse events grade 3-5

abiraterone + ADT and docetaxel + ADT arms

	AAP + ADT vs. docetaxel + ADT	
	AAP + ADT (n=373)	ADT + Doc (n=172)
AE, n (%)		
Endocrine disorders	49 (13)	15 (9)
Febrile neutropenia	3 (1)	29 (17)
Neutropenia	4 (1)	22 (13)
Cardiovascular disorders	32 (9)	6 (3)
Hypertension	-	-
MI	-	-
Cardiac dysrhythmia	-	-
Musculoskeletal disorders	33 (9)	9 (5)
Gastrointestinal disorders	28 (8)	9 (5)
Hepatic disorders	32 (9)	1 (1)
Increased ALT levels	-	-
Increased AST levels	-	-
General disorders	21 (6)	18 (10)
Fatigue	-	-
Oedema	-	-
Respiratory disorders	11 (3)	12 (7)
Dyspnoea	-	-
Laboratory abnormalities	11 (3)	9 (5)
Hypokalaemia	-	-

Network meta-analysis safety results

- Only LATITUDE and GETUG-AFU 15 could be included in an indirect treatment comparison of the safety of AAP + ADT vs. docetaxel + ADT

Safety outcome	Odds ratio	Statistical significance
AST	***	***
ALT	***	
Any grade anaemia	***	***
Constipation	***	
Fatigue	***	
Peripheral oedema	***	
Hot flushes	***	***

LATTITUDE: Quality of life summary

Quality of life measure	Results
EQ-5D-5L visual analogue scale and utility score	Sustained improvements with AAP + ADT vs ADT until disease progression
Functional Assessment of Cancer Therapy-Prostate (FACT-P)	Time to FACT-P score worsening: • AAP + ADT: 12.9 months (95% CI 9.0, 16.6) • ADT: 8.3 (95% CI 7.4, 11.1) **HR (time to worsening QoL)** **0.85 (95% CI 0.74, 0.99)**
Brief Fatigue Inventory (BFI)	AAP + ADT → 35% reduction in the time to BFI worse fatigue intensity compared with ADT (HR= 0.65 [95% CI: 0.53 to 0.81])
Median time to pain progression measured by Brief Pain Inventory short form	• AAP + ADT: not reached • ADT: 16.6 months **HR (pain progression)** **0.70 [95% CI: 0.583-0.829]**

Network meta-analysis, quality of life results: FACT-P

Base case	LATITUDE ITT AAP + ADT vs. ADT	CHAARTED HVD Docetaxel + ADT vs. ADT	ITC results AAP + ADT vs. Docetaxel + ADT	Bayesian probability that AAP is better than Docataxel
FACT-P, differences in mean change from baseline (95% CI for trial results; CrI for ITC results)				
3 months	*** ***	*** ***	4.20 (1.18–7.19)	99.7%
6 months	*** ***	*** ***	2.49 (-0.56–5.51)	94.5%
9 months	*** ***	*** ***	3.07 (-0.13–6.24)	97.0%
12 months	*** ***	*** ***	2.35 (-0.88–5.54)	92.3%

CI, confidence interval; CrI, credible interval; ITC, indirect treatment comparison

Network meta-analysis, quality of life results: Brief Pain Inventory

Base case	LATITUDE ITT	CHAARTED HVD	ITC results	Bayesian probability that AAP is better than Docataxel
	AAP + ADT vs. ADT	Docetaxel + ADT vs. ADT	AAP + ADT vs. Docetaxel + ADT	
BPI, differences in mean change from baseline (95% CI for trial results; 95 CrI for ITC results)				
3 months	*** ——— ***	*** ——— ***	-0.15 (-0.40 to 0.10)	88.0%
6 months	*** ——— ***	*** ——— ***	-0.76 (-1.03 to 0.50)	100.0%
9 months	*** ——— ***	*** ——— ***	-0.85 (-1.13 to 0.58)	100.0%
12 months	*** ——— ***	*** ——— ***	-0.45 (-0.72 to 60.18)	99.9%

CI, confidence interval; CrI, credible interval; ITC, indirect treatment comparison

ERG comments on NMA

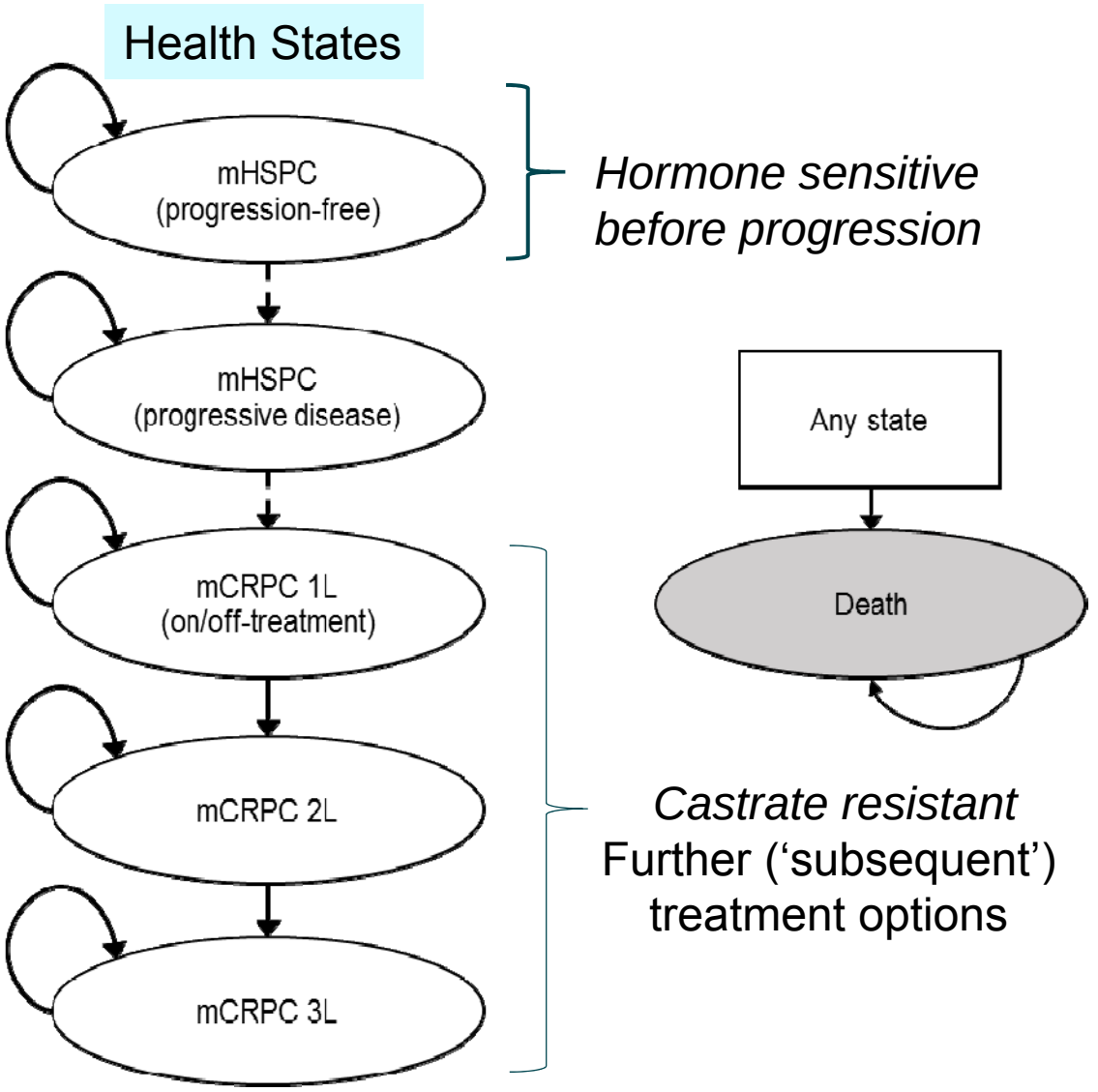
- Bayesian network meta-analysis a reasonable approach
- Preferred random effects model to company's fixed effect model
  - Using random effects model for OS resulted in a lower HR but wider credible intervals. **HR 0.894, 95% CrI 0.258 to 2.979**
  - Not possible to use random effects for PFS (only 2 studies with PFS)
- In comparison including docetaxel +ADT trials :
  - Heterogeneity between studies: patient characteristics (newly diagnosed, and/or primary progressive; high volume/high risk); variable ADT and docetaxel doses between studies; varying previous and subsequent treatments; reporting variations; different definitions of progression free survival; length of studies
  - ERG have "huge reservations for taking [indirect comparison of AAP + ADT vs. docetaxel + ADT] forward to economic modelling …"
  - ERG confirm that abiraterone at least equivalent to docetaxel → but estimates might not be robust

Key Issues: clinical

- Are there people who can take:
  - ADT, but not abiraterone + ADT? Who are they?
  - abiraterone + ADT but not docetaxel + ADT ? Who are they?
- For abiraterone + ADT vs. ADT, are estimates for overall survival from LATITUDE robust? If not, is this accounted for in part by:
  - Differences in follow-on treatments in LATITUDE vs. NHS?
  - Differences in when treatment stops in LATITUDE vs. NHS?
- For abiraterone +ADT vs. docetaxel + ADT, which estimate of clinical effectiveness is most robust?
  - Direct, randomised, evidence from STAMPEDE for broader population?
  - Indirect non-randomised, unadjusted evidence from network meta analysis?
- How is quality of life on and after:
  - Abiraterone + ADT? /Docetaxel + ADT?
- Is there any further data from STAMPEDE that would support the company submission?

Cost effectiveness model

- First 5 months: Company used Kaplan Meier data from LATITUDE.
- 5 months + Multi-state Markov model, cycle length 1 week for first year, every 28 days thereafter
- Modelled cohort based on LATITUDE mean age 67 years
- Time horizon 20 years
- Company: used this approach rather than a partitioned survival semi Markov model (used in TA259, 391, 316, 377) “to allow flexibility to explore assumptions around subsequent therapy and post progression survival”



1L = 1st line; 2L = 2nd line; 3L = 3rd line

Overview: transitions between health states

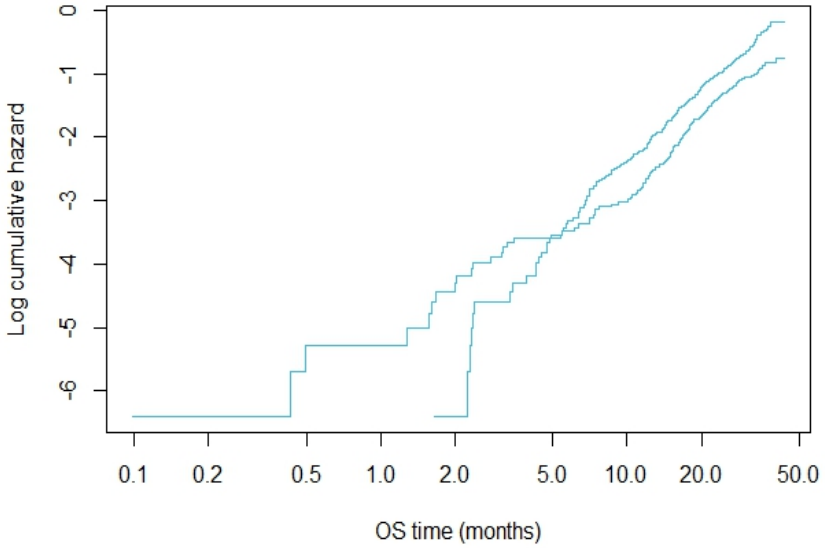
Transition probabilities

Transition from	Transition to	Source
mHSensitive PC pre-progressed disease	mHSensitive PC progressed disease	rPFS from LATITUDE
mHSensitive PC progressed disease	mCastrate Resistant PC 1st treatment	mean-treatment free interval from LATITUDE (extrapolated with an exponential distribution)
From one subsequent line of treatment for castrate resistant prostate cancer	another subsequent line of treatment for castrate resistant cancer	TA387 model survival estimaes (abiraterone for metastatic hormone-relapsed prostate cancer before chemotherapy)
Alive (in any health state)	Dead	Trial data + age-adjusted general population mortality from Office for National Statistics

Company's rationale for using Kaplan Meier data for first 5 months

Log cumulative hazard plots of OS (left) and rPFS (right) show proportional hazards after 5 months → company used Kaplan Meier data in its model for the first 5 months and then used multi-state modelling, assuming proportional hazards, thereafter

Overall Survival



rPFS

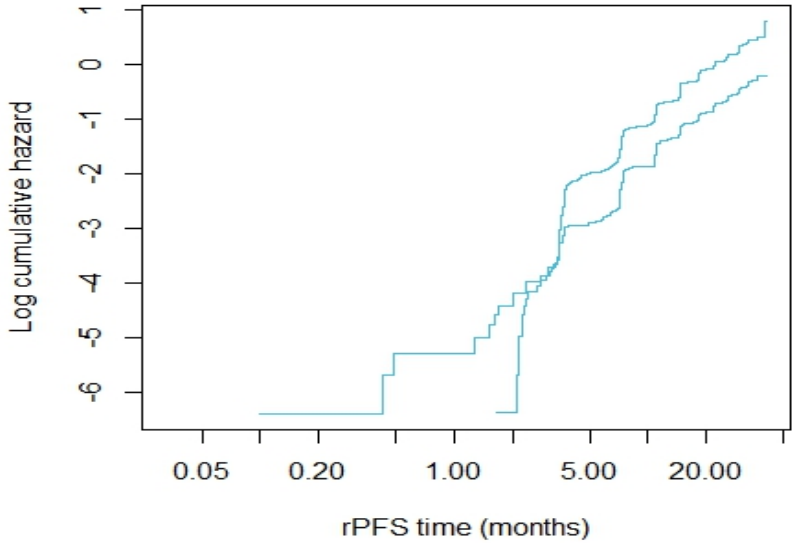


Figure 26 + 27 company submission page 118 (cumulative hazard plots)

Transitions for subsequent therapies in mCRPC health states

- Company: PFS data for subsequent treatment from LATITUDE were not used
  - Low number of patients receiving subsequent therapies within the trial & use of non-UK standard treatments
- Modelled survival outputs from model for TA387 (AAP for mCRPC before chemotherapy). Data extrapolated from COU-AA-302 (see slides 40 + 41)
- All active treatments were assumed to have equal clinical effectiveness* The weighted average survival (and treatment costs) was calculated based upon the expected market share of each treatment in UK practice (see slide 42)†
- Transition probabilities after the 1st line mCRPC health state (to 2nd and 3rd line treatments for mCRPC) estimated by using mean health state durations from TA387 and assuming a constant probability over time
- Using survival outputs from TA387 model overestimates survival in all treatment arms compared with LATITUDE overall survival Kaplan Meier curves ‡
  - Company used a “calibration factor” to adjust the modelled overall survival to reflect LATITUDE (see slides 43 + 44)¥

Summary: modelling of castrate resistant states using TA387 modelled survival

- The choice of survival curves from TA387 to apply in current model dependent on 1st treatment for castrate resistant prostate cancer

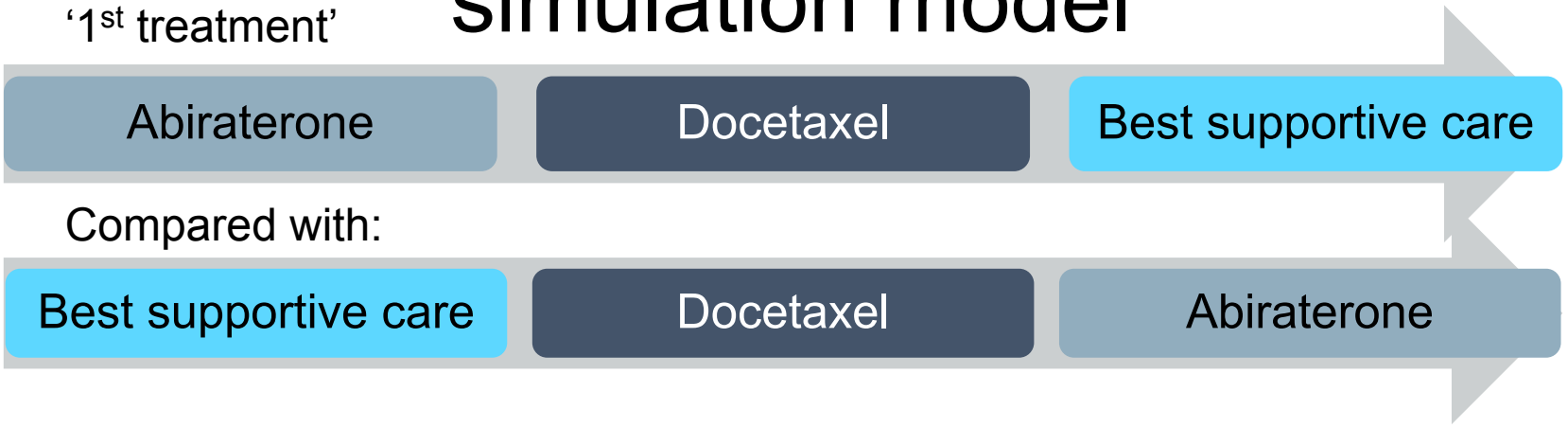
1st treatment castrate resistant current model*	Survival estimates from TA387	costs
Active • Docetaxel • Abiraterone • Enzalutamide • Cabizitaxel • Radium-223	All active treatments assumed to have same effectiveness. Used survival curves for abiraterone from TA387 model	% of people receiving each type of active treatment for castrate resistant prostate cancer, and best supportive care from market share estimates*
Non active best supportive care	Used survival curves for best supportive care from TA387 model	

- Market share estimates also used to estimate % of people receiving active treatments or best supportive care for 2nd and 3rd treatments. But active/non active 2nd and 3rd treatments don't affect survival in model

Recap: clinical evidence informing TA387 modelling from COU-AA-302

Population n = 1088	Asymptomatic or mildly symptomatic patients: • ECOG 0 or 1 • Worse pain last 24 hrs score 0-3 • No visceral metastases
Intervention	Abiraterone + prednisolone (or prednisone) n = 546
Comparison	Placebo + prednisolone (or prednisone) n = 542
Dates	Enrolled April 2009 to June 2010
Co-primary endpoints	Radiographic PFS (rPFS) and overall survival
Treatment length	Until progression or: adverse events, start of new anticancer tx, patient had medications prohibited by trial or withdrew consent
Results	3rd interim analysis (used in modelling): - Median OS 35 months with abiraterone, 30 months with placebo, hazard ratio 0.79, p=0.015 (p<0.003 required for statistical significance) - Median rPFS 17 vs 8 months, hazard ratio 0.52, p<0.0001

Recap: TA387 company's discrete event simulation model



Model input	Company
Prediction equations	17 prediction equations Include baseline covariates
Population	83% of intention-to-treat (ITT) population with data on covariates ('full covariate subgroup')
Distribution for time on first treatment	Log-logistic in base case; Weibull in sensitivity analyses

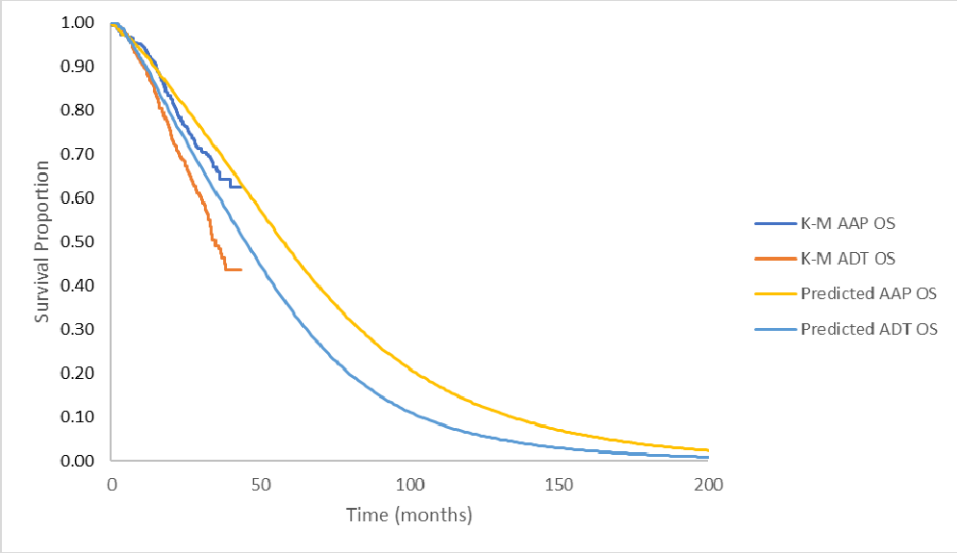
Subsequent treatment market shares for mCRPC used in current model

Treatment	Base Case			Scenario: LATITUDE		
	AAP + ADT	ADT alone	Docetaxel + ADT	AAP + ADT	ADT alone	Docetaxel + ADT
1L mCRPC						
BSC	10%	5%	5%	35%	25%	25%
Enzalutamide	0%	35%	39%	10%	13%	39%
AAP	0%	35%	39%	3%	9%	34%
Docetaxel	60%	15%	0%	51%	51%	0%
Cabazitaxel	0%	0%	12%	1%	0%	0%
Radium-223	30%	10%	5%	1%	2%	2%
2L mCRPC						
BSC	65%	45%	60%	84%	75%	75%
Enzalutamide	0%	10%	5%	4%	8%	10%
AAP	0%	10%	5%	1%	4%	7%
Docetaxel	0%	10%	0%	3%	5%	0%
Cabazitaxel	15%	5%	5%	4%	5%	5%
Radium-223	20%	20%	25%	3%	2%	2%
3L mCRPC						
BSC	90%	90%	95%	96%	91%	91%
Enzalutamide	0%	0%	0%	1%	2%	3%
AAP	0%	0%	0%	1%	2%	3%
Docetaxel	0%	0%	0%	1%	1%	0%
Cabazitaxel	2%	1%	1%	1%	2%	2%
Radium-223	8%	9%	4%	1%	1%	1%

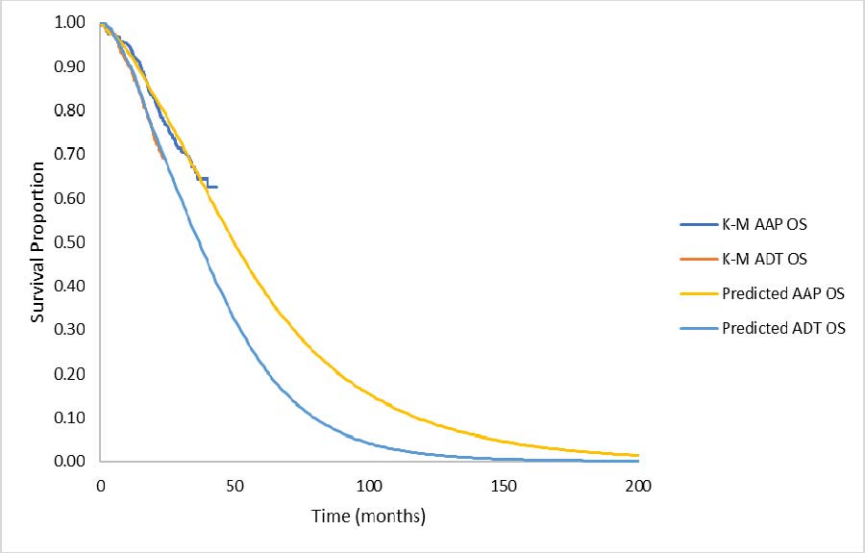
Modelled overall survival estimates

MSM modelling using TA387 model outputs

1)



2)



Without calibration
Predicted OS higher than Kaplan-Meier data

With calibration
Using calibration factor of HR 2.62

Company's alternative approach for modelling mCRPC health state transitions

- Alternative approach using multi state modelling analysis of LATITUDE data for all states including the castrate resistant health states
  - ERG refers to this as the "MSM model"
- Despite the transition probabilities in the model being based on LATITUDE data, 1st line mCRPC treatment discontinuation was estimated from mean times spent on 1st line mCRPC treatment during the COU-AAP-302 trial

Comparison of MSM/TA387 and MSM model

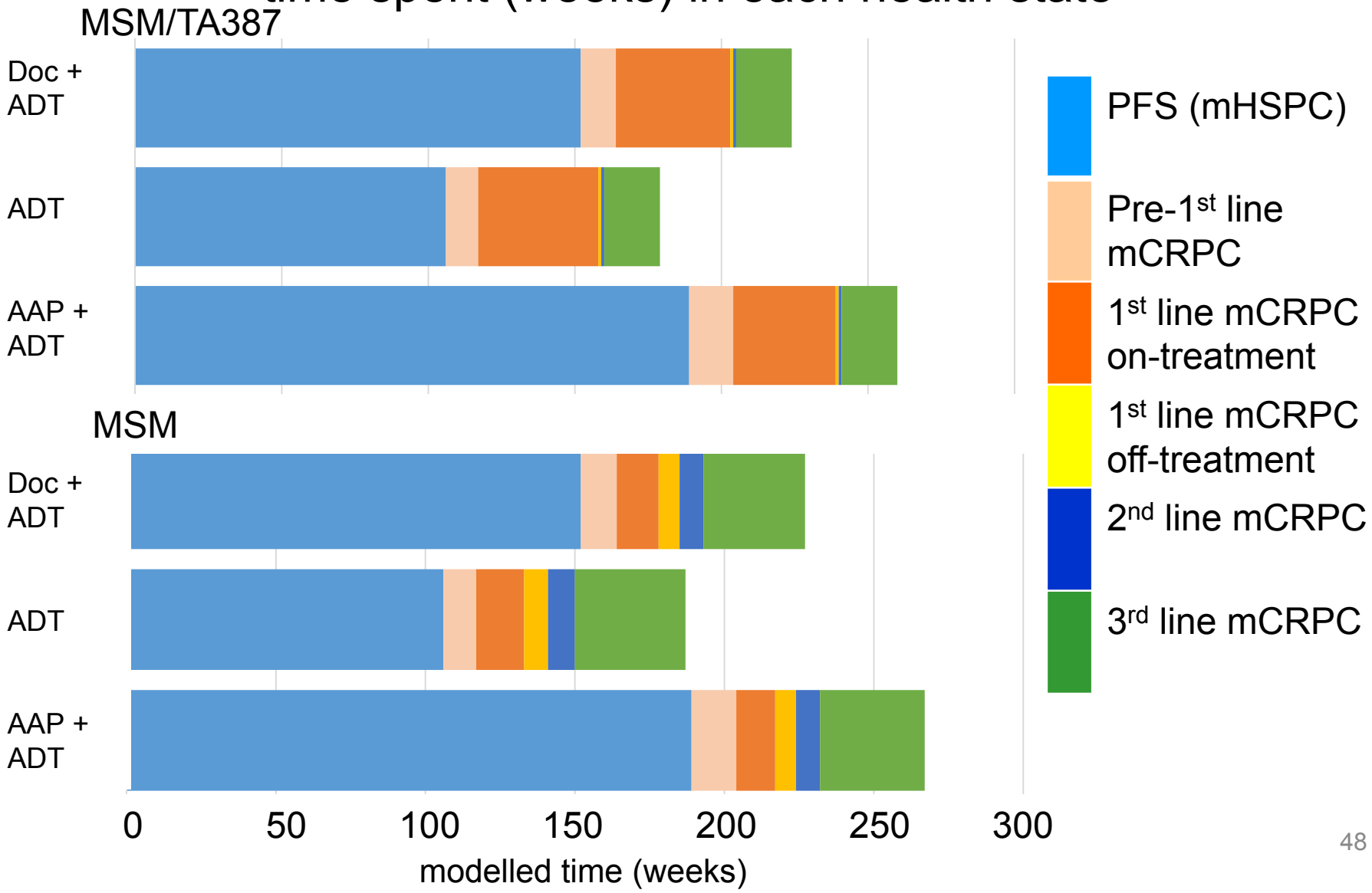
Time spent (weeks) in each health state

	MSM/TA387 model			MSM Model		
	AAP+ADT	ADT	DOC+ADT	AAP+ADT	ADT	DOC+ADT
PFS	189	106	152	189	106	152
mCRPC						
pre 1st line Tx	15	11	12	15	11	12
1st line On Tx	35	41	39	13	16	14
1st line Off Tx	1	1	1	7	8	7
2nd line	1	1	1	8	9	8
3rd line	19	19	19	35	37	34
OS Total	260	178	225	267	187	227

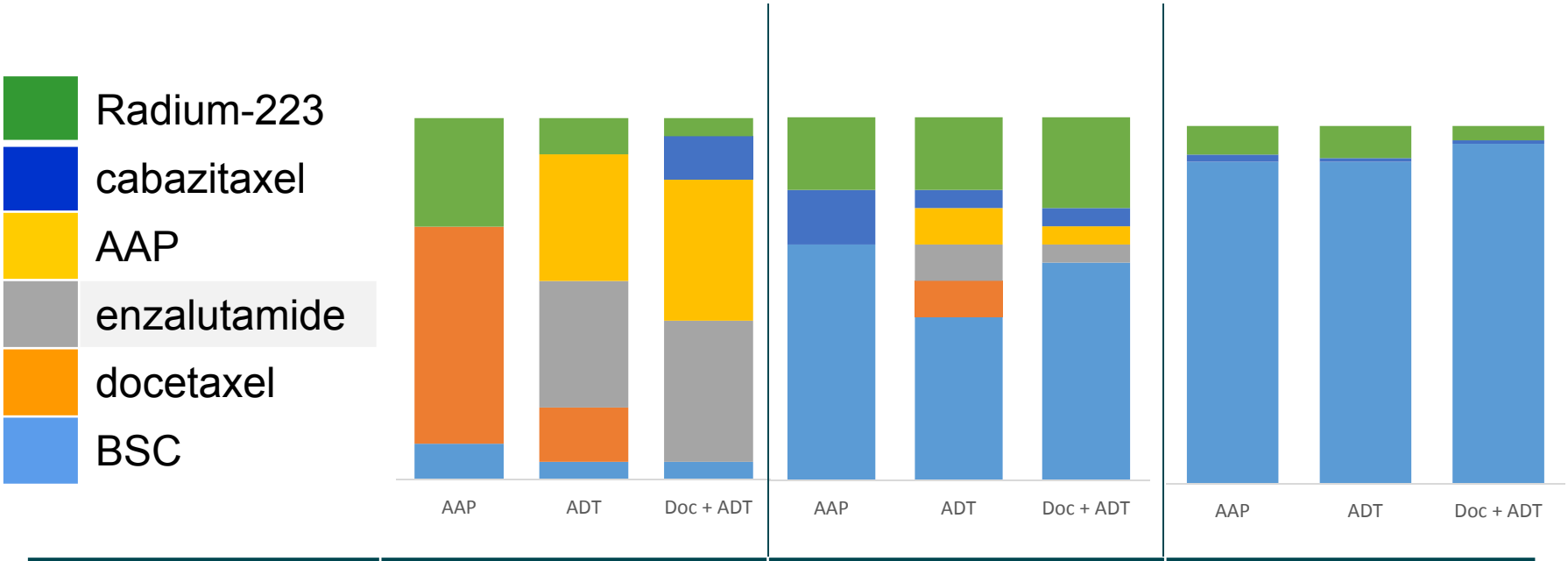
The red boxes show key differences between the modelled outcomes using these 2 approaches

Comparison of MSM/TA387 and MSM model

time spent (weeks) in each health state



Recap: proportion of people receiving different mCRPC treatment options



	1st line mCRPC			2nd line mCRPC			3rd line mCRPC		
	AAP + ADT	ADT	Doc + ADT	AAP + ADT	ADT	Doc + ADT	AAP + ADT	ADT	Doc + ADT
Drug + admin (£1000s)	***	***	***	***	***	***	***	***	***

ERG comments on the modelling approach for mCRPC health states 1/2

Co**mpany's base case approach**

- Base case using multistate modelling with some input from TA387 discrete event simulation modelled (ERG refers to as MSM/TA387 model) coupled with a 'calibration factor' is a complicated, non-statistical way of fitting curves to LATITUDE data
  - Fitting of the MSM/TA387 model OS curves to LATITUDE OS curves seems to negate the reason for adopting the MSM/TA387 modelling approach.
  - Instead, the company could have used the usual well-established statistical methods to fit curves to the Kaplan Meier data from LATITUDE
- Uncertainty about what 1st line mCRPC treatment proportions should be applied to subsequent AAP + ADT, ADT and docetaxel + ADT treatments for mHSPC
- Not clear whether NICE approval of abiraterone for mHSPC would, over time, lead to mHSPC patients receiving more than one novel agent for their metastatic prostate cancer

ERG comments on the modelling approach for mCRPC health states 2/2

Comparison of base case MSM/TA387 modelling approach and company's alternative MSM approach

- Base case MSM/TA387 model and alternative MSM models differ in the proportion of mCRPC survival spent on 1st line mCRPC treatment and time spent on 3rd line mCRPC treatment
  - 1st line mCRPC treatment options include more costly active treatments
  - 3rd line mCRPC treatment option mostly best supportive care
- MSM model estimates a smaller survival gain for AAP + ADT vs. ADT compared with MSM/TA387 model
- Concerned that both the MSM/TA387 model and the MSM model do not accurately reflect costs and benefits of the 1st treatment for mCPRC after a person's cancer has progressed on their initial treatment for mHSPC
  - For the ADT and Docetaxel + ADT arms the first treatment for mCPRC includes more expensive treatment options like abiraterone or enzalutamide, whereas a greater proportions people receiving AAP + ADT may receive cheaper options like docetaxel or have best supportive care for mCRPC

Sources of utility data

Health state	Quality of life data	Utility values used
mHSPC Pre- and post-progression mHSPC on/off abiraterone	EQ-5D-5L from LATITUDE was collected at baseline, monthly from cycles 2 to 13 and every 2 months thereafter until end of study treatment or progression and every 4 months until 60 months, or death or loss to follow-up	• Mapped to EQ-5D-3L utility score using crosswalk algorithm (Van Hout) • + regression analysis of trial data to identify factors likely to influence patients' QoL
mHSPC on/off docetaxel	health states describing typical patient: 1) High risk mHSPC currently receiving ADT 2) High risk mHSPC currently receiving ADT + Docetaxel 3) High risk mHSPC who has completed 6 cycles of docetaxel and receiving ADT alone	Company commissioned Time Trade-Off (TTO) study. Non-randomly selected group of 200 members of public asked to value a description of patient experience in these health states
mCRPC health states	From TA387, included an increment of 0.021 for people receiving abiraterone as a subsequent treatment	
Adverse events	Literature review (from literature estimates of 14 SAEs and for grouped SREs)	Decrement for SAEs and SREs of *** Used in base

Modelled utility value by health state

- Baseline utility (EQ-5D-3L) for people with newly diagnosed MHSPC from LATITUDE was ***
- Effect of being on- or off-treatment from regression analysis of LATITUDE, were applied to this value for AAP + ADT and ADT.
- Data from the time trade off study was applied for docetaxel

State	Utility value		
	AAP + ADT	ADT	Docetaxel + ADT
mHSPC pre-progressed	*** ***	***	*** ***
mHSPC pre-progressed (with AE/SRE)	*** ***	***	*** ***
mHSPC progressed	***	***	***
mHSPC progressed (with AE/SRE)	***	***	***
1L mCRPC on-treatment	***	***	***
1L mCRPC on-treatment (with AE/SRE)	***	***	***
1L mCRPC off-treatment	***	***	***
2L mCRPC	***	***	***
3L mCRPC	***	***	***

ERG comments on the time trade off study

ERG extracted the key differences in the health state descriptions of experience on ADT, on doctaxel + ADT and on ADT after docetaxel (table 60 ERG report)

ADT	DOC+ADT	ADT (post DOC+ADT)
**********	**********	**********
	**********	**********
	**********	**********
	**********	**********
	**********	**********
	**********	**********
**********	**********	**********
**********	**********	**********
**********	**********	**********
**********	**********	**********
**********	**********	**********

ERG comments utility values for docetaxel

Plausibility that quality of life is worse after docetaxel

- Assumption that quality of life worse after docetaxel (+ ADT) compared with ADT alone not consistent observations reported in literature:
  - GETUG-AFU 15 (Joly et al., 2010): EORTC-ALA-C30 questionnaire. Docetaxel + ADT is associated with an initial deterioration [in quality of life], at 12 months there is no difference in overall quality of life between docetaxel + ADT and ADT
  - CHAARTED (Morgans et al., 2018): FACT-P. Docetaxel + ADT FACT-P scores were significantly lower than ADT at 3 months (difference -3.09, p=0.02), but significantly higher than ADT at 12 months (difference + 2.85, p=0.04), but differences did not exceed the minimum clinically meaningful change at any time point. Authors concluded "[results suggestive that] ADT + Docetaxel is not associated with a greater long-term negative impact on QOL [than ADT]"
- The utility decrement assumed for while a person is on docetaxel is not applied when docetaxel is taken after abiraterone + ADT

ERG comments on company's utility values based on EQ-5D from LATITUDE

- Quality of life estimates collected every 3 months possibly confounded by a greater proportion of people progressing earlier with ADT monotherapy
- Regression analysis from LATITUDE is only partially applied in the model
  - utility decrements for serious adverse events (SAEs) and skeletal related events (SRE's) were derived from the literature
- Utility decrement for SAEs and SREs was an order of magnitude lower than the decrements derived from the LATITUDE regression analyses.

The quality of life values in the model are therefore above those observed in LATITUDE

Drug costs used in the model

- Commercial access agreement for abiraterone is used Confidential patient access schemes (PAS) are in place for some of the 2nd, 3rd and 4th line treatments in the model → ERG provide results in confidential appendix.

	Company	ERG confidential appendix
Abiraterone	CAA for TA387	
Docetaxel	eMIT £20.44 / 160 mg vial	
ADT	Goserelin, leuprorelin, triptorelin, bicalutamide (weighted average based on prescription data) costs from UK National Schedule of Reference costs	
Enzalutamide	List price	PAS discounted price
Cabazitaxel	List Price	PAS discounted price + wastage rebate
Radium 223	List price	PAS discounted price

Drug and admin costs used in the model

Drug	Abiraterone	Docetaxel	ADT			
			Goserelin	Leuprorelin	Triptorelin	Bicalutamide
Cost per pack	confidential	£20.44	£65.00	£191.59	£226.80	£4.13
Pack size	56 tablets (500mg)	160 mg vial	3.6 mg [a]	11.25 mg [a]	11.25 mg [a]	50 mg [a]
Acquisition cost per dose	Confidential	£46.75	£65.00	£191.59	£226.80	£0.15
Admin cost per dose	£0.00	£259.76	£10.85	£10.85	£10.85	£0.00
Number of doses / tx cycles	7.00	1.00	0.25	0.08	0.08	7.00

ADT use is assumed to be equally balanced between goserelin, leuprorelin and triptorelin with 30% of these patients also receiving bicalutamide

Company's estimate of treatment compliance on abiraterone

Figure is confidential

ratio

Area under progression free survival KM curve:

Area under time to treatment discontinuation curve

- The areas under the curves are around **months for the rPFS KM curve and ** months for TTD KM curve, which results in a ratio of *** time on treatment compared to time in rPFS. This ratio was applied to the abiraterone drug costs in the model

ERG comments on treatment compliance assumptions

- Treatment compliance estimate for abiraterone for mHSPC seems low compared the Clinical Study Report data on compliance
- ERG estimated treatment compliance of **% for AAP + ADT and **% for ADT based on the Clinical Study Report for LATITUDE
- The treatment compliance estimate for docetaxel for mHSPC is not applied to the same range of costs as the compliance estimate for abiraterone (i.e did not adjust admin costs for docetaxel for treatment compliance)
- The treatment compliance estimates do not take into account that they reflect discontinuations during the relevant trials. This mainly affects mCRPC treatments in the AAP + ADT arm

Resource use

Drug	Abiraterone		Docetaxel		ADT
Scheduled resource use (4 weekly)	wk 0-12	£248.35	On Tx	£244.19	£68.65
	wk 13+	£144.68	Off Tx	£151.86	
Unscheduled (4 weekly)	£1192.28		£1192.28		£1513.06
Key: ADT, androgen deprivation therapy; AE, adverse events; MRU, medical resource use; Tx, treatment					

- Scheduled resource use includes visits and frequency in mHSPC and mCRPC from 5 clinicians. For abiraterone costs of blood test + oncologist visit every 2 weeks for first 3 months included
- Unscheduled resource use includes frequency of hospitalisations, imaging and radiotherapy from LATITUDE for mHSPC, trial data from COU-AA-302 used for mCRPC health states. Docetaxel assumed to be equivalent to abiraterone
- Costs of hospital visits from UK National Schedule of Reference costs
- Model implemented one-off cost of terminal care of £7,583 (UK study Round et al., 2015 inflated to 2018 costs)

ERG comments resource costs

- Company model assumes a bone scan at ** weeks and every ** weeks thereafter at a cost of £292 for people in the modelled docetaxel + ADT arm.
  - Costs of bone scans are not included for people receiving AAP + ADT or ADT
- ERG cannot find evidence that mHSPC patients who have finished their course of docetaxel and are only receiving ADT in the docetaxel + ADT arm have more routine bone scans than mHSPC patients on AAP + ADT
- No data in the Summary of Product Characteristics for abiraterone or docetaxel to support this company assumption

Adverse event costs

Drug	Abiraterone	Docetaxel	ADT
Annual cost of AE	£632.33	£1,104.58	£579.65
Key: ADT, androgen deprivation therapy; AE, adverse events			

- Included costs of managing grade 3 or 4 adverse events
- Frequency of adverse events came from trial data
- Unit costs for each adverse event same as TA387
- The annual probability and cost by treatment arm of diarrhoea, neuropathy, neutropenia, febrile neutropenia, thrombocytopenia, anaemia, oedema, hypokalaemia, hypertension, arthralgia, asthenia, dyspnoea, nausea, vomiting and skeletal events are reported in table 30 page 143 company submission

Cost effectiveness results

- All results are shown for the modelled cost effectiveness estimates when the list prices for enzalutamide, cabazitaxel and radium-233 are used in the modelling.
- The results, when the patient access schemes for these technologies have been applied in the model by the ERG, are shown in a confidential appendix to this pre-meeting briefing

Company base case results

Deterministic

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	*******	3.43	2.33	19,066	1.56	1.09	**17,418**
AAP + ADT	*******	4.99	3.42				
Docetaxel + ADT	*******	4.32	2.82	10,618	0.67	0.60	**17,828**
AAP + ADT	*******	4.99	3.42				

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

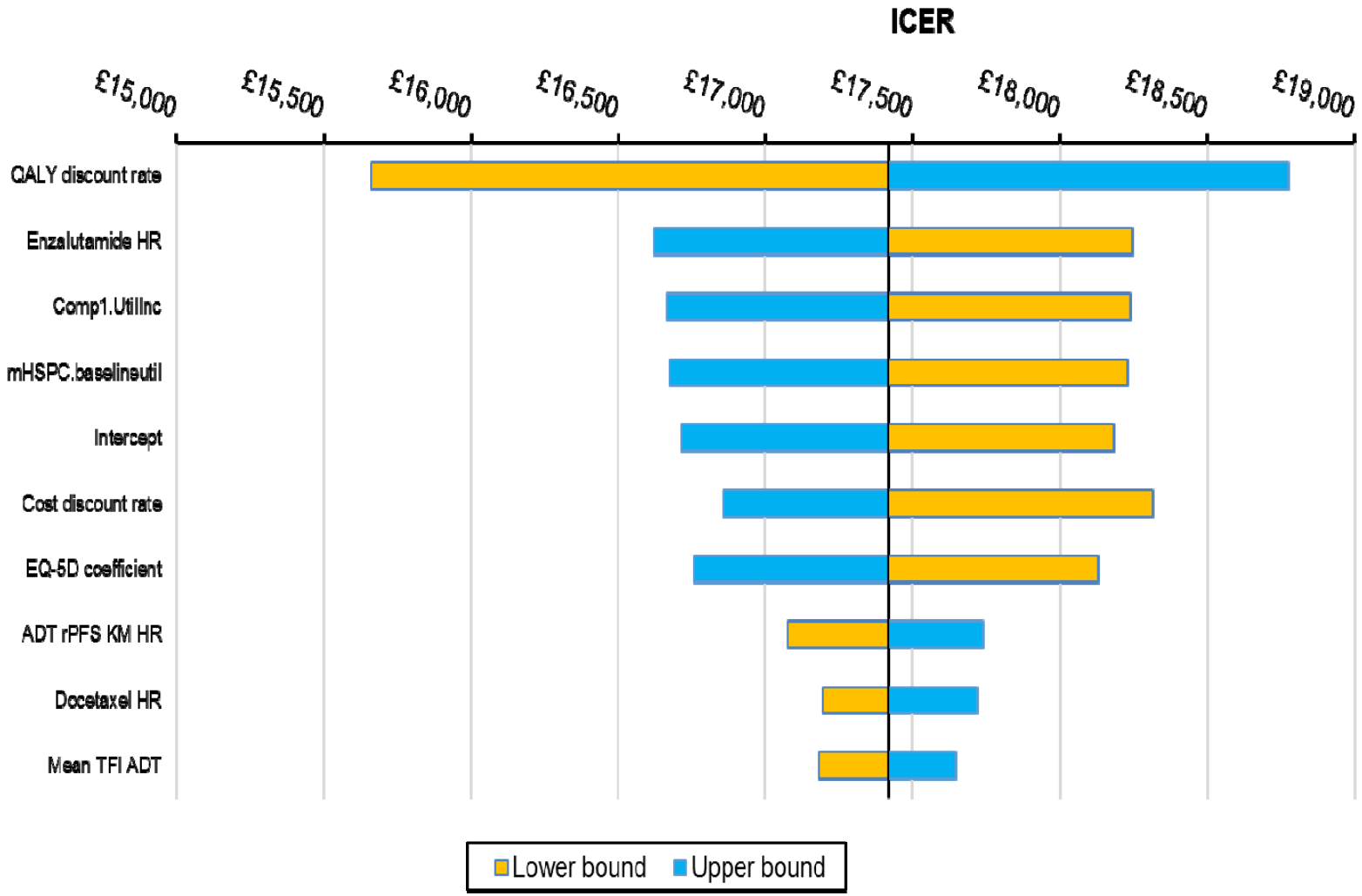
Probabilistic

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	********	3.43	2.33	19,105	1.57	1.10	**17,417**
AAP + ADT	********	5.00	3.42				
Docetaxel + ADT	********	4.35	2.84	10,686	0.66	0.59	**18,234**
AAP + ADT	********	5.00	3.42				

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

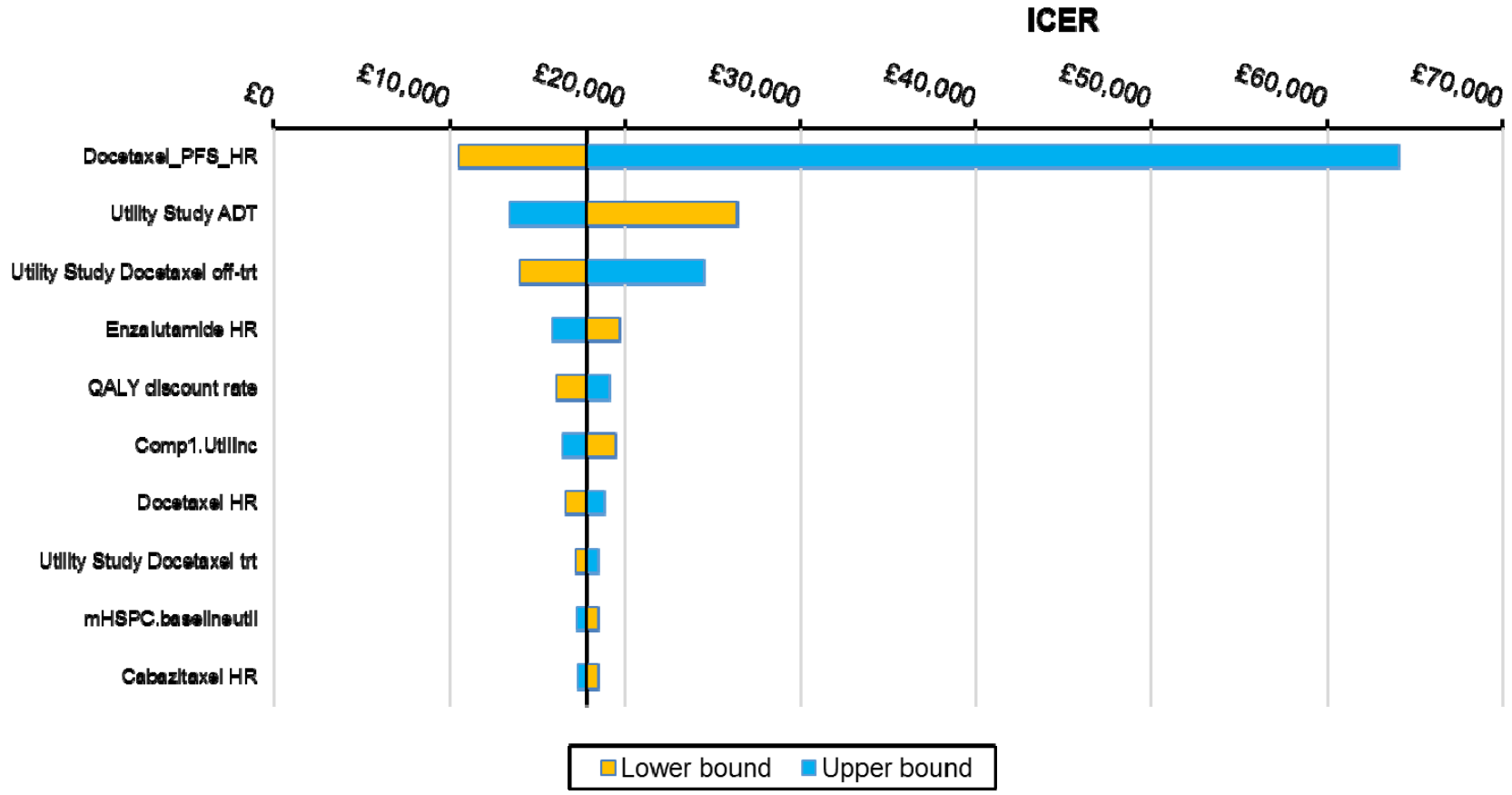
Deterministic sensitivity analysis

AAP + ADT vs. ADT. Company submission figure 39 page 155



Deterministic sensitivity analysis

AAP + ADT vs Docetaxel + ADT. Company figure 40 page 155



Company's scenario analyses

selected scenarios that had an impact on ICERs

Model assumption	Scenario	ICER vs ADT alone	ICER vs docetaxel + ADT
Base Case		£17,418	£17,828
Loss of exclusivity	**********	*********	*********
Definition of progression	Time to stopping treatment used as an alternative definition of progression to rPFS	£14,079	£11,287
Survival and subsequent therapy source	Survival estimates and subsequent therapy market shares estimated from LATITUDE + MSM model	£21,504	£22,218
AA utility increment	Applied until death	£16,775	£16,656
	No increment applied	£18,697	£20,394
Docetaxel utility decrement	On-treatment decrement applied only (no post-docetaxel utility decrement)	£17,418	£20,027
Subsequent treatment ITC	Different HR are applied for each subsequent treatment based on subsequent therapy ITC	£17,129	£17,095
Docetaxel Vial wastage	Set to zero	£15,997	£15,077
AE/SRE HRQL source	Values sourced from regression	£17,510	£31,389

Comparison of MSM/TA387 and MSM results

Company base case (MSM/TA387 model)

	LYs	QALYs	Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	4.993	3.420	*********				
ADT	3.430	2.325	*********	1.563	1.095	£19,066	£17,418
DOC + ADT	4.322	2.824	*********	0.672	0.596	£10,618	£17,828

MSM model

	LYs	QALYs	Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	5.129	3.397	*********				
ADT	3.597	2.303	*********	1.532	1.094	£22,356	£20,438
DOC +ADT	4.365	2.753	*********	0.764	0.644	£17,329	£26,909

N.B. the results using the MSM modelling approach were prepared by the ERG using current practice estimates for the proportion of people receiving each subsequent treatment (rather than using subsequent treatment proportions from LATITUDE as the company had done in its scenario analysis using the MSM approach). These data are reported in table 48 ERG report

ERG exploratory analyses

- The ERG have presented their exploratory analyses using the MSM/TA387 modelling approach and the MSM modelling approach separately

ERG sensitivity analyses on treatment sequences in mCRPC states

	mCRPC line of treatment	ADT	Abiraterone + ADT	Docetaxel + ADT	ICER 1) vs. ADT 2) vs Doc
SA1	1st, 2nd, 3rd	All BSC			1) £23,752 2) £30,788
SA2	1st	All enzulatamide			1) £20,095 2) £27,488
	2nd, 3rd	All BSC			
SA3	1st	All enzalutamide			1) £18,920 2) £25,646
	2nd , 3rd	All cabazitaxel 2nd line then radium-233 3rd line			
SA4	1st	enzalutamide	docetaxel	Enzalutamide	1) £2,785 2) dominant
	2nd, 3rd	All BSC			
SA5	1st	enzalutamide	Docetaxel	Enzalutamide	1) £1,608 2) Dominant
	2nd, 3rd	All cabazitaxel 2nd line then radium-233 3rd line			
SA6	1st	All enzalutamide			1) £19,155 2) £24,625
	2nd	docetaxel	docetaxel	cabazitaxel	
	3rd	cabazitaxel	cabazitaxel	Radium-233	

ERG's exploratory analyses

changes made to company base case

ERG change	Slide for reference
1) Apply all LATITUDE quality of life regression results (for mHSPC and mCRPC health states) i.e regression disutility values for adverse events not literature values	55
2) No post-docetaxel utility decrement in mHSPC health state	54
3) Compliance estimates for abiraterone costs in mHSPC from clinical study report compliance data, using mid-point values. Apply compliance percentages in the DOC + ADT arm in the same manner as the AAP + ADT arm	59
4) Same number of bone scans in docetaxel + ADT arm (pre- and post docetaxel) as in AAP +ADT arm	61
5) Revised treatment proportions mCRPC 1st line that do not differentiate the proportions of people receiving BSC between arms	42
6) Apply corrections for minor modelling errors (described on pages 137-138 ERG report)	none
The ERG exploratory base case included all of these changes	

ERG exploratory base case results

Deterministic results using MSM/TA387 model structure

	LYs	QALYs	Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	5.030	3.289	*********				
ADT	3.505	2.213	*********	1.525	1.076	£19,362	£17,992
DOC	4.360	2.845	*********	0.671	0.444	£13,965	£31,439

Deterministic results using MSM model structure

	LYs	QALYs	Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	5.129	3.249	*********				
ADT	3.597	2.158	*********	1.532	1.091	£22,751	£20,855
DOCE	4.365	2.761	*********	0.764	0.488	£20,353	£41,697

ERG scenario analyses 1/2
around ERG exploratory base case

1) Use Kaplan Meier data for 4 or 7 months (rather than 5) and multi-state modelling transition probability matrices thereafter
2) Apply same probability of receiving 1st line mCRPC treatment for people who had AAP + ADT or Docetaxel + ADT as their treatment for mHSPC (in company base case, the proportion of people receiving treatment for mCRPC after docetaxel + ADT depended on the hazard ratio for rPFS for Docetaxel + ADT compared with AAP + ADT. This resulted in fewer people having 1st line treatment for mCRPC after docetaxel + ADT than after AAP +ADT)
3) 1st line mCRPC treatment effectiveness estimates from company's indirect treatment comparison of 1st line mCRPC treatments (i.e. better rPFS with enzalutamide than abiraterone rather than assuming equal clinical effectiveness of active treatments)
4) Scenario 3 + all people receive enzalutamide rather than abiraterone for mCRPC
5) Apply a quality of life increment for ADT (after docetaxel) compared with ADT of half the quality of life increment for AAP + ADT (compared with ADT from the LATITUDE regression analyses

ERG scenario analyses 2/2
around ERG exploratory base case

6) Apply a quality of life decrement for after docetaxel compared with ADT of ***** as per the company base case **(reverse change 2 in ERG base case)**

7) Use the utility decrements for SAEs and SREs from literature (as in company base case) rather than LATITUDE regression values **(reverse change 1 in ERG base case)**

8) Apply the LATITUDE quality of life regression that does not differentiate the SAE coefficient between modelled treatment arms

9) Apply the company base case assumptions on the proportion of people who receive each 1st, 2nd and 3rd line mCRPC treatment **(reverse change 5 in ERG base case)**

10) Apply the treatment compliance for abiraterone from company base case that is derived by the company from the LATITUDE rPFS and time to treatment discontinuation Kaplan Meier curves **(reverse change 3 in ERG base case)**

11) Apply the company's assumptions on the number of bone scans whilst on docetaxel and after docetaxel (that is, more scans needed on and after treatment with docetaxel with abiraterone + ADT) **(reverse change 4 in ERG base case)**

ERG scenario analyses results

MSM/TA387 model

	AAP+ADT vs ADT			AAP+ADT vs DOC+ADT		
	Δ QALYs	Δ Costs	ICER	Δ QALYs	Δ Costs	ICER
Base case (ERG exploratory)	1.076	*********	£17,992	0.444	*********	£31,439
01a: KM 4mth	1.106	*********	£17,479	0.460	*********	£30,270
01b: KM 7mth	1.036	*********	£18,453	0.419	*********	£34,479
02: Same prob PPS Tx	..	..	..	0.441	*********	£33,897
03: Diff effect mCRPC Tx	1.059	*********	£17,687	0.425	*********	£31,001
04: 03 + ENZA Tx prop.	1.049	*********	£12,118	0.414	*********	£16,714
05: DOC QoL increment	..	..	..	0.396	*********	£35,255
06: DOC QoL decrement	..	..	..	0.516	*********	£27,077
07: Company SAE/SRE QoL	1.112	*********	£17,417	0.563	*********	£24,805
08: Original LATITUDE QoL	1.086	*********	£17,828	0.436	*********	£32,046
09: Company mCRPC prop.	1.069	*********	£18,336	0.437	*********	£32,499
10: Company AAP % use	1.069	*********	£16,837	0.437	*********	£28,840
11: Company DOC scans	1.076	*********	£18,181	0.444	*********	£26,285

ERG scenario analyses results

MSM model (no cPAS)

	AAP+ADT vs ADT			AAP+ADT vs DOC+ADT		
	Δ QALYs	Δ Costs	ICER	Δ QALYs	Δ Costs	ICER
Base case	1.091	*********	£20,855	0.488	*********	£41,697
01a: KM 4mth	1.127	*********	£20,295	0.503	*********	£40,258
01b: KM 7mth	1.036	*********	£21,407	0.462	*********	£44,826
02: Same prob PPS Tx	..	..	..	0.483	*********	£43,544
03: Diff effect mCRPC Tx	1.091	*********	£20,858	0.488	*********	£41,704
04: 03 + ENZA Tx prop.	1.093	*********	£18,733	0.490	*********	£37,562
05: DOC QoL increment	..	..	..	0.440	*********	£46,253
06: DOC QoL decrement	..	..	..	0.560	*********	£36,366
07: Company SAE/SRE QoL	1.127	*********	£20,182	0.610	*********	£33,386
08: Original LATITUDE QoL	1.101	*********	£20,666	0.480	*********	£42,425
09: Company mCRPC prop.	1.091	*********	£21,690	0.488	*********	£43,562
10: Company AAP % use	1.084	*********	£19,735	0.481	*********	£39,491
11: Company DOC scans	1.091	*********	£20,903	0.488	********	£36,676

Key Issues: cost effectiveness

- **Survival model outputs**: Is survival after disease progression dependent on:
  - 1st treatment received?
  - Follow-on treatments in castrate resistant disease?
  - Is it plausible that post progression survival same across modelled treatment arms
- **Survival -MSM/TA387 vs. MSM approach**: Which data best model survival in mCRPC after progressing in mHSPC?
  - LATITUDE for hormone sensitive disease extrapolated?
  - or trial (COU-AA-302) for castrate resistant disease before chemotherapy TA387
    - Do the patient groups/ treatment pathways match?
- **Utility**: Are the values plausible by treatment and adverse events plausible? Can STAMPEDE provide quality of life data?
- **Costs**: Do the follow-on treatment reflect NHS reality?
- **Costs**: What is the expected frequency of bone scans for mHSPC cancer, does this differ by treatment?
- **Costs**: What is the expected compliance to treatment on abiraterone? Should this be included in model?
- **Model outputs**: Are they valid?

Authors

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- with input from the Lead Team (**William Turner, Nigel Westwood, Nicholas Latimer**)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer [ID945]

Document A

Company evidence submission summary for committee

Janssen confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

6th February 2018

File name	Version	Contains confidential information	Date
ID945_AbirateronemHSPC_Form A_FINAL - 060218 [ACIC]	**V1.0**	**Yes**	**06/02/2018**

Instructions for companies

This is the template you should use to summarise your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission summary must not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted. Please submit a draft summary with your main evidence submission. The NICE technical team may request changes later.

When cross referring to evidence in the main submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

Submission summary

A.1 Background

The treatment landscape in metastatic prostate cancer has significantly evolved over the past six years. In 2012, NICE first recommended abiraterone acetate with prednisone/prednisolone (AAP) for the treatment of men with metastatic castrate resistant prostate cancer (mCRPC), post-chemotherapy [TA259].[1] In 2016, NICE recommended AAP for the treatment of men pre-chemotherapy in mCRPC [TA387],[2] acknowledging the benefit of earlier treatment with novel agents. Other new treatments (such as enzalutamide, cabazitaxel and radium-223) also gained NICE recommendation during this time period.

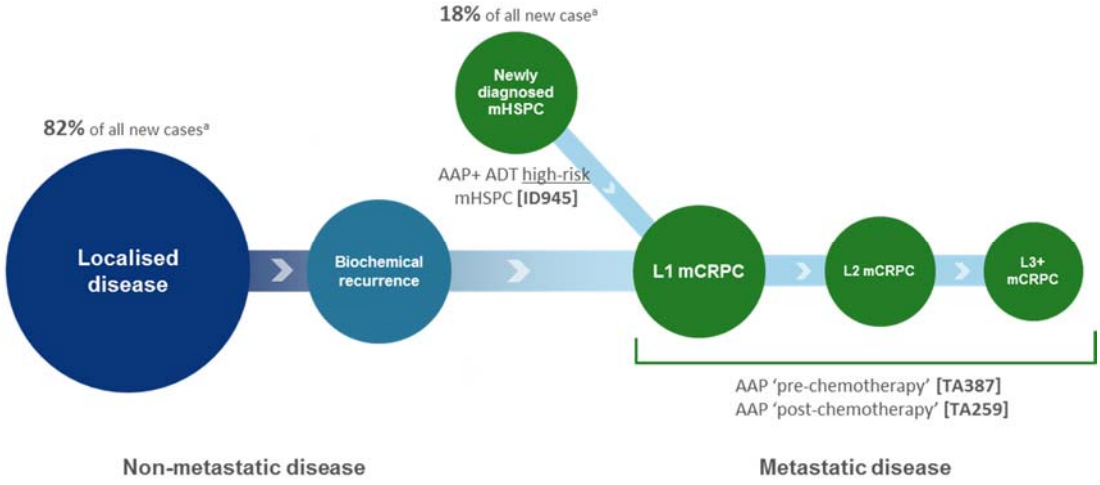
Subsequently, a study known as CHAARTED shifted the paradigm once more.[3] These data showed that giving docetaxel (i.e. chemotherapy) in addition to androgen deprivation therapy (ADT) to men who are newly diagnosed with metastatic hormone sensitive prostate cancer (mHSPC) (i.e. before they have become resistant to hormone therapy) improved health outcomes further still. Results from a landmark UK-based study (STAMPEDE)[4] reaffirmed this and, although docetaxel + ADT is unlicensed in this specific setting, NHS England released a clinical commissioning policy to support its use in newly diagnosed mHSPC in response to these data.[5]

As illustrated Figure 1, AAP received its third licensed indication from the European Medicines Agency in November 2017 for the treatment of adult men with newly diagnosed high-risk mHSPC, in combination with ADT.[6] AAP + ADT is now the only licensed treatment in mHSPC, capable of delaying the initiation of chemotherapy and disease progression, prolonging survival and, importantly, maintaining patients' quality of life.[7] AAP has an established safety profile with over six years of clinical experience in the NHS. A series of published data have shown that AAP + ADT will most likely become the treatment of choice for patients with mHSPC to maximise health outcomes and prolong quality of life.[8-11]

In September 2022, AAP will go off-patent in the UK and its price will inevitably decrease significantly due to generic entry. Loss of exclusivity already occurred in 2017 in other countries (such as the US), so launch of generics in the UK in 2022 will

be rapid, meaning AAP (+ ADT) will thereafter become even more cost-effective across all indications.

Figure 1: Use of AAP in prostate cancer



Notes: [a] Cancer Research UK Incidence Statistics
Key: AAP; abiraterone acetate with prednisone/prednisolone; ADT, androgen deprivation therapy; L, line of therapy; mCRPC, metastatic castrate resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer

A.2 Health condition

Men with newly diagnosed high-risk mHSPC represent an orphan-sized patient population in the UK, equating to 4,400 new cases per year (see Appendix M).[12] These men experience a high clinical, psychological and economic burden of disease.

Prostate cancer is the most common male cancer in the UK, with over 46,700 men diagnosed in 2014.[12] Approximately 18% of new cases present with metastases at first diagnosis, meaning the cancer is diagnosed too late for curative treatment to be possible and has already spread through the body.[12] A typical man diagnosed at this stage is in his mid-to-late sixties and, often, only diagnosed after developing worrying symptoms, such as urinary problems, bone pain, tiredness or unexpected weight loss.[13] Symptoms can be highly debilitating and impactful on quality of life.[13] The psychological burden of receiving such a diagnosis is hard to quantify.[14]

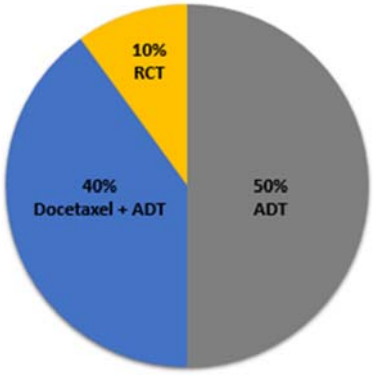
Men with newly diagnosed mHSPC have a poorer prognosis than those who were originally diagnosed with localised disease whose cancer which since spread beyond the prostate.[15, 16] For men classified 'high-risk' at diagnosis, the outlook is even worse as their life expectancy is generally less than three years on conventional hormone

therapy.[17-19] This is because high-risk disease is an aggressive cancer which is likely to advance more quickly.[17] As well as impacting survival, quicker progression to mCRPC is associated with reduced health-related quality of life (HRQL), increased healthcare costs and greater medical resource use (MRU), affecting both patients and the wider NHS.[20, 21] A man with high-risk disease is defined as having two of the following three poor prognostic factors: a Gleason score of ≥8 (describing the aggressiveness of the tumour), the presence of ≥3 lesions on a bone scan, or the presence of visceral metastases (both describing the extent of tumour spread). [22] Approximately 50% of men with newly diagnosed mHSPC are likely to have high-risk prognostic factors at diagnosis.[22, 23]

A.3 Clinical pathway of care

Historically, ADT has been the standard of care (SOC) in mHSPC and it is still used as monotherapy to treat 50–60% of these men in the UK today.[24-26] Although most men initially respond to ADT, the vast majority develop progressive disease within one to two years.[27] Docetaxel + ADT is also now used in this setting because of its reported survival benefits,[3, 28] although real-world data suggest usage has plateaued at 40% of the mHSPC population.[24, 29] Whilst ADT alone does not elicit comparable survival benefits, docetaxel chemotherapy is associated with greater toxicity. As a result, some patients in the UK prefer to delay chemotherapy and would choose to receive ADT alone.

Figure 2: Current management of newly diagnosed high-risk mHSPC in the UK

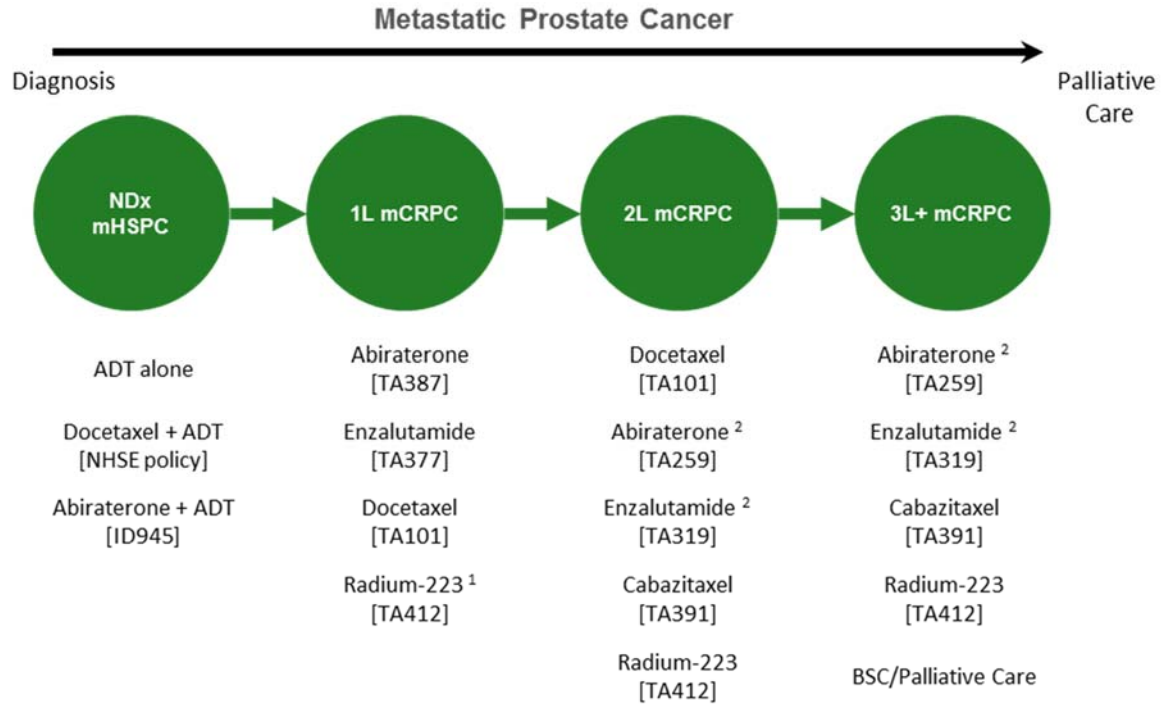


Key: ADT, androgen deprivation therapy; RCT, randomised controlled trial.

The current management of men with newly diagnosed high-risk mHSPC in the NHS is shown in Figure 2 and has been validated by clinical experts.[30] This also acknowledges the significant proportion of men who are enrolled into randomised controlled trials (RCTs) in the UK.[31]

For the 18% of men (see Figure 1) whose prostate cancer is diagnosed after their disease has already metastasised, the care pathway has evolved quite considerably and thus treatment in metastatic prostate cancer can now be considered in terms of sequential lines of therapy (i.e. first-line treatment for mHSPC followed by a sequence of suitable regimens [1L, 2L, etc.] for mCRPC). Several novel agents are now available and the order in which a patient may receive them is determined by prior treatment, NICE recommendation and NHS policy. The clinical pathway of care is thus illustrated by Figure 3.

Figure 3: Metastatic prostate cancer clinical pathway of care



Key: ADT, androgen deprivation therapy; BSC, best supportive care; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NDx, newly diagnosed; NHSE, National Health Service England.
Notes: [1], If docetaxel is contraindicated or not suitable; [2], Use of abiraterone or enzalutamide in mCRPC is dependent on the prior use of docetaxel and/or prior abiraterone or enzalutamide, as per respective NICE guidance.

A.4 Equality considerations

Even though docetaxel is a generic, inexpensive drug with reported survival benefits, not all men with newly diagnosed high-risk mHSPC in the UK undergo treatment. Indeed, 20% of men are considered clinically unsuitable for chemotherapy at diagnosis[30] and others are simply unable to receive it for reasons beyond clinical

prognostic factors. In clinical practice, the overarching decision to undertake early chemotherapy lies between a patient and their clinician. It is essential a clinician can also account for psychological, social and economic factors in making informed judgement regarding which treatment is best suited to an individual patient. As substantiated by UK clinical experts,[30] these commonly include, but are not limited to:

- The presence of a carer or loved one for support, both for attending chemotherapy clinics and managing potential side effects.
- Where a man lives, be it isolated or accessible by public transport to attend chemotherapy clinics, with or without a carer.
- The emotional state required to endure the toxicity of chemotherapy, which is often understated.
- Religious beliefs that can prevent a man from pursuing chemotherapy due to the alcohol content in docetaxel.
- Being unwilling to undertake treatment.

These factors could realistically prevent a man with newly diagnosed high-risk mHSPC from undertaking treatment with docetaxel + ADT and thus compromise their survival in the absence of any alternative life-prolonging therapy.

A.5 The technology

Table 1: Technology being appraised – B.1.2 (p10-11)

UK approved name and brand name	Abiraterone acetate (Zytiga®)
Mechanism of action	Abiraterone acetate (AA) is converted, *in vivo*, to abiraterone, a potent androgen biosynthesis inhibitor that selectively inhibits the enzyme 17α-hydroxylase (CYP17). CYP17 catalyses the conversion of pregnenolone and progesterone into the testosterone precursors, dehydroepiandrosterone (DHEA) and androstenedione.[6] CYP17 inhibition also results in increased mineralocorticoid production by the adrenals via a feedback loop which culminates in increased adrenocorticotropic hormone (ACTH) secretion. By inhibiting the production of both DHEA and androstenedione, AA blocks androgen biosynthesis at all sites in the body, including the testes, adrenal glands and prostatic tumour. Treatment with AA decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH agonists (or orchiectomy).[32, 33]
Marketing authorisation/CE mark status	Positive Committee for Medicinal Products for Human Use (CHMP) opinion was received on 12th October 2017. Marketing authorisation (MA) was subsequently granted on 20th November 2017.[6]
Indications and any restriction(s) as described in the	Abiraterone acetate is indicated with prednisone or prednisolone for:

<table>
<tr><td>summary of product characteristics</td><td>

the treatment of newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT)
the treatment of metastatic castration-resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated
the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.[6]

The full SPC and EPAR are presented in Appendix C.
</td></tr>
<tr><td>Method of administration and dosage</td><td>AA is administered orally at a recommended dose of 1,000mg (two 500mg tablets) as a single daily dose in combination with 5mg prednisolone daily in mHSPC or 10mg daily in mCRPC.[6]</td></tr>
<tr><td>Additional tests or investigations</td><td>Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly.
During treatment of patients with significant risk for congestive heart failure, blood pressure, serum potassium fluid retention, and other signs and symptoms of congestive heart failure should be monitored every two weeks for three months, then monthly thereafter and abnormalities corrected.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>The NHS list price of AA 500mg tablets x 56 = £2,735.00.
Treatment is continued until disease progression. Median duration of treatment in men with newly diagnosed high-risk mHSPC is 24 months.[7]
<table>
<tr><td>Drug cost [list price]</td><td>£2,735 [28 days]</td></tr>
<tr><td>Packs per year</td><td>365/28 = 13</td></tr>
<tr><td>Drug cost per patient per year*</td><td>£35,652.68</td></tr>
</table>
*Maximum drug cost presented, assuming all patients who are initiated on abiraterone acetate stay on treatment for a full year.</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>  </td></tr>
</table>

	[redacted]

Key: AA, abiraterone acetate; CYP17, 17α-hydroxylase; DHEA, dehydroepiandrosterone; EPAR, European Public Assessment Report; LHRH, luteinising-hormone-releasing hormone; PAS, patient access scheme; SPC, summary of product characteristics.

A.6 Decision problem and NICE reference case

The company submission is broadly consistent with the final NICE scope and the NICE reference case, as detailed and justified in Table 2.

Table 2: The decision problem – B.1.1 (p8-9)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale for difference from final NICE scope
Intervention	AAP + ADT		
Population	Adults with newly diagnosed high-risk metastatic hormone-naïve prostate cancer	Adults with newly diagnosed high-risk mHSPC	As per the MA wording: AAP is indicated for the treatment of newly diagnosed high-risk mHSPC in adult men in combination with ADT. While the LATITUDE trial used the term mHNPC, this is effectively the same as newly diagnosed mHSPC because, by default, if a patient is newly diagnosed they are hormone naïve.
	• ADT alone (orchidectomy, LHRH agonist or bicalutamide monotherapy) • Docetaxel +ADT	• ADT alone (LHRH agonist) • Docetaxel + ADT	Orchidectomy and bicalutamide monotherapy are rarely used in the UK. In addition, there is no difference in the clinical outcomes between LHRH agonists, bicalutamide mono or orchidectomy.[29]
Outcomes	• OS • PFS • PSA response • AEs • HRQL		
Economic analysis	Cost effectiveness in terms of incremental cost per QALY	Pairwise ICERs	Sources of evidence differ for the comparison versus ADT alone and the comparison versus docetaxel + ADT therefore results cannot be combined into incremental analysis
	• Lifetime horizon • Costs from an NHS and PSS perspective • Include any CAA		

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; MA, marketing authorisation; mHNPC, metastatic hormone-naïve prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer.

A.7 Clinical effectiveness evidence

Table 3: Summary of evidence for clinical effectiveness

Study title	LATITUDE (NCT01715285)[7]	STAMPEDE (NCT00268476)[34, 35]
Study design	Double-blind Phase III RCT.	Multi-stage, multi-arm, open-label RCT.
Population	Newly diagnosed high-risk mHSPC.[a] [High-risk is defined as having 2 of the following: Gleason score of ≥8, the presence of ≥3 lesions on a bone scan, or the presence of visceral metastases]	Prostate cancer that was: Newly diagnosed metastatic or node-positive disease, or High-risk locally advanced (with at least two of the following: tumour stage of T3/T4, Gleason score 8–10, PSA level ≥40ng/ml), or Relapsed disease after prior radical surgery or radiotherapy, with high-risk features.
Intervention(s)	AAP + ADT	AAP + ADT
Comparator(s)	Placebo + ADT	ADT, Docetaxel + ADT
Outcomes specified in the decision problem	**Co-primary endpoints:** • OS • rPFS **Secondary endpoints:** • Time to initiation of chemotherapy • Time to subsequent therapy for prostate cancer • Time to SRE[c] • Time to PSA progression • **Safety** • Time to treatment discontinuation • HRQL, including BPI-SF, FACT-P, BFI and EQ-5D-5L • Best overall response	**Primary endpoints:** • OS • FFS[b] **Secondary endpoints:** • Safety • Symptomatic skeletal events • PFS • PSA-specific survival • HRQL, including EQ-5D and EORTC QLQ-C30 with the prostate-specific module QLQ PR25[d]
Reference to section in submission	B.2.3 [p25-32] B.2.6 [p39-59] B.2.7 [p60-62] B.2.8 [p63-70]	B.2.3 [p33-34] B.2.6 [p40-46, Appendix K] B.2.7 [p62, Appendix K] B.2.8 [p67-68]

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; BFI, Brief Fatigue Inventory; BPI-SF, Brief Pain Inventory-Short Form; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQoL; FACT-P, Functional Assessment of Cancer Therapy – Prostate; FFS, failure-free survival; HRQL, health-related quality of life; mHSPC, metastatic hormone sensitive prostate cancer; OS, overall survival; PFS, progression-free survival; PSA, prostate specific antigen; QLQ, Quality of Life Questionnaire; RCT, randomised controlled trial; rPFS, radiographic progression-free survival; SRE, skeletal-related event.
Notes: [a], Patients could have received up to 3 months treatment with ADT prior to randomisation; [b], FFS is defined as radiologic, clinical, or PSA progression, or death from prostate cancer; [c], SRE rates used in the model; [d], HRQL data has not yet been published from the STAMPEDE study.

STAMPEDE was not used to inform the base case of the economic model because it includes a population of patients broader than the licensed indication for AAP + ADT; it was instead included in sensitivity analysis where appropriate. Clinical data from STAMPEDE provide strong supporting evidence for the benefit of AAP + ADT; it represents the single largest evidence base investigating AAP + ADT in the mHSPC setting, and data are specific to UK clinical practice.

A.8 Key results of the clinical effectiveness evidence

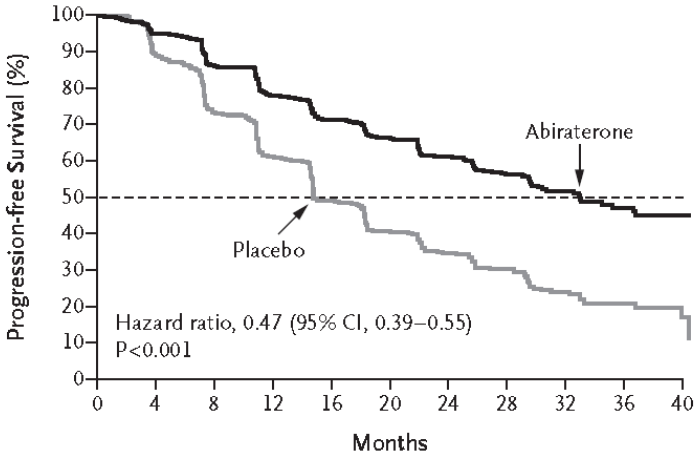
A summary of key clinical data from LATITUDE and STAMPEDE is provided in Table 4, at the end of this section.

A.8.1 Progression-free survival

LATITUDE

At the first interim analysis (IA1), median radiographic progression-free survival (rPFS) was 33.0 months in the AAP + ADT group and 14.8 months in the ADT group. As illustrated by Figure 4, treatment with AAP + ADT was associated with a **53% reduction in the risk of radiographic progression or death** compared with ADT alone (HR=0.47 [95%CI: 0.39–0.55]; p<0.001).

Figure 4: Radiographic progression-free survival of AAP + ADT vs ADT alone



No. at Risk											
Abiraterone	597	533	464	400	353	316	251	177	102	51	21
Placebo	602	488	367	289	214	168	127	81	41	17	7

Key: CI, confidence interval; ITT, intention-to-treat; KM, Kaplan–Meier; rPFS, radiographic progression-free survival. **Source:** Fizazi et al. 2017[7]

STAMPEDE

While rPFS was not an endpoint specified in STAMPEDE, and the subgroup of patients with metastatic disease in the study was broader than the licensed indication for abiraterone in mHSPC, the results for the comparable endpoint of failure-free survival (FFS) (defined as biochemical [PSA] failure, radiologic or clinical progression, or death from prostate cancer) provide strong supporting evidence for the benefit of AAP + ADT over ADT. In the metastatic subgroup, compared to ADT alone, treatment with AAP + ADT was associated with:

- a **57% reduction in the risk of progression or death from prostate cancer** (HR=0.43 [95%CI: 0.36–0.52]; p=NR).
- a **69% reduction in the risk of biochemical failure, progression or death from prostate cancer** (HR=0.31 [95%CI: 0.26–0.37]; p<0.0001).

The *post-hoc* analysis from STAMPEDE comparing AAP + ADT with docetaxel + ADT was conducted for the population of patients who were recruited contemporaneously within the STAMPEDE trial. Of note, this analysis was pre-specified, and thus not statistically powered to detect clinical differences between treatments. Even so, results from the metastatic subgroup showed that, compared to docetaxel + ADT, treatment with AAP + ADT was associated with:

- a **31% reduction in the risk of progression or death from prostate cancer** (HR=0.69 [95%CI: 0.50–0.95]; p=NR).
- a **44% reduction in the risk of biochemical failure, progression or death from prostate cancer** (HR=0.56 [95%CI: 0.42, 0.75]; p<0.001).[35]

These significant results were also observed in the STAMPEDE ITT population, further supporting the superiority of AAP + ADT in delaying disease progression in men with newly diagnosed high-risk mHSPC.

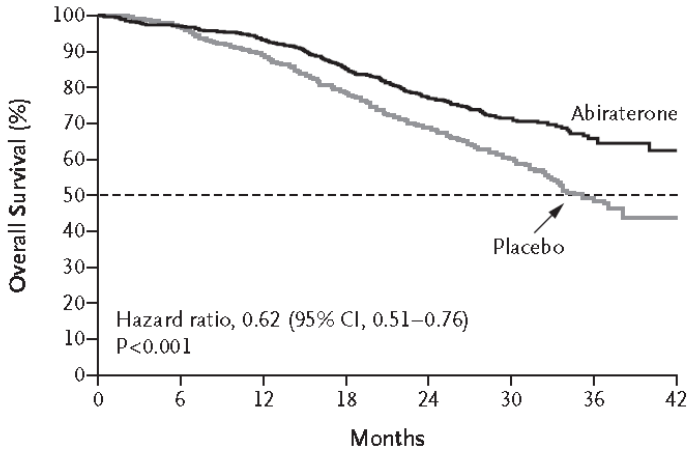
A.8.2 Overall survival

LATITUDE

At IA1, a total of 406 deaths were observed; 169 (28%) in the AAP + ADT group and 237 (39%) in ADT group. Median OS was 34.7 months in ADT group and not reached in the AAP + ADT group, indicating that more than 50% of this patient group were still alive after a median follow-up of 30.4 months. As shown in Figure 5, treatment with AAP + ADT was associated with a **38% reduction in the risk of death** compared with ADT alone (HR=0.62 [95%CI: 0.51–0.76]; p<0.001).

Of note and worth emphasising, the results show a patient's total life expectancy on treatment with ADT alone (34.7 months) is of similar magnitude to the median time a patient spent progression-free on treatment with AAP + ADT (33 months [median rPFS]). Such data are particularly important for those men who are unable to receive chemotherapy in mHSPC.

Figure 5: Overall Survival of AAP + ADT vs ADT alone



Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; CI, confidence interval. **Source:** Fizazi et al. 2017[7]

STAMPEDE

In the metastatic subgroup from STAMPEDE, 150 deaths had occurred in the AAP + ADT group, and 218 (43%) deaths had occurred in the ADT group at the time of the analysis. Treatment with AAP + ADT was associated with a **39% reduction in the risk of death** compared with ADT alone (HR=0.61 [95%CI: 0.49–0.75]; p<0.0001). Although this subgroup is broader than the licensed indication for abiraterone, these survival data strongly support the OS results from LATITUDE.

The *post-hoc* analysis of AAP + ADT versus docetaxel + ADT did not show a statistically significant difference in OS in the metastatic subgroup (HR=1.13 [95%CI: 0.77–1.66]), although these data should be interpreted with caution; this analysis was not pre-specified and thus not statistically powered to detect differences in survival.

Table 4: Summary of Key Clinical Data – B.2.6 (p46)

Study	LATITUDE [ITT]		STAMPEDE [Metastatic subgroup]		STAMPEDE [Metastatic subgroup] *Post-hoc*	
Treatment	AAP + ADT	ADT alone [a]	AAP + ADT	ADT alone [a]	AAP + ADT	Docetaxel + ADT
ITT	597	602	960	957	377	189
Metastatic (%)	597 (100)	602 (100)	500 (52.1)	502 (52.5)	227 (60.2)	115 (60.8)
Patient population	NDx high-risk mHSPC		mHSPC			
Data cut	31-Oct-16		10-Feb-17		04-Mar-17	
Median follow-up	30.4 months		40 months		48 months	
Progression-free survival						
	Radiographic PFS		**PFS** [b]			
Events (%)	239 (40.0)	354 (58.8)	173 (34.6)	301 (60.0)	94 (41.4)	62 (53.9)
Median	33	14.8	-	-	-	-
[95% CI]	29.57-NR	14.69-18.27	-	-	-	-
HR	0.47		0.43		0.69	
[95% CI]	0.39-0.55		0.36-0.52		0.50-0.95	
p-value	<0.0001		-		0.02	
Failure-free Survival [c]						
HR	-	-	0.31		0.56	
[95% CI]	-	-	0.26-0.37		0.42-0.75	
p-value	-	-	-		<0.001	
Overall Survival						
Events (%)	169 (28.3)	237 (39.4)	150 (30.0)	218 (43.4)	89 (39.2)	38 (33.0)
Median	NR	34.7	-	-	-	-
[95% CI]	NR-NR	33.05-NR	-	-	-	-
HR	0.62		0.61		1.13	
[95% CI]	[0.51-0.76]		0.49-0.75		0.77-1.66	
p-value	<0.0001		0.195×10^{-7}		0.53	

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; DOT, duration of treatment; HR, hazard ratio; IQR, inter-quartile range; ITT, intent to treat; mHSPC, metastatic hormone sensitive prostate cancer; NDx, newly diagnosed; NR, not reached; OS, overall survival; rPFS, radiographic progression-free survival; PSA, prostate-specific androgen; SRE, skeletal-related events; Tx, treatment.
Notes: [a], Placebos + ADT; [b], PFS defined as radiologic or clinical progression or death from prostate cancer, [c], FFS defined as radiologic, clinical, PSA progression or death from prostate cancer, [d] analysis was not pre-specified therefore not powered to detect differences in survival
Source: Fizazi et al. 2017[7]; LATITUDE CSR, 2017[36]; James et al. 2017[34]; Sydes et al. 2017[35]; Rydzewska et al. 2017.[37]

A.8.3 Health-related quality of life

When patients progress to develop mCRPC, their HRQL is severely impacted and evidence has shown this is significantly worse for men with aggressive, high-volume (or similarly high-risk) disease.[16] As such, providing access to a treatment which can improve and/or delay deterioration in their quality of life is of upmost importance.

Several quality of life questionnaires were used in LATITUDE to investigate how high risk mHSPC patients' HRQL changed over time, when treated with AAP + ADT versus ADT alone: EQ-5D-5L,[38] Functional Assessment of Cancer Therapy – Prostate (FACT-P),[39] Brief Fatigue Inventory (BFI)[40] and Brief Pain Inventory - Short Form (BPI-SF).[41]

Results consistently demonstrated that treatment of AAP + ADT significantly delayed the deterioration in HRQL for patients with high-risk mHSPC, versus ADT alone, as measured by both the EQ-5D-5L and FACT-P questionnaires (EQ-5D-5L, HR=0.81 [p=0.0038]; FACT-P, HR=0.85 [p=0.0322])[11] This meant patients who were treated with AAP + ADT benefited from a higher quality of life, for a longer time, compared to those given ADT alone.

- **EQ-5D-5L**

Patients' responses to the Visual Analogue Scale (VAS) and their utility scores were significantly improved (p<0.05) when treated with AAP + ADT in LATITUDE, resulting in a utility increment for AAP + ADT of [redacted]. These results indicate that patients treated with AAP + ADT believed their abilities to walk about, wash and dress themselves, perform their usual activities, and function with less pain/discomfort and less anxiety/depression had increased over time; patients also sustained these improvements until progression. (Figure 6A).

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

Patients treated with AAP + ADT in LATITUDE reported consistent delays in pain and prostate cancer symptom progression, as well as degradation of functional status, compared with ADT alone (HR=0.75 [95%CI: 0.65–0.87]; p=0.0001) (Figure 6B).[11] More patients treated with AAP + ADT reported less severe level of pain, less

burdensome symptoms and more energy, allowing them to enjoy their time as they wish, be it with their family or just day-to-day activities.

- **Brief Fatigue Inventory (BFI)**

Treatment with AAP + ADT significantly reduced the risk of BFI worst fatigue intensity progression by 35% compared with ADT (HR=0.65 [95%CI: 0.53–0.81]; p=0.0001).[11] Significant improvements in fatigue were observed early and maintained throughout with AAP + ADT, meaning patients generally feel less tired, less lethargic and more able to spend time doing the things of value to them, regardless of their disease and treatment. (Figure 6C).

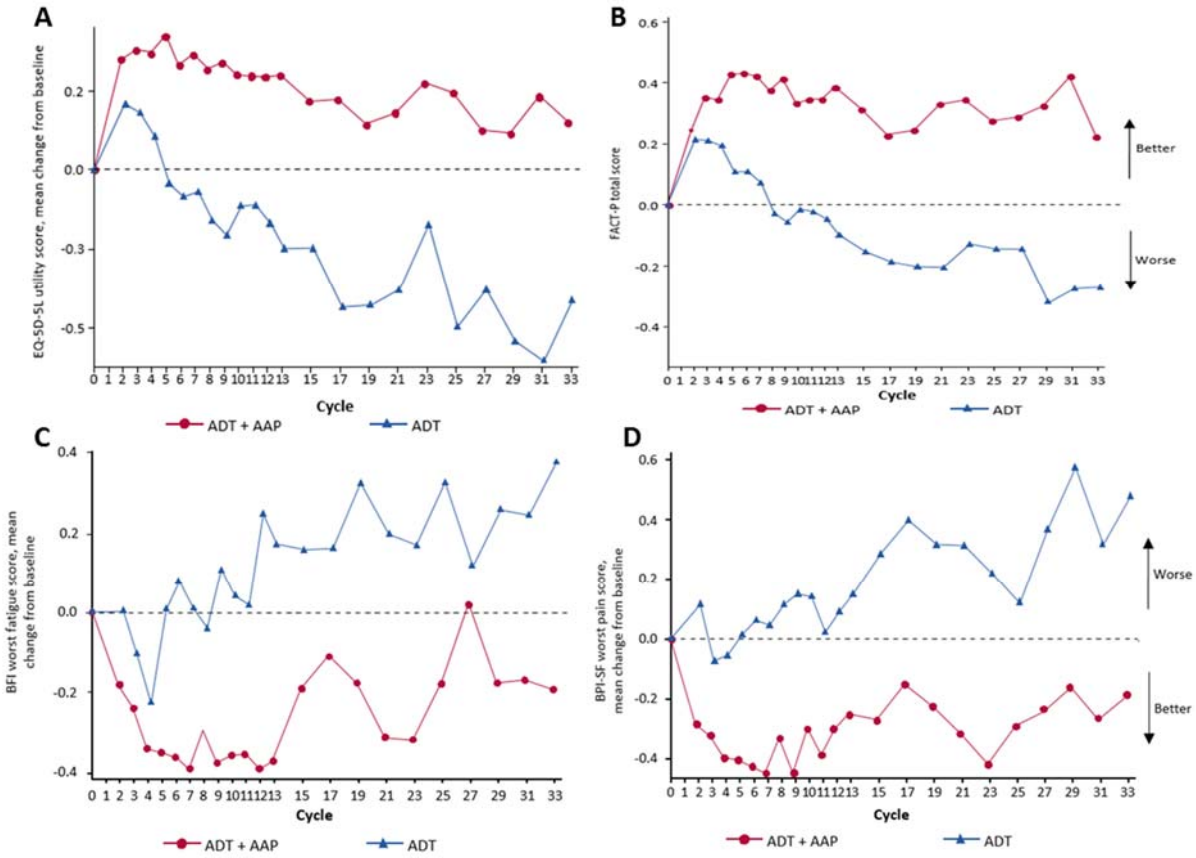
- **Brief Pain Inventory-Short Form (BPI-SF)**

Time to pain progression was defined as the time interval from randomisation to the first date a patient experienced a ≥30% increase from baseline in the BPI-SF worst pain intensity observed at two consecutive evaluations ≥4 weeks apart. Treatment significantly delayed the progression of pain compared to ADT alone by 31% (HR=0.70 [95% CI: 0.58–0.83], p<0.0001).[11]

Mean changes from baseline in worst pain intensity, pain interference, and average pain progression improved with AAP + ADT versus ADT alone at most time points evaluated (Figure 6D).[11] These improvements were observed as early as Cycle 2 and maintained through Cycle 33, meaning patients on AAP + ADT reported reduction in pain as early as two months after starting treatment.

Since patients treated with AAP + ADT consistently reported less severe pain, treatment allowed them to go on with their lives more comfortably and enjoy time as they wish, be it spending time with the family, doing day-day-chores, or activities elsewhere.[11]

Figure 6: PRO measures for EQ-5D-5L, FACT-P and BFI – B.2.6 (p48-53)



A= EQ-5D-5L, **B**=FACT-P, **C**=BFI, **D=**BPI-SF
Key: BFI, Brief Fatigue Inventory; CI, confidence interval; EQ-5D-5L, EuroQoL 5-Dimension 5-Level; VAS, visual analogue score; FACT-P, Functional Assessment of Cancer Therapy – Prostate Cancer
Source: Chi et al. 2018.[11]

A.8.4 Secondary Endpoints

In addition to meeting both co-primary endpoints in LATITUDE, AAP + ADT showed consistently significant benefit in all pre-specified secondary endpoints. Indeed, compared with ADT alone, treatment with AAP + ADT:

- **Significantly delayed time to subsequent therapy for prostate cancer**

Median time to subsequent therapy was not reached in the AAP + ADT group versus 21.6 months for the ADT group (HR=0.42 [95%CI: 0.35–0.50], p<0.0001) (Figure 7A).

- **Significantly delayed time to life-extending subsequent therapy**

At IA1, twice as many patients from the ADT group had required life-extending subsequent therapy versus the AAP + ADT group (40.9% vs 20.9%, respectively). AAP + ADT significantly delayed the time to initiating life-extending subsequent

therapy (HR=0.37 [95%CI: 0.29–0.45]; p<0.0001). Docetaxel was the most common treatment after AAP + ADT or ADT alone (17.8% and 31.1%, respectively).

- **Significantly delayed time to initiation of chemotherapy**

The median time to initiation of chemotherapy was not reached in the AAP + ADT group and was 38.9 months in the ADT group (HR=0.44 [95%CI: 0.35–0.56]; p<0.0001). This translated to a 56% reduction in risk of initiating chemotherapy and represents an endpoint of considerable value to patients (Figure 7B).

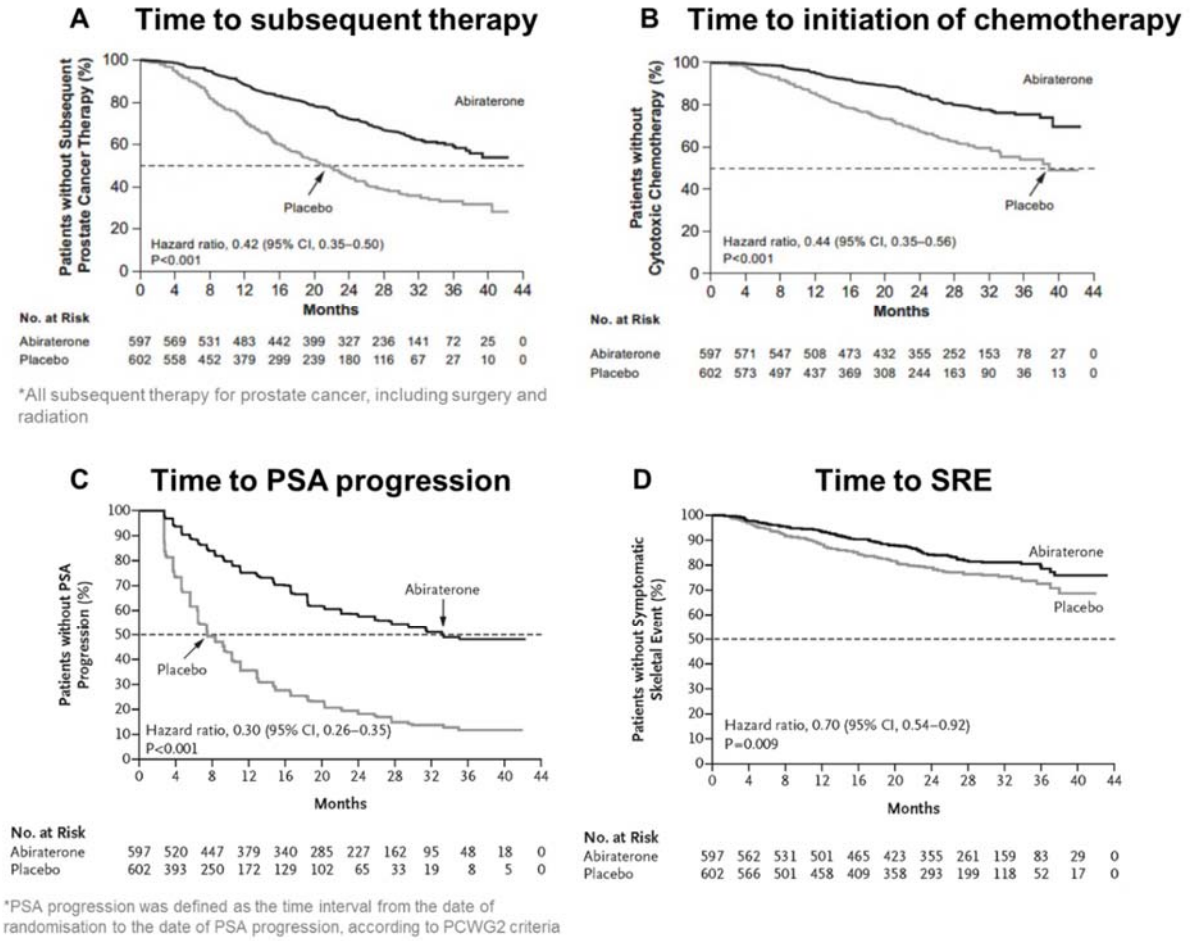
- **Significantly delayed time to PSA progression [PCWG2 criteria][42]**

Median time to PSA progression with AAP + ADT was 33.2 months, and only 7.4 months with ADT (HR=0.30 [95% CI: 0.26–0.35], p<0.0001) (Figure 7C).

- **Significantly reduced the risk of skeletal-related events (SREs)**

Although the median time to SRE was not reached for either treatment group, AAP + ADT showed a significant reduction in the risk of SREs versus ADT (HR=0.70 [95%CI: 0.54–0.92], p=0.0086), which is beneficial for patients given SREs are associated with both increased pain and significant healthcare costs to patients (Figure 7D).

Figure 7: Time to event analyses for subsequent treatment, initiation of chemotherapy, PSA progression and first SRE – B.2.6 (p54-59)



Key: CI, confidence interval; PSA, prostate specific antigen; SRE, skeletal related event.
Source: LATITUDE CSR (2017)[36]

A.9 Evidence synthesis

Four trials were identified that provided relevant evidence for consideration in this submission. Table 5 provides a summary of the trials used to derive estimates of comparative effectiveness.

Table 5: Trials used for evidence synthesis – B.2.10 (p75-78)

	LATITUDE	GETUG-AFU 15	CHAARTED	STAMPEDE
NCT number	NCT01715285	NCT00104715	NCT00309985	NCT00268476
Trial population	NDx HR mHSPC	mHSPC	mHSPC	mHSPC
Comparison(s)	• AAP+ADT • ADT alone	• Docetaxel+ADT • ADT alone	• Docetaxel+ADT • ADT alone	• SOC • AAP+SOC • Docetaxel+SOC
Prior adjuvant hormonal therapy	Not permitted, except for up to 3 months of ADT or 1 course of palliative radiation or surgical therapy	Permitted if ADT discontinued 12 months before study entry	Permitted if duration of ADT ≤24 months and progression occurred >12 months after completion	Permitted if ADT discontinued 12 months before study entry + ≤12 month in duration
Population/ subgroup of interest	ITT	Newly diagnosed high-volume[a] subgroup	Newly diagnosed high-volume[a] subgroup	Metastatic subgroup
# pts with mHSPC	1,198	385	790	1,817[b]
% NDx mHSPC	100%	71%	75%	100%
Pts high-volume[a]	79.7% (955/1,198)	52% (202/385)[c]	65% (514/790)	Not reported[d]
Median age, yrs (range)	67 (33-92)	64 (57–70)	64 (36–91)	65 (42–84)
Gleason score 8–10	98%	56%	61%	70%
Performance status of 0–1	97.5%	Not reported	98%	99%
Median follow-up	30.4 months	83.9 months	53.7 months	40 months[e]
Primary endpoint	Median OS	Median OS	Median OS	Median OS

Key: ADT, androgen deprivation therapy; ITT, intent to treat; OS, overall survival; PSA, prostate-specific antigen; SOC, standard of care
[a]High-volume disease defined as visceral metastases and/or ≥4 bone metastases with at least one metastasis beyond the pelvis or vertebral column
[b]Number of patients with metastatic prostate cancer at randomisation
[c]High volume disease was retrospectively defined following the CHAARTED definition
[d]An analysis of patients with high-volume mHSPC in the STAMPEDE trial is not currently available
[e]Median follow-up reported for all randomised patients

1. Evidence synthesis: AAP + ADT versus ADT alone

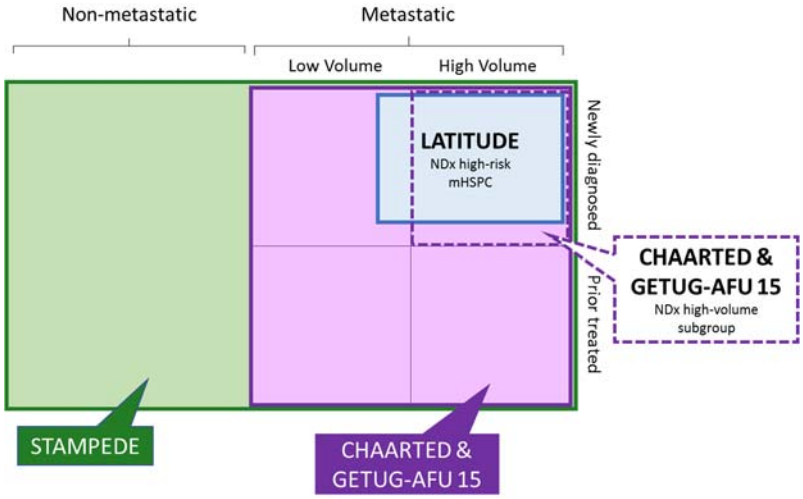
The LATITUDE trial provides randomised, robust head-to-head evidence of AAP + ADT versus ADT alone in newly diagnosed high-risk mHSPC and is therefore the most appropriate source of data to inform this comparison. LATITUDE also provides the direct safety data relevant to this comparison.

2. Evidence synthesis: AAP + ADT versus docetaxel + ADT

Indirect treatment comparison (ITC) was used to derive estimates of relative effectiveness between AAP + ADT and docetaxel + ADT in newly diagnosed high-risk mHSPC. Four studies had potentially comparable trial populations, study design and

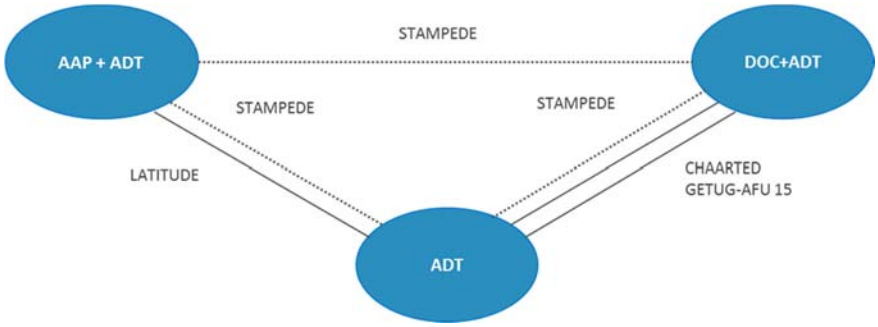
outcomes. As illustrated in Figure 9, the newly diagnosed high-volume subgroups from CHAARTED and GETUG-AFU 15 were most comparable to the ITT population from LATITUDE and therefore used in the base case; the metastatic population from STAMPEDE is broader than the licensed indication for abiraterone and thus reserved for scenario analysis.

Figure 8: Comparison of trial populations – B.2.10 (p73)



The network of trials is illustrated in Figure 9. As discussed in B.2.10, there was heterogeneity between the measures used to determine disease progression across all four trials in the network. GETUG-AFU 15 was the only other trial to utilise rPFS as an endpoint, thus enabling a like-for-like comparison with LATITUDE.

Figure 9: Comparison of trial populations and ITC network – B.2.10 (p80)



Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; DOC, docetaxel,
Notes: Continuous lines represent trials contributing to the base case. Dotted lines represent the addition of STAMPEDE in sensitivity analyses.

The results of the base case Bayesian ITC for PFS and OS are detailed in Table 6. Results showed a positive trend towards AAP + ADT having the highest probability of being the optimal treatment for delaying disease progression and extending survival

(93% and 72% probability, respectively). This holds true for all ITC iterations tested in scenario analyses presented in B.2.10 (p81).

Table 6: Base case Bayesian ITC of AAP + ADT vs docetaxel + ADT

Outcome for Base Case	AAP + ADT vs. ADT alone	ADT alone vs. docetaxel + ADT		AAP + ADT vs. docetaxel + ADT	
	LATITUDE	CHAARTED	GETUG-AFU 15	ITC	
	ITT	NDx HV	NDx HV	HR [95% CrI]	P_{AA-Doc}
OS HR [95% CI]	0.62 (0.51, 0.76)	0.63 (0.49, 0.81)	0.78 (0.54, 1.12)	**0.92 (0.69, 1.23)**	**71.8%**
rPFS[a] HR [95% CI]	0.47 (0.39, 0.55)	-	HV:[b] 0.61 (0.44, 0.83)	**0.76 (0.53, 1.10)**	**92.9%**

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; CrI, credible interval; HR, hazard ratio; HV, high-volume; ITT, intent-to-treat; NDx, newly diagnosed; OS, overall survival; rPFS, radiographic progression-free survival
Notes: $PA_{A>Doc}$, Bayesian pairwise probability for AAP+ADT being more effective compared with DOC+ADT; [a], Definitions of rPFS differed across trials, [b], included prior treated

While not used to inform the economic model, it is important to highlight two additional independent ITCs which have been published (Vale et al, 2017[9] and Wallis et al, 2017).[10] Both strongly support the consistent trend in benefit with AAP + ADT over docetaxel + ADT for extending survival and delaying disease progression (see B.2.10).

Bayesian ITCs were also conducted for FACT-P (i.e. functional status) and BPI-SF (i.e. pain) scores to assess the relative difference in PROs between AAP + ADT and docetaxel + ADT. Results showed that treatment with AAP + ADT elicited benefits in patients' HRQL versus docetaxel + ADT from three months and were sustained for at least one year after treatment.[43] Results are further detailed in B.2.10 (p86).

A.9.1 Safety Outcomes

AAP has an established safety profile with over six years of clinical experience in the NHS. No new safety signals were identified in LATITUDE compared to those already characterised through previous trials in mCRPC. AAP + ADT was well tolerated, with a comparable incidence of TEAEs to ADT alone. In line with its known safety profile, the most frequently reported grade 3/4 TEAEs were mineralocorticoid-associated AEs. All events were however medically manageable, only rarely required treatment discontinuation, and seldom led to serious consequences. These findings were further supported by results from STAMPEDE.

Comparison of safety outcomes between AAP + ADT and docetaxel + ADT was only possible through Bayesian ITC of the LATITUDE and GETUG-AFU 15 trials. The results, detailed in B.2.10 (p82-84), showed a [redacted]. These findings are supported by real-world experience data with docetaxel + ADT, reporting that the rates of grade ≥3 neutropenia and febrile neutropenia were as high as 36.3% and 18.2%, respectively. Although populations may vary, these same AEs were only reported in 0.5% and 0.2% of patients treated with AAP + ADT in the LATITUDE study.

A.10 Key clinical issues

All analyses are based on clinical data from LATITUDE IA1, at which the median follow-up of patients was 30.4 months follow-up. Whilst the median OS was not reached in the AAP + ADT group, compared to 34.7 months in the ADT group, these data show more than half of the treatment group were still alive at IA1. A second interim analysis (IA2) of the study is due imminently. Indeed, additional data from IA2 could reaffirm long term predictions, after appropriate adjustments have been made for crossover permitted following the independent data and safety monitoring committee's unanimous recommendation to unblind the trial based on compelling IA1 results.[7]

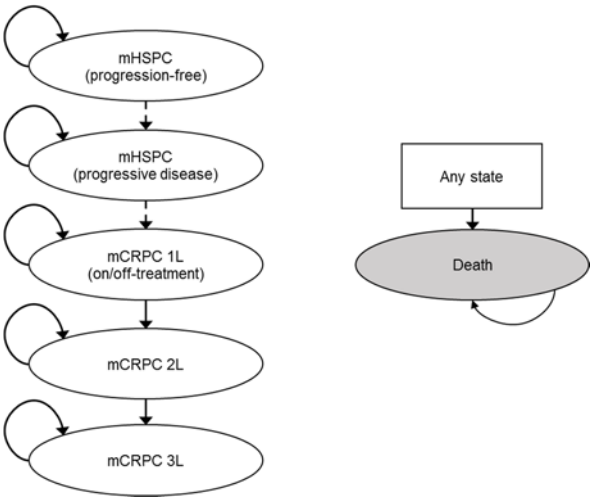
Most patients in LATITUDE went on to receive subsequent therapies upon progression to mCRPC; 40% of patients treated with ADT alone received life-extending subsequent therapy whilst only 20% of patients treated with AAP + ADT did. Given the study follow-up period was not long enough to capture the entire treatment pathway for the majority of patients, there is still uncertainty around the impact of subsequent therapy on survival, and minimal data to inform survival analysis adjusted for non-permitted sequences in the UK.

The newly diagnosed high-volume mHSPC subgroups from CHAARTED and GETUG-AFU 15 and the ITT population from LATITUDE informed the base case ITC. The comparability of these populations has been validated by both published literature and *post-hoc* analysis of LATITUDE.[22] Full details on the Bayesian ITC methods are presented in B.2.10.

A.11 Overview of the economic analysis

An overview of the modelling approach is provided in Table 7 with full details and justifications presented in B.3.2.

Table 7: Over of the model approach

Model approach	A *de novo* Markov model was developed to evaluate the cost-effectiveness of AAP + ADT in men with newly-diagnosed high-risk mHSPC compared to docetaxel + ADT and ADT alone.
Model structure B.3.2 (p106)	 **Key:** 1L, first-line; 2L, second-line; 3L, third-line; mCRPC, metastatic castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer.
Transition probabilities	Transition probabilities were estimated from LATITUDE trial data using multi-state modelling (MSM).[30]
Definition of progression	rPFS was used in the base case and time to subsequent treatment (TTST) was tested in scenario analysis.
Model outcomes	Health effects were measured in terms of life years (LYs) and quality-adjusted life years (QALYs).
Time horizon	Costs and health effects were accrued over a 20-year time horizon, which is equivalent to lifetime given the typical age a patient is diagnosed with mHSPC (i.e. the mean age in LATITUDE was 67 years).
Cycle length	Cycle length was weekly for the first 52 weeks of the model, increasing to 28 days thereafter. This allowed the model to accurately capture the costs of docetaxel which is given every three weeks over a maximum of 18 weeks. It also minimises the computational burden of the model.

A.12 Incorporating clinical evidence into the model

AAP + ADT vs ADT alone: The Kaplan-Meier data from LATITUDE for rPFS, TTST and OS were applied directly into the model for the first five months, after which the transition probabilities estimated through the MSM analysis were applied.

AAP + ADT vs docetaxel + ADT: HRs derived from the Bayesian ITC for docetaxel + ADT versus AAP + ADT were applied to the estimated transition probabilities for AAP + ADT; the mean HRs for rPFS and OS were 0.76 and 0.92, respectively.

Time on treatment: LATITUDE data were used to conduct a restricted means analysis to estimate the mean time on treatment relative to the mean time spent in rPFS (ratio of [redacted] for AAP + ADT).

Post-progression survival: The mean treatment-free interval (TFI) was estimated for both treatment arms to give the average time between rPFS and the start of subsequent therapy. A constant transition probability was estimated by applying an exponential distribution to the mean TFI values for each treatment arm.

In the base case, survival during the mCRPC phase was estimated in three steps:

1. Survival curves were taken from the base case analysis in the previous appraisal of AAP and BSC in mCRPC [TA387], which were extrapolated from the COU-AA-302 study. All life-extending subsequent therapies in mCRPC were assumed to have the same relative effectiveness as AAP, as validated by clinical experts in prostate cancer.[30]

2. The weighted average survival was calculated based upon the expected market share of each treatment in UK practice, as validated by clinical experts.[30]

3. The curves were then calibrated to adjust for the population differences between LATITUDE and COU-AA-302. Extrapolated curves were validated by a UK clinical expert in prostate cancer with all deemed to project clinically plausible estimates, as illustrated in B.3.3.

The model also explored a scenario where the long-term survival from LATITUDE was estimated by the transition probabilities from the MSM analysis alone, without the inclusion of external survival data. Subsequent therapies were costed as per LATITUDE in line with the effectiveness data.

Time on treatment was modelled in a time-dependent manner during 1L mCRPC to accurately capture treatment costs. Transition probabilities after the 1L mCRPC health

state were estimated by using mean health state durations from the previous submission of AAP [TA387], and assuming a constant probability over time.

Safety: The frequencies with which patients were assumed to experience a range of grade 3/4 AEs and SREs were taken from the literature for each comparator in mHSPC and subsequent therapy in mCRPC. The frequencies were estimated as annual probabilities from the relevant clinical trial data for each treatment.

A.13 Health-related quality of life data

In the LATITUDE trial, HRQL was measured using the EQ-5D-5L; the crosswalk algorithm by van Hout et al.[44] was used to map values to the EQ-5D-3L scale in line with NICE DSU guidance. Full detail on how utilities for the model were derived from LATITUDE is provided in in B.3.4 (p130-136).

A HRQL treatment effect was applied to patients receiving AAP in mHSPC and, in line with past appraisals, the AAP treatment effect from TA387 was applied to those who received AAP in mCRPC. As docetaxel was not an intervention investigated within LATITUDE, values derived from the Time-Trade Off (TTO) utility study were used which included an on- and off-treatment effect associated with docetaxel. The on-treatment effect was applied for the time patients received docetaxel, and the off-treatment effect was applied for the remainder of the pre-progression period.

The utility of patients in the 2L and 3L mCRPC states was estimated by using utility values from TA387 to estimate the relative utility decline of patients over time. These relative values were then applied to the utility value of progressed patients estimated from the LATITUDE utility analysis. AE disutilities from the literature were applied in the base case. A summary of the utility values included in the model is presented in B.3.4 (p136).

A.14 Cost and healthcare resource

Costs for drug acquisition, administration, AEs, and monitoring (scheduled and unscheduled MRU) were all considered; full detail on costs and healthcare resource use is provided in B.3.5 and a summary of all cost parameters included in the model is presented in Appendix R.

A.15 Key model assumptions and inputs

Table 8: Key model assumptions and inputs – B.3.6 (p147-149)

Assumption	Justification	Submission
There is a link between progression status and OS.	In utilising external data from the COU-AA-302 trial, the model assumes that there is no relative PPS benefit for AAP + ADT compared to ADT alone or docetaxel + ADT. Evidence from previous prostate cancer trials has demonstrated that PFS is a strong predictor of OS, and therefore confirms that this is a clinically plausible assumption.[45, 46] This also results in predicted OS curves which provide a good fit to the KM data from LATITUDE (presented in Section B.3.3). As the existence of a PPS survival benefit is uncertain, assuming no additional benefit in the absence of clear evidence was the most conservative assumption, but the chosen model structure gives us the flexibility to test this.[29]	Section B.3.2
Utility status is dependent on treatment, progression and AEs.	Analysis of EQ-5D data from LATITUDE indicated that each of these coefficients were significant when assessed both univariately and as part of the regression equation.	Section B.3.4
AAP treatment effect utility coefficient is applied for the period patients are assumed to receive AA.	The regression analysis was coded to look at the difference between the two arms regardless of whether patients were on or off treatment. Therefore, applying this for a shorter period of time under-estimates the treatment effect gained from being treated with AAP, and is therefore a conservative assumption. Scenarios are explored where the treatment effect is applied until death and where it is set to zero.	Section B.3.4
Proportional hazards assumption holds after five months for OS and PFS within LATITUDE.	Inspection of the log cumulative hazard plots for OS, rPFS and TTST revealed that the curves diverged up until five months, before remaining parallel with one another. KM data were therefore directly inputted into the model for the first five months, before the transition probabilities estimating through MSM are applied.	Section B.3.3
Subsequent therapies received within LATITUDE are not in line with permitted UK clinical practice.	A number of life-prolonging subsequent therapies were received by patients in LATITUDE, with more patients in the ADT arm receiving active subsequent therapies compared to the AAP arm. The IPCW analysis demonstrates this imbalance between treatment arms diluted the relative survival benefit of AAP + ADT vs ADT. Findings from the clinical advisory board also confirm different proportions of these subsequent therapies would be given in UK clinical practice.[30] The model structure allows for adjustment of the costs and efficacy of subsequent therapies, and therefore has the flexibility to explore different assumptions. Scenarios are explored where the proportions of subsequent therapy assumed are in line with clinical practice or LATITUDE	Section B.3.5

Assumption	Justification	Submission
	data. The uncertainty around this is best represented by presenting the range of ICERs from each scenario.	
Radiographic progression is a suitable proxy for disease progression.	This was firstly based on the findings from the clinical advisory board[30] where clinicians stated that they believe radiographic progression to be the most objective measure of progression, and a good predictor of a change in HRQL. The selection was also made based on the availability of patient-level data in LATITUDE, as well as precedent from previous prostate cancer submissions.	Section B.3.2
The vast majority of patients will receive three or fewer lines of active treatment for mCRPC.	This assumption was validated during the clinical advisory board[30], with clinicians stating that patients would typically receive up to three active therapies, followed by BSC. In LATITUDE, only a small number of patients received more than three lines of active subsequent therapy.	Section B.3.2
The results from the ITC including high-volume patients from docetaxel trials are translatable to the population within the marketing authorisation.	The analysis undertaken to investigate whether high-volume disease was an effect modifier in the LATITUDE trial found there to be no statistically significant treatment interaction effect in the outcomes for patients with high-volume versus non-high-volume disease within LATITUDE. Therefore, the results from the ITC were assumed to be translatable to the population within the marketing authorisation.	Section B.3.2
ADT is received until death.	This is reflective of UK practice, as advised by UK clinicians. It is also supported by TA404 (degarelix for treating advanced hormone-dependent prostate cancer). This is a conservative assumption as patients in the AAP+ADT arm have longer OS compared to those treated with ADT alone or docetaxel+ADT. Therefore, this assumption increases treatment costs for patients treated with AAP+ADT relative to patients on docetaxel+ADT or ADT alone.	Section B.3.5
Docetaxel is given for a maximum of six cycles.	This is applied according to NHS commissioning policy. This is also in line with the dosing schedules used in the CHAARTED and STAMPEDE studies and reflects UK clinical practice. In GETUG-AFU 15, patients received up to nine cycles of docetaxel. Therefore, the model overestimates docetaxel effectiveness relative to the cost, and therefore, assuming six cycles of therapy is a conservative assumption.	Section B.3.5

Key: AA, abiraterone acetate; AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; AE, adverse event; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HRQL, health-related quality of life; HVD, high volume disease; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weighted; ITC, indirect treatment comparison; PFS, progression free survival; PPS, post-progression survival; mCRPC, metastatic castration resistant prostate cancer; MSM, multi-state modelling; OS, overall survival; rPFS, radiographic progression free survival; TTST, time to subsequent therapy.

A.16 Base-case ICER (deterministic)

[redacted]

Results show that, under the confidential CAA, AAP + ADT is a highly cost-effective use of NHS resources in men with newly diagnosed high-risk mHSPC, regardless of the comparator treatment considered. [redacted]

Table 9: Base case results – B.3.7 (p151)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	3.43	2.33	19,066	1.56	1.09	17,418
AAP + ADT	[redacted]	4.99	3.42				
Docetaxel + ADT	[redacted]	4.32	2.82	10,618	0.67	0.60	17,828
AAP + ADT	[redacted]	4.99	3.42				

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

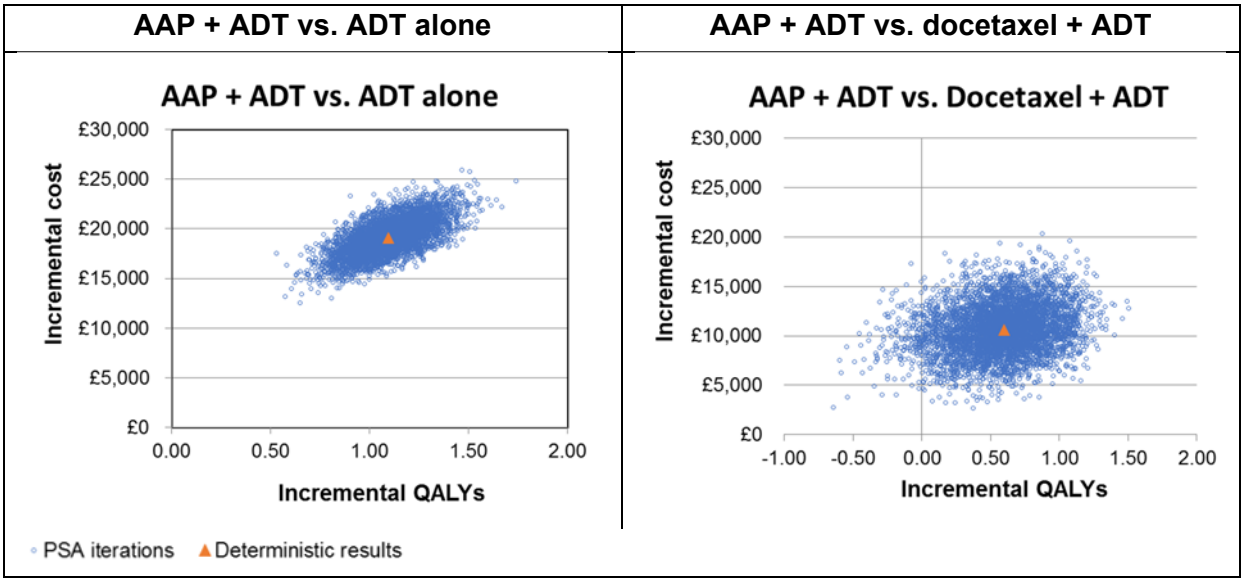
A.17 Probabilistic sensitivity analysis

Table 10: PSA results - B.3.8 (p151)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	3.43	2.33	19,105	1.57	1.10	17,417
AAP + ADT	[redacted]	5.00	3.42				
Docetaxel + ADT	[redacted]	4.35	2.84	10,686	0.66	0.59	18,234
AAP + ADT	[redacted]	5.00	3.42				

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

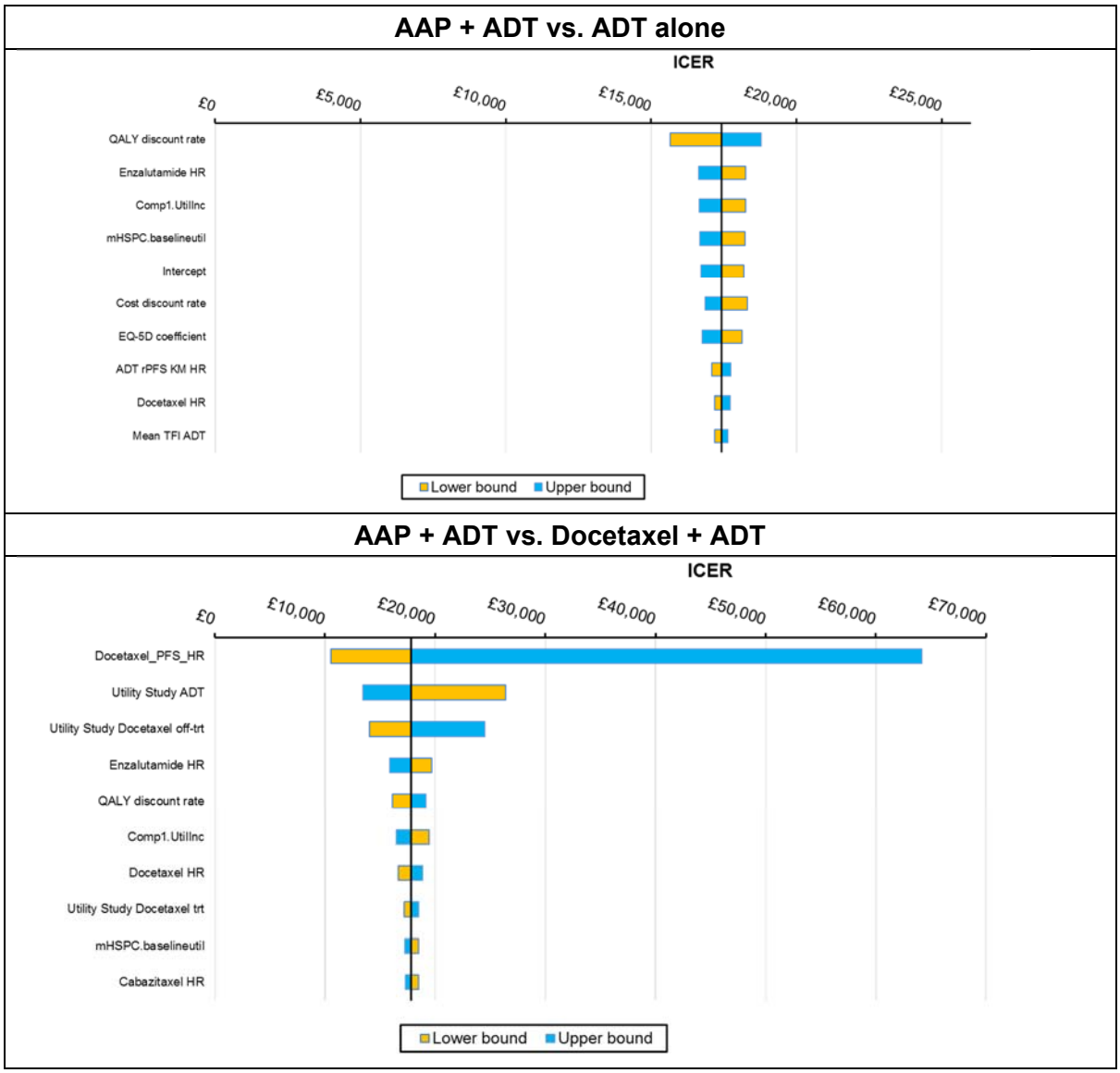
Figure 10: Scatterplots of probabilistic results for AAP + ADT vs. ADT alone and vs. docetaxel + ADT B.3.8 (p152)



Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

A.18 Key sensitivity and scenario analyses

Figure 11: Tornado diagrams for AAP + ADT vs. ADT alone - B.3.8 (p155)



Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival; QALY, quality-adjusted life year; rPFS, radiographic progression-free survival; TFI, treatment free interval

Table 11: Key scenario analyses – B.3.8 (p157)

Model assumption	Scenario	ICER vs ADT alone	ICER vs docetaxel + ADT
Base Case		**£17,418**	**£17,828**
Probabilistic		**£17,417**	**£18,234**
Loss of exclusivity	[redacted]	[redacted]	[redacted]
Definition of progression	TTST used as an alternative definition of progression	£14,079	£11,287

Model assumption	Scenario	ICER vs ADT alone	ICER vs docetaxel + ADT
Survival and subsequent therapy source	Survival estimates and subsequent therapy market shares estimated from LATITUDE data alone	£21,504	£22,218
ITC	ITC including STAMPEDE	£17,418	£17,813
Time horizon	15 years	£17,508	£18,048
	10 years	£18,100	£19,435
	5 years	£25,856	£33,085
AA utility increment	Applied until death	£16,775	£16,656
	No increment applied	£18,697	£20,394
Docetaxel utility decrement	On-treatment decrement applied only	£17,418	£20,027
AE disutilities	Using literature values alone	£17,414	£17,818
	Set to zero	£17,361	£17,578
mCRPC utilities	Assumed constant through mCRPC	£17,508	£17,975
AA increment (mCRPC)	AA increment from TA387 removed during mCRPC	£17,333	£17,667
Subsequent treatment ITC	Different HR are applied for each subsequent Tx based on subsequent therapy ITC	£17,129	£17,095
Vial wastage	Set to zero	£15,997	£15,077
Docetaxel cost source	MIMS price is assumed	£20,273	£16,305
AE/SRE HRQL source	Values sourced from regression	£17,510	£31,389

A.19 Innovation

Abiraterone was discovered in the UK and it is the first novel agent to be licensed in mHSPC in combination with ADT.[6] It has been described by the Chief Executive of the Institute of Cancer Research in London as a *"highly innovative treatment that not only improves survival rates but has lower rates of side-effects than conventional therapies*".[47] AAP already has an established efficacy and safety profile in mCRPC, and these new trial data strongly support its earlier use in the treatment pathway to optimise health outcomes and prolong patients' HRQL.[7, 11, 34] Results from LATITUDE and STAMPEDE have excited the clinical community, and the Chief Investigator of STAMPEDE was quoted saying *"these are the most powerful results I've seen from a prostate cancer trial – it's a once in a career feeling. This is one of the biggest reductions in death I've seen in any clinical trial for adult cancer."*[47]

These data give patients with newly diagnosed metastatic disease hope for the future and should not be underestimated, especially for those who cannot receive chemotherapy. AAP + ADT is an innovative regimen that not only demonstrates gains in survival, but improves quality of life and delays progression to mCRPC, a disease state which is associated with increased healthcare costs and further reduced HRQL.[20, 21]

Patients' preferences are exceedingly important to acknowledge, although challenging to quantify and rarely accounted for in cost-effectiveness analysis. Many men cannot access chemotherapy, and others are not willing to undertake the course of chemotherapy at this stage in their lives;[30] AAP + ADT significantly delays the time to chemotherapy and provides these men with the only alternative life-prolonging treatment option.[7]

Lastly, AAP is an oral treatment taken at home, alongside the required routine monitoring, while the uptake of docetaxel in early prostate cancer is likely to have increased the burden on chemotherapy clinics which are already overstretched. As such, uptake of AAP + ADT in the NHS will benefit both patients and their carers/loved ones currently faced with the choice between undergoing docetaxel + ADT through chemotherapy clinics, or continued ADT monotherapy with fewer survival benefits.

A.20 Budget impact

The net budget impact described in Table 12 is based upon the assumption that AAP + ADT will be funded by the NHS from October 2018.

Table 12: Budget impact – Budget Impact submission (p23)

	Year 1 2018	Year 2 2019	Year 3 2020	Year 4 2021	Year 5 2022
Eligible population for AAP + ADT	3,462	3,490	3,517	3,546	3,574
Population expected to receive AAP + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of the treatment pathway without AAP+ADT	£964,623	3,393,207	9,202,562	£18,060,378	£27,234,091
Cost of the treatment pathway with AAP+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Please see separate Budget Impact submission and Appendix M for epidemiology figures.					

A.21 Interpretation and conclusions of the evidence

AAP + ADT offers significant survival benefit to those men currently treated with ADT alone.

AAP + ADT is associated with a clinically and statistically significant survival benefit compared to ADT alone, demonstrating a **38% reduction in the risk of death** and a **53% reduction in the risk of radiographic progression or death**. Results from the STAMPEDE metastatic subgroup demonstrated comparable significant benefit.

AAP + ADT offers benefit in PFS and at least comparable, but likely superior, benefit in survival benefit to those men currently treated with docetaxel + ADT.

Results from Bayesian ITC demonstrated AAP + ADT had a **71.8% and 92.9% probability of superiority with regards to OS and rPFS**, respectively, compared to docetaxel + ADT. The direct comparison of AAP + ADT versus docetaxel + ADT from STAMPEDE supported such findings, showing AAP + ADT significantly **reduced the risk of FFS by 44% and the risk of PFS by 31%** compared to docetaxel + ADT. Results of two independent NMAs both provided further support for AAP + ADT likely being the optimal treatment option in this patient cohort.

AAP + ADT significantly improves pain, fatigue and patients' HRQL, sustaining these benefits at least until disease progression.

Compared to ADT alone, AAP + ADT showed a significant reduction in the risk of pain progression, risk of fatigue progression, and worsening of HRQL.

Results of the ITC showed treatment with AAP + ADT was [redacted]

AAP + ADT offers a favourable benefit–risk profile to those men currently treated with ADT alone.

AAP + ADT has an established safety profile with six years of clinical experience in the NHS. Treatment with AAP + ADT was well tolerated with comparable incidence of TEAEs to ADT alone.

AAP + ADT offers an alternative treatment option, with favourable long-term safety profile, to those men currently treated with docetaxel + ADT.

Data published on real-world experience with docetaxel + ADT, since it became routinely available through the NHS, reported the rates of grade ≥3 neutropenia and febrile neutropenia to be as high as 36.3% and 18.2%, respectively. While there are potential variations in populations, these same AEs were only reported in 0.5% and 0.2% of patients treated with AAP + ADT in the LATITUDE study.

AAP + ADT provides the option to delay chemotherapy in those men who do wish to undertake immediate treatment with docetaxel + ADT.

This is particularly relevant to patients wishing to delay exposure to the potential toxicities associated with chemotherapy. Indeed, these benefits are particularly important for men who are either unsuitable for, or unable to receive, chemotherapy at diagnosis. Acknowledging the importance of patient preference, AAP + ADT provides the only efficacious alternative to ADT alone for these men.

Under the confidential CAA, AAP + ADT provides a cost-effective use of NHS resources regardless of the comparator considered.

Cost-effectiveness analyses have showed AAP + ADT is cost-effective, regardless of the comparator considered. AAP + ADT is associated with an ICER of £17,828/QALY when compared to docetaxel + ADT and an ICER of £17,418/QALY when compared to ADT alone.

Under the confidential CAA, AAP + ADT provides an affordable treatment option to the NHS in all patients with newly diagnosed high-risk mHSPC.

When all costs associated with the treatment pathway are considered over a three-year period, AAP + ADT results in a net budget impact of [redacted] in Year 1, 2 and 3, respectively. These figures account for the full licensed indicated population of AAP + ADT, acknowledging the distribution of comparator treatments currently used to manage these patients.

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Single technology appraisal

Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer [ID945]

Document B

Company evidence submission

IA2 addendum

March 2018

File name	Version	Contains confidential information	Date
ID945_AbirateronemHSPC_IA2 Addendum_FINAL – 170418 [ACIC]	**1.0**	**Yes/no**	**17/04/2018**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Contents

Tables and figures

Clinical effectiveness results of the relevant trials

This document provides updated key efficacy data from the pre-planned second interim analysis (IA2) of the LATITUDE trial. The objective of this IA2 was to obtain results of updated overall survival (OS) and other secondary endpoints. All data presented herein are taken from the updated clinical study report (CSR), which is based on a cut-off date of 2nd October 2017, at which point median follow-up was 41.36 months.[1] Of note, the final analysis of radiographic progression-free survival (rPFS) was planned after 565 events and was therefore reached at the first interim analysis (IA1) and presented in the pivotal CSR provided to NICE at time of original submission; as such, results for this endpoint have not been updated and are not presented in this document.

Consistent with the results presented at IA1, the significant benefit of adding abiraterone acetate plus prednisolone (AAP) to androgen deprivation therapy (ADT) was maintained with longer follow-up for both OS and secondary endpoints; this was despite [redacted] out of 602 patients ([redacted]) in the ADT alone group having crossed over to receive open-label treatment with AAP + ADT. As such, the results of IA2 confirm the value of AAP + ADT in men with newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC).

Patient disposition

A total of 597 patients in the AAP + ADT group and 602 patients in the ADT alone group were included in both the intention-to-treat (ITT) and safety populations. At the time of IA2, treatment was ongoing for 205 ([redacted]%) patients in the AAP + ADT group and 70 ([redacted]%) patients in the ADT alone group. The most common reasons for discontinuation remained progressive disease, reported for [redacted]% and [redacted]% of patients in the AAP + ADT and ADT alone groups, respectively. Adverse events (AEs) led to treatment discontinuation for [redacted]% of patients in the AAP + ADT group and [redacted]% of patients in the ADT alone group.

Treatment exposure

The median total treatment duration was [redacted] months for patients in the AAP + ADT group and [redacted] months for the ADT group, with a total of [redacted]% patients in the AAP + ADT group and [redacted]% of patients in the ADT alone group having received ≥24

cycles of treatment. As of 2nd October 2017, [redacted]/602 ([redacted]) patients in the ADT alone group had crossed over to receive AAP + ADT at IA2, with a median duration of exposure to subsequent AAP + ADT of [redacted] months.

Overall survival

At the time of IA2, [redacted] deaths were observed; [redacted] in the AAP + ADT group and [redacted] in the ADT alone group. As shown in Figure 1, median OS was [redacted] in the AAP + ADT group (95% confidence interval [CI]: [redacted]) and was [redacted] months (95% CI: [redacted]) in the ADT alone group. Treatment with AAP + ADT resulted in a [redacted]% reduction in the risk of death compared with ADT alone (hazard ratio [HR]=[redacted] [95%CI: [redacted]]; p[redacted]). At four years, the majority ([redacted]%) of patients in the AAP + ADT group were still alive, compared to only [redacted]% of patients in the ADT alone group, reaffirming the sustained survival benefit of AAP + ADT.

Figure 1: KM plot of OS [LATITUDE, ITT population]

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; ITT, intention-to-treat; KM, Kaplan–Meier; OS, overall survival.
Source: LATITUDE IA2 CSR Addendum, 2018.[1]

As illustrated by the comparison of Kaplan-Meier (KM) plots presented in Figure 2, the significant survival benefit associated with AAP + ADT over ADT alone was

sustained after a longer duration of follow-up, thus substantiating the robustness of results.

Figure 2: KM plot of OS at IA1 vs. IA2 [LATITUDE, ITT population]

Secondary endpoints

Treatment with AAP + ADT was [redacted] to ADT alone for all secondary efficacy endpoints.

Time to pain progression

As shown in Figure 2, median time to pain progression was [redacted] months in the AAP + ADT group and [redacted] months in the ADT alone group, resulting in a [redacted]% reduction in the risk of pain progression (HR=[redacted] [95% CI: [redacted]]; p[redacted]). The 48-month event-free rate was [redacted]% for AAP + ADT and [redacted]% for ADT alone. These results indicate that treatment with AAP + ADT prolonged the time before patients' pain got worse, suggesting it would allow men to carry on with their lives more comfortably.

Figure 3: KM plot of time to pain progression [LATITUDE, ITT population]

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; ITT, intention-to-treat; KM, Kaplan–Meier.
Source: LATITUDE IA2 CSR Addendum, 2018.[1]

Time to subsequent therapy for prostate cancer

As shown in Figure 3, treatment with AAP + ADT significantly extended the time to subsequent therapy for prostate cancer. While the median time to subsequent therapy was [redacted] in the AAP + ADT group, it was [redacted] months in the ADT alone group (HR=[redacted] [95% CI: [redacted]]; p[redacted]).

Figure 4: KM plot of time to subsequent prostate cancer therapy [LATITUDE, ITT population]

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; ITT, intention-to-treat; KM, Kaplan–Meier.
Source: LATITUDE IA2 CSR Addendum, 2018.[1]

A summary of subsequent therapy received is presented in Table 1. A total of [redacted]% of AAP + ADT patients and [redacted]% of ADT alone patients received subsequent therapy for prostate cancer. The most common subsequent therapy was docetaxel, received by [redacted]% of patients in the AAP + ADT arm and [redacted]% of patients in the ADT alone arm, followed by bicalutamide (received by [redacted]% and [redacted]% of patients, respectively) and enzalutamide (received by [redacted]% and [redacted]%, respectively).

Table 1: Subsequent therapy for prostate cancer [LATITUDE, ITT population]

	AAP + ADT (n=597)	ADT alone (n=602)
Received subsequent therapy, n (%)	[redacted]	[redacted]
Received subsequent systemic therapy, n (%)	[redacted]	[redacted]
Antineoplastic agents	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Endocrine therapy	[redacted]	[redacted]
Bicalutamide	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]
Corticosteroids for systemic use	[redacted]	[redacted]
Subsequent surgery/procedures, n (%)	[redacted]	[redacted]
Radiotherapy (to bone)	[redacted]	[redacted]
Radiotherapy (other than bone)	[redacted]	[redacted]
Surgery (to bone)	[redacted]	[redacted]
Surgery (other than bone)	[redacted]	[redacted]

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; ITT, intention-to-treat.
Source: LATITUDE IA2 CSR Addendum, 2018.[1]

Time to life-extending subsequent therapy for prostate cancer

As shown in Figure 4, the median time to life-extending subsequent therapy was [redacted] in the AAP + ADT group but was [redacted] months in the ADT alone group, demonstrating that AAP + ADT delayed the need for initiation of life-extending subsequent therapy (HR=[redacted] [95% CI: [redacted]]; p[redacted]).

Figure 5: KM plot of time to life-extending subsequent prostate cancer therapy [LATITUDE, ITT population]

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; ITT, intention-to-treat; KM, Kaplan–Meier.
Source: LATITUDE IA2 CSR Addendum, 2018.[1]

Table 2 provides an updated summary of life-extending subsequent therapy for prostate cancer. Life-extending therapy was reported for [redacted]% of patients in the AAP + ADT group compared with [redacted]% of patients in the ADT alone group. The most frequently used life-extending therapy was docetaxel ([redacted]% AAP + ADT and [redacted]% ADT alone), followed by enzalutamide ([redacted]% and [redacted]%, respectively) and AAP ([redacted]% and [redacted]%, respectively). Of note, Table 2 only shows subsequent therapy use after treatment discontinuation had occurred. As such, the [redacted] patients who had crossed over to AAP at time of IA2 are not counted here as this is not considered subsequent therapy.

Table 2: Life-extending subsequent therapy [LATITUDE, ITT population]

	AAP + ADT (n=597)	ADT alone (n=602)
Received life-extending subsequent therapy, n (%)	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]
Radium-223	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]
AAP	[redacted]	[redacted]

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; ITT, intention-to-treat.
Source: LATITUDE IA2 CSR Addendum, 2018.[1]

Time to initiation of chemotherapy

As shown in Figure 5, the median time to initiation of chemotherapy was [redacted] in the AAP + ADT group but was [redacted] months in the ADT alone group, demonstrating that treatment with AAP + ADT significantly delayed the time until patients required chemotherapy (HR=[redacted] [95% CI: [redacted]; p[redacted]). This translated to a [redacted]% reduction in the risk of initiation of chemotherapy, a particularly important endpoint for those men who would prefer to choose not to undertake chemotherapy in mHSPC. As detailed in Table 1, the majority of patients who received subsequent therapy for their prostate cancer received docetaxel chemotherapy, suggesting that treatment with AAP in this setting does not impair men's ability to receive chemotherapy later in their disease course.

Figure 6: KM plot of time to initiation of chemotherapy [LATITUDE, ITT population]

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; ITT, intention-to-treat; KM, Kaplan–Meier.
Source: LATITUDE IA2 CSR Addendum, 2018.[1]

Time to next skeletal-related event (SRE)

As shown in Figure 6, treatment with AAP + ADT significantly reduced the risk of SREs by [redacted]% (HR=[redacted] [95% CI: [redacted]], p[redacted]), although the median time to SRE was [redacted] in either arm. The 48-month event-free rate was [redacted]% for AAP + ADT and [redacted]% for ADT alone.

Figure 7: KM plot of time to next SRE [LATITUDE, ITT population]

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; ITT, intention-to-treat; KM, Kaplan–Meier.
Source: LATITUDE IA2 CSR Addendum, 2018.[1]

Exploratory endpoints

Progression-free survival following subsequent therapy

Progression-free survival following subsequent therapy (PFS2) was defined as the time from randomisation to the second disease progression during follow-up after systemic subsequent therapy, or death from any cause. Among the [redacted] ([redacted]) patients in the AAP + ADT group and [redacted] ([redacted]) patients in the ADT alone group who received systemic subsequent therapy, [redacted] ([redacted]%) and [redacted] ([redacted]%) experienced PFS2 events, respectively.

The median PFS2 was longer with initial AAP + ADT treatment ([redacted] months) compared with initial ADT alone treatment ([redacted] months), however this did not reach statistical significance (HR=[redacted] [95% CI: [redacted]]; p[redacted]). It should be noted that PFS2 was based on investigator-assessed progression (defined as clinical, radiographic or prostate specific antigen [PSA] progression) after first subsequent

therapy, and this progression was not based on a protocol-defined criterion definition.

Subgroup analysis

Subgroup analyses for OS are presented in Figure 7. Consistent with the results for IA1, the point estimates of treatment effect of AAP + ADT on OS were favourable for all subgroups (HRs ranging from [redacted]) and consistent with the overall study results, except for the subgroup of patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 (HR=[redacted]). For this subgroup, nine additional death events were reported; however, the small sample size (n=40) precludes drawing any meaningful conclusion.

Figure 8: Subgroup analyses of OS [LATITUDE, ITT population]

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; LDH, lactate dehydrogenase; NE, not evaluable; PSA, prostate specific antigen.
Source: LATITUDE IA2 CSR Addendum, 2018.[1]

Exploring adjustments to survival

Since the results reported at IA1 provided strong evidence for the clinical effectiveness of AAP + ADT, the independent data and safety monitoring committee (IDMC) unanimously recommended the trial be unblinded to allow patients from the control arm to crossover to receive active treatment with AAP + ADT.

Indeed, at the time of IA2, [redacted] out of the 602 patients in the ADT alone arm had crossed over to receive AAP + ADT; however, the median duration of exposure to subsequent AAP + ADT in these patients was only [redacted] months. While within-trial crossover may impact estimates of OS in some cases, and hence necessitate subsequent statistical adjustments in survival, the level of exposure to AAP + ADT experienced at IA2 in these [redacted] patients is insufficient to warrant further adjustment at this stage. As highlighted in Document B (p43), the cross-over adjustment conducted at IA1 using the IPCW method demonstrated that any treatment switching biases against AAP + ADT. Therefore, by not conducting further analyses, the incremental survival benefit of AAP + ADT is likely underestimated and hence the results presented are conservative.

Furthermore, since LATITUDE was an international trial, some patients had access to subsequent therapies that would not be available to patients in UK clinical practice. To attempt to make these results more applicable to the UK setting, *post-hoc* analyses were conducted to explore the use of various methods described in the NICE TSD 16 guidance.[2] Aligned with that discussed in Document B (p43), the 2-Stage method, the rank preserving structural failure time (RPSFT) method and inverse probability censoring weighting (IPCW) were considered for adjusting OS data for patients who switched to other therapies which are not permitted in sequence in the NHS.

Given the issues that exist with the 2-Stage method and RPFST, previously discussed in Document B (p43), the IPCW approach was again used to adjust for treatment switching at IA2. While sample sizes were slightly greater than at IA1 ([redacted] rather than [redacted] for AAP + ADT, and [redacted] rather than [redacted] for ADT alone), they remain small for the relevant treatments of interest, with limited follow-up and an imbalance in patient characteristics between switchers and non-switchers. As such, these

analyses are still not robust enough to consider of additional value at this time. This analysis again demonstrates that a disproportionate number of patients in the ADT arm went on to receive active subsequent treatments which are not available in UK clinical practice; therefore, in not conducting further analyses, the incremental survival benefit of AAP + ADT is likely underestimated and are hence the results presented are conservative.

Comparative effectiveness estimates

Importantly, all HRs remained stable from IA1 to IA2. It should be noted that the impact of cross-over and the fact that more patients from the ADT alone arm received life-extending subsequent therapy, and started earlier, than those in the AAP + ADT arm, has not been corrected explaining the slight increase in HR. A comparison of these HR between IA1 and IA2 is presented in Table 3. The consistency in these results further substantiates the clinical benefit of AAP + ADT vs. ADT alone. Furthermore, because there is little change in the HRs between IA1 to IA2, there is likely to be minimal impact on the indirect treatment comparison (ITC) of AAP + ADT vs. docetaxel + ADT. As such, the ITC results are expected to be similar.

Table 3: Hazard ratios in IA1 versus IA2

	IA1	**IA2**
Median follow-up	30.4 months	[redacted] months
Overall survival	0.62	[redacted]
Time to next skeletal-related event	0.70	[redacted]
Time to pain progression	0.70	[redacted]
Time to subsequent therapy for prostate cancer	0.42	[redacted]
Time to initiation of chemotherapy	0.44	[redacted]
Time to life-extending subsequent therapy	0.37	[redacted]

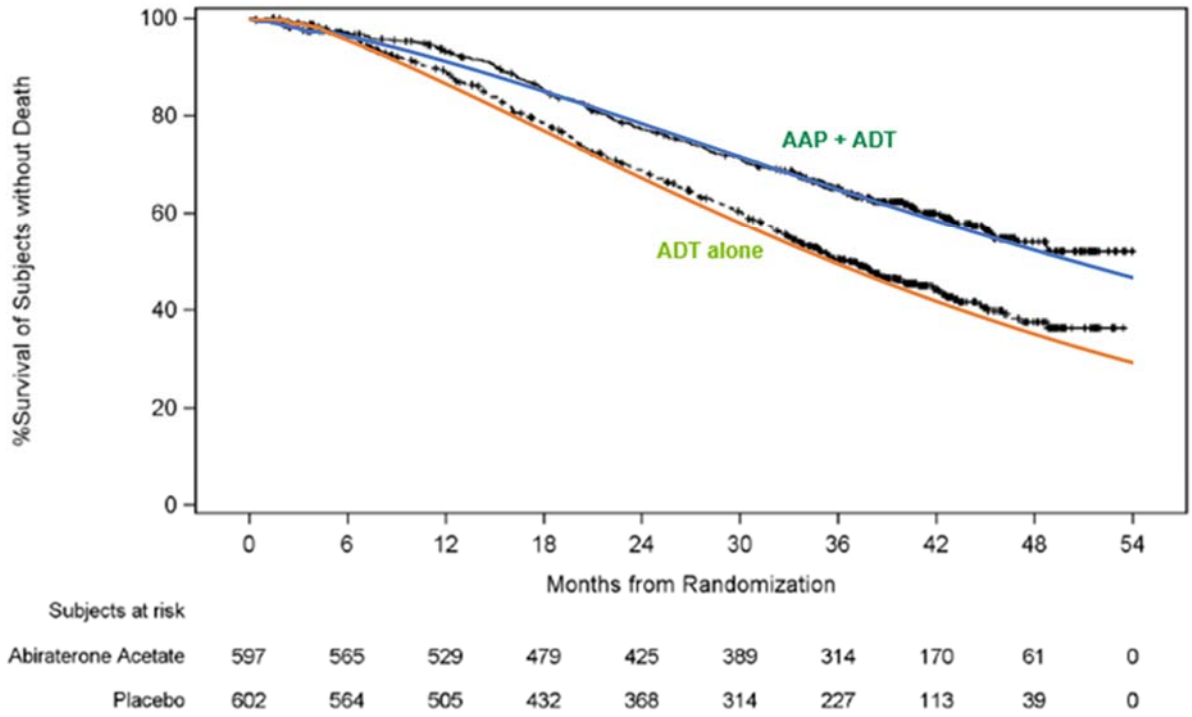
Key: IA, interim analysis.
Source: LATITUDE Clinical Study Report[3]; LATITUDE IA2 CSR Addendum, 2018.[1]

Conclusion

As the HRs for OS and secondary endpoints remained consistent between IA1 and IA2, it is reasonable to infer that the cost-effectiveness estimates for AAP in this setting are also likely to remain consistent, with no need to change the key

conclusions that were made in Janssen's original submission for this appraisal. As such, it was felt that updated economic analyses were not warranted at this point in time. Figure 8 presents the IA2 KM plot of OS against the predicted OS from the cost-effectiveness model, utilising the scenario where the model estimates survival using LATITUDE data. This graph demonstrates that the model still provides a good prediction of OS when the updated IA2 data is used, further demonstrating that the cost-effectiveness estimates will likely remain consistent.

Figure 9: KM plot of OS vs predicted model survival



Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; KM, Kaplan–Meier; OS, overall survival.
Source: LATITUDE IA2 CSR Addendum, 2018.[1]

In summary, the results from IA2 reaffirm the conclusions previously drawn in Document B, that treatment with AAP + ADT is an efficacious and cost-effective use of NHS resources in men with newly diagnosed high-risk mHSPC, when utilised under the confidential commercial access arrangement (CAA), regardless of the comparator treatment considered.

References

1. Janssen Research & Development. Report of Updated Data from Study 212082PCR3011: Interim Analysis #2. (Clinical Study Report) 12 January 2018 2018. Data on File.
2. Latimer NR and Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. 2014. Available at: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0088914/pdf/PubMedHealth_PMH0088914.pdf. Accessed: 26 January 2018.
3. Janssen Research & Development. A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High Risk, Metastatic Hormone-Naive Prostate Cancer (mHNPC). (Clinical Study Report) 2017. Data on File.

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Single technology appraisal

Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer
ID945

Dear xxxxxx,

The Evidence Review Group, Aberdeen HTA group, and the technical team at NICE have looked at the submission received on 5th February 2018 from Janssen. 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 8th March 2018. Your response and any supporting documents should be uploaded to NICE Docs.

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

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

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 Mary Hughes, Technical Lead (mary.hughes@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 – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **PRIORITY QUESTION:** Please provide a list of all included studies from the clinical effectiveness review. Please indicate which are primary and secondary references. In particular, please clarify whether Gravis 2013 (referenced in Document B) or Gravis 2016 (referenced in Appendix D) is the primary one.

A2. **PRIORITY QUESTION:** Please clarify date limits of the systematic searches. Table 4 in Appendix D specifies 'Sept 2015 - Present' and specifically excluded studies published before 2015. Updated searches were conducted in July 2017. However, the included studies listed on pages 13-16 of the appendices include some that are published prior to 2015.

A3. **PRIORITY QUESTION:** There are references to 2018 citations as data sources in the company submission (i.e., Fizazi 2018 in Table 6, pages 31-32 and Chi 2018 page 47 onwards - Document B). Please clarify how these were identified and why they were included when searching ended in July 2017.

A4. **PRIORITY QUESTION:** Document B pages 40 and 44, Figures 8 (KM plot of FFS- AAP + ADT vs. ADT [STAMPEDE, M1 only]) and 11 (KM plot of OS- AAP + ADT [STAMPEDE, M1 only]): Please indicate if these are ITT results

A5. **PRIORITY QUESTION:** Document B page 65, Table 14 (Treatment emergent Grade 3-4 AEs reported in at least 1% of patients in either treatment) and Appendix F page 37 (post-hoc analyses of LATITUDE): The TEAE are split up between the two documents. Please provide a table including all data from the submission and appendices for all grades.

A6. Document B page 63 (treatment exposure in LATITUDE) refers to treatment duration in terms of cycles. What was the 'average' (mean, median and range) cycle time for abiraterone plus ADT and ADT?

A7. **PRIORITY QUESTION:** Appendix Q (mCRPC ITC methods) page 133 states that it was necessary to assume that mitoxantrone and /or prednisolone are approximately equivalent to placebo/SOC. Please provide a statement on the clinical plausibility of this assumption.

A8. **PRIORITY QUESTION:** Appendix K (Baseline characteristics) page 97 states "Of note, specific patient characteristics were not reported for each treatment arm and are therefore not included in Table 38".: Please clarify which patient characteristics are not included in this table.

A9. **PRIORITY QUESTION:** Appendix K (Baseline characteristics) page 106, Table 40 (Summary of subsequent therapies, AAP + ADT vs. ADT alone, [STAMPEDE trial, ITT]): The proportions (%) provided do not correspond to the numerators and denominators given. Please check these.

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A10. Appendix Q (mCRPC ITC methods) page 136: Did the results of APP versus Radium 223 and AAP versus Enzalutamide include an adjustment for treatment switching?

The ERG have requested that the company provide its responses to questions A11 to A20 in a separate Excel workbook. Please provide the response to each question in a separate worksheet.

A11. **PRIORITY QUESTION:** Please expand the Kaplan Meier data of the *KM_data* worksheet of the model: columns BP:BQ, BV:BW, CE:CF, CK:CL, CT :CU, CZ :DA, DI :DJ, DO :DP to Timepoint, N at risk, N events and N censoring events sufficient to reconstruct the Kaplan Meier curves. Please supply these as a separate workbook rather than adding it to the *KM_data* worksheet of the model (8 tables).

Timepoint	N at risk	N events	N Censoring events
T=0	N=???	0	0
T=???	N=???	N=???	N=???
Etc.	Etc.	Etc.	Etc.

A12. **PRIORITY QUESTION:** Please supply the Kaplan Meier data split by arm for OS and treatment discontinuations (i.e., the parallels to columns C, D, G and H of the *1L_mCRPC_Efficacy* worksheet) of COU-AAP-302: Timepoint, N at risk, N events, N censoring events sufficient to reconstruct the Kaplan Meier curves (4 tables).

Timepoint	N at risk	N events	N Censoring events
T=0	N=???	0	0
T=???	N=???	N=???	N=???
Etc.	Etc.	Etc.	Etc.

A13. **PRIORITY QUESTION:** Please supply the Kaplan Meier TTD data of Figure 6 (TTD KM curve vs. model predicted PFS) of Appendix J (Clinical outcomes and disaggregated results from the model): Timepoint, N at risk, N events, N censoring events sufficient to reconstruct the Kaplan Meier curves (2 tables).

Timepoint	N at risk	N events	N Censoring events
T=0	N=???	0	0
T=???	N=???	N=???	N=???
Etc.	Etc.	Etc.	Etc.

A14. Please supply the ADT Kaplan Meier data of the Document B Figure 42 (Median OS: Predicted vs. CHAARTED) and the corresponding Kaplan Meier data for the docetaxel arm to the extent that it is available: Timepoint, N at risk, N events, N censoring events as available or derived from published papers (2 tables).

Timepoint	N at risk	N events	N Censoring events
T=0	N=???	0	0
T=???	N=???	N=???	N=???

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Etc.	Etc.	Etc.	Etc.

A15. Please define which events were treated as censoring events and which were treated as events for TTD and rPFS and tabulate the totals of each censoring event (i.e, do not aggregate censoring events into a single total) and event separately split by arm for LATITUDE (4 tables).

A16. Please provide the LATITUDE OS Kaplan Meier data split by arm for the Western EU subgroup: Timepoint, N at risk, N events, N censoring events (2 tables).

Timepoint	N at risk	N events	N Censoring events
T=0	N=???	0	0
T=???	N=???	N=???	N=???
Etc.	Etc.	Etc.	Etc.

A17. **PRIORITY QUESTION:** Please provide the calculations underlying the calculation of cells C17:Q26 of the *Adverse_Events* worksheet, preferably in a separate Excel workbook with full referencing as to number of events, number of patients and time period the data applies to, and also whether this data relates to events or patients experiencing these events. Please also provide this data and information for the LATITUDE frequencies in cells G91:G98 of the *Utilities* worksheet.

A18. **PRIORITY QUESTION:** Please split the COU-AAP-302 data of cells H82:H86 of the *Utilities* worksheet by arm. Please also clarify if this is the number of events or the number of patients having experienced an event. Please also provide the corresponding data for LATITUDE, split by arm.

A19. Please provide the patient numbers and durations that underlie the calculation of cells E142:G174 of the *mCRPC_costs* worksheet. If possible, please also provide these patient numbers restricted to the Western EU subgroup.

A20. Please provide the patient numbers and durations that underlie the calculation of cells G91:G98 of the *Utilities* worksheet. Please also outline if this data is restricted to mHSPC or also includes data from when patients are mCRPC.

A21. For LATITUDE the company provides a post-hoc analysis of patients with high volume versus low volume of disease. Please clarify where these data come from and whether they are published or unpublished data.

A22. Appendix Q page 134, Table 55: Please provide an extra column with the time to outcome for all the studies for easy comparison; currently some is given in the text only.

Section B: Clarification on cost-effectiveness data

B1 **PRIORITY QUESTION:** Please supply list of primary and secondary references for both the cost-effectiveness and health related quality of life (HRQL) searches.

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B2 **PRIORITY QUESTION:** Please clarify date limits for searches. For cost effectiveness: Appendix G specifies searches were restricted to 2005-2017 (page 37); however Table 22 includes several published prior to 2005. For HRQL Appendix H specifies searches were restricted to 2005-2017 (page 52); however, the identified studies in Table 29 include several published prior to 2005. Appendix H also specifies 15 studies were selected while Table 29 lists 17.

B3 **PRIORITY QUESTION:** Please clarify the following anomalies in the search strategies:

- Table 18 (Appendix G) has no date limit specified – is this the Embase & MEDLINE search used for 2015-2017 as Table 17 specifies 2005-2015?
- There are two line 6s. (Table 18 and Table 26 in Appendix G) The first appears to be wrong as the number of hits should not be less than line 5. Please clarify
- Table 19 (Appendix G) and Table 27 (Appendix H) date limits are 2015-2017. Were NHS EED & HTA Database searched only for these years?
- Table 25 (Appendix H) specifies date range 2005-2015. Was this search updated in 2017?

B4 Please tabulate the data of Document B Figure 12 (Mean change in EQ-5D-5L VAS and utility scores from baseline LATITUDE, ITT population), augmented with the number of EQ-5D questionnaires completed at each timepoint. Please clarify why this has many more data points through time than table 42 (Results of the descriptive analysis of EQ-5D-5L data: LATITUDE) of Appendix N. Did the regression analysis include all the data points or only the data at the timepoints given in table 42 of Appendix N? Please present table 42 of appendix N split by arm.

B5 To what extent were the end of treatment and follow-up quality of life EQ-5D values included in the RMME (repeated measures mixed-effect) data set and analysed? If these were excluded from the analysis what is the reason for this?

B6 **PRIORITY QUESTION:** Please expand table 43 (Univariate utility regression analysis) of Appendix N to include all the variables that were examined within univariate regressions for significance at the 10% level, including those with p-values above 10%.

B7 **PRIORITY QUESTION:** Please provide the internal report that underlies Document B Table 27 (LATITUDE utility regression results). Please augment Document B Table 27 with coefficient standard errors and p-values. Please also provide the equivalent of model 1 of Document B Table 27, with coefficient standard errors and p-values, for models which estimate:

- a single pooled coefficient for “AE (Ever)”
- a single pooled coefficient for “SRE (Ever)”
- a single pooled coefficient for “AE (Ever)” and a single pooled coefficient for “SRE (Ever)”

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B8 **PRIORITY QUESTION:** To what extent is there statistical evidence from the regression analysis of the LATITUDE EQ-5D data that:

- the impact of having experienced an SAE was different in the AAP+ADT arm than in the ADT arm?

- the impact of having experienced an SRE was different in the AAP+ADT arm than in the ADT arm?

B9 Please provide an Excel workbook that derives the estimates outlined in Document B table 28 (summary of utility values for cost-effectiveness analysis) using the inputs of Document B table 27 (LATITUDE utility regression results).

B10 The submission mentions but does not define "*the utility value for 1L mCRPC based upon the LATITUDE data*". Please clarify how this value is derived and its value.

B11 The model uses 4 utility values from TA387 (C73:C76 of the *Utilities* worksheet) but the submission does not outline how these were derived, and how they relate to the set of final quality of life values of the Appraisal Committee's preferred base case in TA387. Please present this information and comment about the plausibility of these values.

B12 Please confirm that all LATITUDE data used to estimate model inputs (including e.g., MRU – mHSPC rates of resource use) were collected at IA1 and that this was prior to any unblinding of LATITUDE.

B13 With regard to the Kaplan Meier OS (pre-subsequent therapy) please define an event and how this differs from an event in the Kaplan Meier OS curve. Similarly, please define censoring events for the two curves and how these differ. Each Kaplan Meier OS curve of the model appears to have been constrained to be no more than the Kaplan Meier OS (pre-subsequent therapy) curve of the model. Please explain the rationale for this assumption.

B14 The Kaplan Meier PFS curve of the model appears to have been constrained to be no more than the Kaplan Meier TTST (time to subsequent therapy) curve of the model. Please explain the rationale for this.

B15 To avoid any possibility of ambiguity are the MSM analyses based upon the raw LATITUDE data or are they based on data that has been adjusted in some way (e.g, by IPCW)?

B16 **PRIORITY QUESTION:** Please provide a scenario analysis re-running the rPFS MSM analysis for 4+ months - i.e., including an additional month of data, and to 7+ months; excluding an additional two months of data to provide the equivalent of the data in cells C43:J52 of the *Efficacy_data* worksheet); if the latter provides insufficient data and fails to converge please restrict the analysis to the 6+months data.

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B17 For the rPFS modelling it is not clear why the TTST Kaplan Meier curves will provide the correct probabilities for progressed patients moving into 2nd line treatment and death. Please explain the rationale behind this; e.g., the formula I8 = (1-AZ8/AZ7)*EV7 in the *KM_data* worksheet.

B18 **PRIORITY QUESTION:** Please state what number of the 239 AAP+ADT patients and what number of the 354 ADT patients with an rPFS event of table 25 had had a TTST event by IA1. How were those who had had an rPFS event but had not had a TTST event by IA1 treated for the calculation of the mean treatment free interval in table 25, and what is the effect of their exclusion from this calculation? Please provide the data and the data definitions that are required for the calculation of cell C58 of the *Efficacy_data* worksheet and cell K44 of the *Transition_Matrices* worksheet. If these are Kaplan Meier data please supply them in the following format.

Timepoint	N at risk	N events	N Censoring events
T=0	N=???	0	0
T=???	N=???	N=???	N=???
Etc.	Etc.	Etc.	Etc.

B19 Please provide a spreadsheet detailing how the inputs in cells E67:G70 of the *Efficacy_data* worksheet have been calculated from the values reported in table 56 of appendix Q.

B20 **PRIORITY QUESTION:** Please supply the copy of the TA387 model that provided the inputs to cells C25:D1069 and G25:H1069 of the *1L_mCRPC_Efficacy* workbook. Please state what the model settings apply to; e.g., Janssen preferred assumptions of original TA387 submission, ERG preferred assumptions of TA387 prior to 1st AC, etc.

B21 When the "*Estimate calibration factor*" box of the *Calibration* worksheet is pressed it returns a dialogue box which states: "*Solver Results: Solver could not find a feasible solution: Solver cannot find a point for which all constraints are satisfied*". Please outline how to successfully run the *run_Calibration* visual basic subroutine of the model. The combined difference of 1.138 in cell C11 of the *Calibration* worksheet with a CF of 2.616 falls to 1.099 with a CF of 2.8. Please provide an account of this. Please also clarify if when modelling using TTST within the *run_Calibration* visual basic subroutine the text. *Range("C48").Value = "Radiographic progression"* should be amended to *text .Range("C48").Value = "Time to subsequent therapy"* and the subroutine re-run, and if not why not.

B22 How did the model for TA387 estimate costs related to time on treatment with AAP and how does this differ from the approached used in this appraisal? Was an adjustment factor similar to the LATITUDE ratio given on page 127 of Document B applied? If yes, what was its value?

B23 Please provide the data that have been used to calculated the LATITUDE unplanned MRU – mHSPC units per year estimates and outline the timeframe it applies to, why it will not attribute mCRPC resource use to the ADT arm more than to the AAP+ADT arm, and the extent to which it reflects UK clinical practice.

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B24 The submission uses a number of costs of the TA387 assessment (e.g., SAE units costs and unplanned MRU – mCRPC) without showing how these have been derived or explaining what the Assessment Committee view of them was. Please provide more details of the inputs to this and their calculation. Also, what was the cost per surgery event that was applied in TA387?

Section C: Textual clarifications and additional points

C1. **PRIORITY QUESTION:** please provide a List of abbreviations/Glossary of terms

C2. Document B page 86, Table 21: What does SA relate to?

C3. Document B page 33, Figure 6 (Overview of STAMPEDE study design): Please provide a bigger and clearer image, if possible.

C4. The submission (pages 14-15) states that in recent trials patients with high volume mHSPC survived for less than 3 years. The rPFS model estimates an ADT 3 year survival of 51% and a 5 year survival of 22%. The LATITUDE KM data suggests an ADT 3 year survival of 49%. Please clarify.

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Single technology appraisal

Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer
ID945

Dear xxxxxxxxx,

The Evidence Review Group, Aberdeen HTA group, and the technical team at NICE have looked at the submission received on 5th February 2018 from Janssen. 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 8th March 2018. Your response and any supporting documents should be uploaded to NICE Docs.

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

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

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 Mary Hughes, Technical Lead (mary.hughes@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 – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **PRIORITY QUESTION:** Please provide a list of all included studies from the clinical effectiveness review. Please indicate which are primary and secondary references. In particular, please clarify whether Gravis 2013 (referenced in Document B) or Gravis 2016 (referenced in Appendix D) is the primary one.

Clinical effectiveness studies: The list in provided in 'ERG A1' shows primary references with respective secondary references associated with each publication, as indicated via decimal points. Of note, this list is correct, having removed the nine primary references published prior to 2005 (Eisenberger 1998, Denis 1998, Fontana 1998, Bruun 1996, Sagaster 1996, Thorpe 1996, Chodak 1995, Robinson 1995 and Turkes 1987), as per the response to B2.

Gravis 2013 was the primary analysis, and Gravis 2016 was a secondary analysis "to assess the impact of metastatic burden and to update OS data of the GETUG-AFU15 study."

A2. **PRIORITY QUESTION:** Please clarify date limits of the systematic searches. Table 4 in Appendix D specifies 'Sept 2015 - Present' and specifically excluded studies published before 2015. Updated searches were conducted in July 2017. However, the included studies listed on pages 13-16 of the appendices include some that are published prior to 2015.

Searches in the original SLR were conducted until 24th September 2015 and the updates were carried out from 1st September 2015 till 10th July 2017. The list presented in Appendix D (pages 13-16) includes studies found in both the original and update search.

A3. **PRIORITY QUESTION:** There are references to 2018 citations as data sources in the company submission (i.e., Fizazi 2018 in Table 6, pages 31-32 and Chi 2018 page 47 onwards - Document B). Please clarify how these were identified and why they were included when searching ended in July 2017.

These are Janssen-owned publications, which we have been aware of throughout submission development. As such, their publication dates were outside the SLR inclusion time-frame, yet considered important to include regardless as these publications relate to key outcomes from the LATITUDE trial.

- **Fizazi 2018** is a poster publication that outlined additional analysis of the pivotal LATITUDE trial, and thus provided data highly relevant to the submission. Since the poster was presented at the ASCO GU Congress (2018), which occurred the same week Janssen submitted to NICE, it would not have been sourced through conventional SLR methodology. It was necessary to include this publication to enable certain data in the submission to be supplied un-redacted. Please see the final 'Fizazi et al. (2018) – ASCO GU' poster provided.

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- **Chi 2018** is the final publication of the HRQL data from LATITUDE, originally presented at the ESMO EU Congress (2017), and sourced through the SLR detailed. Since the full manuscript was released in January (shortly before submission), it was considered more approach to reference this instead of the slide deck presented at conference.
- Of note, two further poster publications that were presented at the ASCO GU Congress (2018) also published data utilised in the submission, although final versions could not be provided at time of submission. Please see the final 'Li et al. (2018) – ASCO GU' and 'Feyerabend et al. (2018) - ASCO GU' posters provided.

A4. **PRIORITY QUESTION:** Document B pages 40 and 44, Figures 8 (KM plot of FFS- AAP + ADT vs. ADT [STAMPEDE, M1 only]) and 11 (KM plot of OS- AAP + ADT [STAMPEDE, M1 only]): Please indicate if these are ITT results

The STAMPEDE ITT population is composed of patients who had prostate cancer:

- as newly diagnosed and metastatic, node-positive, or high-risk locally advanced (with at least two of following: a tumour stage of T3 or T4, a Gleason score of 8 to 10, and a PSA level ≥40 ng per millilitre) – i.e. the M1 sub-population
- or as a disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (in men no longer receiving therapy, a PSA level >4 ng per millilitre with a doubling time of <6 months, a PSA level >20 ng per millilitre, nodal or metastatic relapse, or <12 months of total ADT with an interval of >12 months without treatment). – i.e. the M0 sub-population

In Document B, Figure 8 (page 40) and Figure 11 (page 44) are based on the M1 sub-population of STAMPEDE, not the ITT STAMPEDE population. This is because the M1 sub-population is more representative of the licensed indication of AAP + ADT in mHSPC, more so than the whole ITT population which consists of both M1 and M0 patients.

Only one figure in Document B (Figure 9) shows data from the ITT population, and this was only presented because the KM plot for the M1 sub-population has not been published by the STAMPEDE group.

A5. **PRIORITY QUESTION:** Document B page 65, Table 14 (Treatment emergent Grade 3-4 AEs reported in at least 1% of patients in either treatment) and Appendix F page 37 (post-hoc analyses of LATITUDE): The TEAE are split up between the two documents. Please provide a table including all data from the submission and appendices for all grades.

Of note, a full list of TEAEs for all grades reported in the ITT population is provided in the table labelled "TSFAE02" of the CSR and these data cover 22 pages. A list of TEAEs for all grade for the post-hoc high-volume sub-group is currently unavailable.

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Data provided in the 'ERG A5' workbook are for grade 3-4 TEAEs that were considered in the economic model and are therefore the most relevant for consideration.

Please see 'ERG A5' workbook which provides the side-by-side comparison of TEAEs for the ITT population and the post-hoc high-volume subgroup.

Please note, in completing this request an error in the number of cardiac disorders was found in Table 14 of Document B; these have been corrected, in line with the LATITUDE CSR.

A6. Document B page 63 (treatment exposure in LATITUDE) refers to treatment duration in terms of cycles. What was the 'average' (mean, median and range) cycle time for abiraterone plus ADT and ADT?

The summary statistics for duration of treatment in LATITUDE is presented in Table 1 below. The median total treatment duration was 24 months (25 cycles with a treatment cycle of 28 days) in the AAP group and 14 months (15 cycles) in the control group. The majority of patients (54.4%) in the AAP + ADT group received 24 or more cycles of treatment, compared to 29.7% of the patients in the control group.

Table 1: Extent of exposure [LATITUDE, ITT population]; Source: CSR, Table 15

	AAP + ADT (n=597)	**ADT alone (n=602)**
Exposure in months		
Mean (SD)	22.31 (11.511)	16.09 (10.502)
Median	23.98	14.28
Range	(0.1; 43.0)	(0.7; 42.6)
Exposure in cycles		
Mean (SD)	24.19 (12.337)	17.41 (11.178)
Median	25.00	15.00
Range	(1.0; 47.0)	(1.0; 47.0)

A7. **PRIORITY QUESTION:** Appendix Q (mCRPC ITC methods) page 133 states that it was necessary to assume that mitoxantrone and /or prednisolone are approximately equivalent to placebo/SOC. Please provide a statement on the clinical plausibility of this assumption.

This assumption was supported by both literature and expert clinical feedback. The publication by Green et al. (2015)[1] found no significant difference in the comparative effectiveness of mitoxantrone plus prednisone over prednisone alone among men with mCRPC. Since prednisolone is considered a standard of care for palliative treatment in the UK, it was considered clinically plausible to assume equivalent effectiveness between the trial control

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arms. At the UK Advisory Board, clinical experts also validated this was a reasonable assumption to enable a linked network.

A8. **PRIORITY QUESTION:** Appendix K (Baseline characteristics) page 97 states "Of note, specific patient characteristics were not reported for each treatment arm and are therefore not included in Table 38".: Please clarify which patient characteristics are not included in this table.

Appendix K presents data from the STAMPEDE study. As this is not a Janssen-led study, data included in the submission are restricted to those that have been made publicly available. At the time of submission, very few patient characteristics for the cohort of patients contemporaneously randomised to AAP + ADT or docetaxel + ADT were available. Data were only reported through an oral presentation made at the ESMO EU Congress (2017) (Sydes et al. 2017). As such, the limited baseline characteristics which were known have been presented within the text of Appendix K rather than within Table 38.

A full manuscript by Sydes et al. (2018) has since been published, providing a larger number of patient characteristics than those available at time of submission. Please see the 'ERG A8' workbook provided based on 'Sydes et al. (2018)' also provide.

A9. **PRIORITY QUESTION:** Appendix K (Baseline characteristics) page 106, Table 40 (Summary of subsequent therapies, AAP + ADT vs. ADT alone, [STAMPEDE trial, ITT]): The proportions (%) provided do not correspond to the numerators and denominators given. Please check these.

These data are directly taken from the primary publication by James et al. (2017). The reason the proportions provided do not correspond to the numerators and denominators given is because some patients may have received more than one subsequent therapy. It is also important to note that it is not possible to establish the order in which patients received subsequent therapies reported in STAMPEDE. Given this is the extent of information published on subsequent therapies in STAMPEDE, unfortunately we do not have the granularity of data necessary to provide further interpretation of these data.

A10. Appendix Q (mCRPC ITC methods) page 136: Did the results of APP versus Radium 223 and AAP versus Enzalutamide include an adjustment for treatment switching?

The mCRPC ITC presented in Appendix Q estimated multiple HRs for AAP versus radium-223, enzalutamide and docetaxel with and without cross-over adjustment. Table 56 in Appendix Q presents the results of the ITC and indicates, for each estimated HR, whether cross-over adjusted HRs were used or not for any of the treatments. The HRs applied in the model for the comparison of AAP to docetaxel and radium-223 utilise cross-over adjusted survival estimates from the COU-AA-302 trial as this survival data was utilised in the base case analysis of the TA387 submission. The HR applied in the model for the comparison of AAP to enzalutamide utilised the cross-over adjusted survival estimates from both the COU-AA-302 and PREVAIL trials, in line with the survival data that was utilised in the previous AAP

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and enzalutamide submissions (TA387 and TA377, respectively). Using these cross-over adjusted HRs assured that there was some consistency in the data used to inform experience of patients in mCRPC across appraisals. Given the high clinical heterogeneity between trials in mCRPC, these results were associated with a large degree of uncertainty. As such, the ITC values were only utilised in scenario analysis, and the base case analysis assumed equal efficacy between each of the active subsequent therapies. This decision was validated by UK clinical experts at the UK Advisory Board.

The ERG have requested that the company provide its responses to questions A11 to A20 in a separate Excel workbook. Please provide the response to each question in a separate worksheet.

A11. **PRIORITY QUESTION:** Please expand the Kaplan Meier data of the *KM_data* worksheet of the model: columns BP:BQ, BV:BW, CE:CF, CK:CL, CT :CU, CZ :DA, DI :DJ, DO :DP to Timepoint, N at risk, N events and N censoring events sufficient to reconstruct the Kaplan Meier curves. Please supply these as a separate workbook rather than adding it to the *KM_data* worksheet of the model (8 tables).

Please see the 'ERG A11' workbook provided. The timepoint, N at risk, N events and N censoring events data for each Kaplan Meier curve (as seen in columns BP:BQ, BV:BW, CE:CF, CK:CL, CT:CU, CZ:DA, DI:DJ, DO:DP in the KM_data worksheet of the model) are provided within separate tabs.

A12. **PRIORITY QUESTION:** Please supply the Kaplan Meier data split by arm for OS and treatment discontinuations (i.e., the parallels to columns C, D, G and H of the *1L_mCRPC_Efficacy* worksheet) of COU-AAP-302: Timepoint, N at risk, N events, N censoring events sufficient to reconstruct the Kaplan Meier curves (4 tables).

Please see the 'ERG A12' workbook provided. The timepoint, N at risk, N events and N censoring events data for each Kaplan Meier curve (i.e., the parallels to columns C, D, G and H of the 1L_mCRPC_Efficacy worksheet) are provided within separate tabs.

A13. **PRIORITY QUESTION:** Please supply the Kaplan Meier TTD data of Figure 6 (TTD KM curve vs. model predicted PFS) of Appendix J (Clinical outcomes and disaggregated results from the model): Timepoint, N at risk, N events, N censoring events sufficient to reconstruct the Kaplan Meier curves (2 tables).

Please see the 'ERG A13' workbook provided. The timepoint, N at risk, N events and N censoring events data for each Kaplan Meier curve ('KM TTD - AAP+ADT' and 'KM TTD - ADT alone' as in Figure 6 of Appendix J) are provided within separate tabs.

A14. Please supply the ADT Kaplan Meier data of the Document B Figure 42 (Median OS: Predicted vs. CHAARTED) and the corresponding Kaplan Meier data for the docetaxel arm to the extent that it is available: Timepoint, N at risk, N events, N censoring events as available or derived from published papers (2 tables).

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The 'model ADT' curve within Document B Figure 42 was the model-predicted OS of the ADT alone arm. As described in Section B.3.3 of Document B, the model-predicted OS was partially derived utilising the OS KM data from the LATITUDE trial for the first five months of the model. The timepoint, N at risk, N events and N censoring events for the LATITUDE OS KM data for ADT alone is provided as part of clarification question A11. Please refer to the ADT OS tab of the 'ERG A11' workbook provided. Please note that beyond the first five months, other sources were used in the extrapolation of OS to estimate long-term outcomes, as described in Table 24 of Document B.

As the patient-level data from CHAARTED were unavailable, the KM curve was digitised from the CHAARTED publication (Sweeney et al. 2015).[2] The curve that was digitised from the manuscript was Figure 1: Graph B, which presented data for patients with high-volume disease. Please see the 'ERG A14' workbook provided which presents the digitised data for ADT. The docetaxel curve was not digitised from CHAARTED as the predicted survival for docetaxel + ADT from the model is estimated from a network of evidence taken from multiple sources found in the literature, hence providing a more appropriate estimation of survival than CHAARTED.

A15. Please define which events were treated as censoring events and which were treated as events for TTD and rPFS and tabulate the totals of each censoring event (i.e, do not aggregate censoring events into a single total) and event separately split by arm for LATITUDE (4 tables).

Events and censors for TTD were not provided in the patient-level trial data. As a result, a variable indicating the occurrence of a treatment discontinuation event was created, taking into account both treatment duration and overall survival events:

- It was assumed that a TTD event had effectively occurred for patients who died at the time of discontinuation.
- If OS was equal to treatment duration, the OS event variable was assumed to be an appropriate indication of the treatment discontinuation event variable. For example, if a patient had an equal OS time to their treatment duration and whose death was reported, it was assumed that they must also have experienced a treatment discontinuation event (i.e. it is not clinically plausible to remain on treatment after death).
- Likewise, for patients who had an OS time equal to treatment duration and who were still alive at time of the analysis (i.e. censored OS), it was assumed that the lack of information could not allow the treatment duration variable to be classed as an event (and so TTD was also censored).

The totals of each TTD event and censored TTD events by arm are presented in Table 2 and Table 3, respectively.

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Table 2: Totals of each TTD event by arm

	Totals of each TTD event	
Event description	**AAP + ADT (n=597)**	**ADT alone (n=602)**
OS time larger than treatment duration (i.e. the patient discontinued treatment before they died)	[redacted]	[redacted]
OS time equal to treatment duration and OS was an event (i.e. the patient discontinued treatment due to their death)	[redacted]	[redacted]
TTD events (total)	[redacted]	[redacted]

Table 3: Totals of each TTD censoring event by arm

	Totals of each TTD censored event	
Event description	**AAP + ADT (n=597)**	**ADT alone (n=602)**
OS time equal to treatment duration and OS was censored (i.e. the patient was still on treatment at time of IA1)	[redacted]	[redacted]
TTD censored events (total)	[redacted]	[redacted]

An rPFS event was categorised within the clinical trial dataset because of the following reasons: presence of bone lesion, soft tissue lesion, soft and bone lesion, or death. The totals of each rPFS event by arm are presented in Table 4. An rPFS censored event was defined as no progression or death. The time assigned to the censored rPFS event was defined as either the date of the last non-PD radiographic assessment, missed 2 assessments, subsequent therapy initiation or randomization date (see section 3.11.3.6.1 of the CSR). The totals of each rPFS censoring event by arm are presented in Table 5.

Table 4: Totals of each rPFS event by arm

	Totals of each rPFS event	
Event description	**AAP + ADT (n=597)**	**ADT alone (n=602)**
rPFS: bone lesion	[redacted]	[redacted]
rPFS: death	[redacted]	[redacted]
rPFS: soft and bone lesion	[redacted]	[redacted]
rPFS: soft tissue lesion	[redacted]	[redacted]
rPFS events (total)	[redacted]	[redacted]

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Table 5: Totals of each rPFS censoring event by arm

	Totals of each rPFS censored events	
Censoring event description	**AAP + ADT (n=597)**	**ADT alone (n=602)**
No progression or death: Last non-PD radiographic assessment	[redacted]	[redacted]
No progression or death: Missed 2 assessments	[redacted]	[redacted]
No progression or death: Randomization date	[redacted]	[redacted]
No progression or death: Subsequent therapy initiation	[redacted]	[redacted]
rPFS censored events (total)	[redacted]	[redacted]

A16. Please provide the LATITUDE OS Kaplan Meier data split by arm for the Western EU subgroup: Timepoint, N at risk, N events, N censoring events (2 tables).

Please see the 'ERG A16' workbook provided. The timepoint, N at risk, N events and N censoring events data for each OS Kaplan Meier curve (AAP + ADT and ADT alone for the Western EU subgroup) are provided within separate tabs, as requested.

Whilst the UK falls within Western Europe, undue focus should not be placed on the Western EU subgroup. In the UK, NHS England has a specific commissioning algorithm whereby only one novel agent (i.e. AAP or enzalutamide) is permitted across a patient's treatment pathway in metastatic prostate cancer. This recognises that there is a lack of evidence to support the clinical benefit in sequencing these therapies.

Upon review of the other 10 countries included in the Western EU subgroup, the majority (n=8) allow the use of enzalutamide after AAP and visa-versa. Denmark and Sweden do however have similar prescribing algorithm to the UK. As such, Janssen do not believe the Western EU subgroup should be considered any more generalisable to the UK than the whole ITT population. Please see the country review tab in the 'ERG A16' workbook provided.

Most importantly to note, whilst pre-specified in the LATITUDE trial, **subgroup analyses were not formally powered to detect differences in trial outcomes**. As such, we believe that the ITT population and not the Western EU subgroup, remains the most relevant population for consideration.

A17. **PRIORITY QUESTION:** Please provide the calculations underlying the calculation of cells C17:Q26 of the *Adverse_Events* worksheet, preferably in a separate Excel workbook with full referencing as to number of events, number of patients and time period the data applies to, and also whether this data relates to events or patients

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experiencing these events. Please also provide this data and information for the LATITUDE frequencies in cells G91:G98 of the *Utilities* worksheet.

Please see the provided "ERG A17" workbook which contains the rates for each AE by the treatment patients receive, and the references for each value. Each sheet within the workbook contains the information from each reference that was used to estimate the AE rates.

Of note, we identified a transcription error in the values used in the model for enzalutamide.

There were differences in the follow-up time, and therefore the time period that the AE rates are calculated from. The model currently makes a simplifying assumption that the AE rates can be appropriately applied by converting the AE rates in each of the trials to annual rates. Where mean follow-up times are not reported in the trial, the median follow-up has been used instead to allow for an approximate calculation of annual AE rates. The attached CE model also utilises the correct enzalutamide values and therefore corrects for the transcription error:

- To apply the new method of estimating AE rates for each treatment, switch cell "C48" on the "Controls" sheet named "Controls.AE.frequency" to "Yes".
- To apply the corrected in the model, switch cell "C50" on the "Controls" sheet named "C50" to "Yes".

Table 6 summarises the impact these changes have on the ICER.

Table 6: Impact on ICER when accounting for model revisions

	AAP + ADT vs. ADT alone		**AAP + ADT vs. Docetaxel + ADT**	
	Original ICER	**Revised ICER**	**Original ICER**	**Revised ICER**
Applying: new method for estimating AE rates for each treatment only	£23,287	£22,665	£28,616	£26,875
Applying: corrected enzalutamide AE rates only		£23,306		£28,647

Please see the updated CE model provided which includes the ability to correct for these errors.

A18. PRIORITY QUESTION: Please split the COU-AAP-302 data of cells H82:H86 of the *Utilities* worksheet by arm. Please also clarify if this is the number of events or the number of patients having experienced an event. Please also provide the corresponding data for LATITUDE, split by arm.

Firstly, please note that there was an incorrect reference contained in the model as the data presented in cells "H82:H86" on the "Utilities" worksheet are sourced from the PREVAIL trial, which investigates enzalutamide in mCRPC before chemotherapy, as opposed to the COU-

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AA-302 trial. The PREVAIL trial data were used as the trials investigating AAP in mCRPC (COU-AA-301 and COU-AA-302) did not report data in an appropriate format to allow for the estimation of an SRE utility decrement.

The values utilised from PREVAIL were used in the previous NICE submission for enzalutamide TA377: Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. The data utilised, split by the enzalutamide and placebo arms of the trial, can be found in Table B59 of the company submission for TA377 and are also presented below. SRE rates for enzalutamide and placebo were calculated based on the number of events over the treatment emergent period (patient-years, 1,149.7 for enzalutamide and 494.9 for placebo in Stable Disease health state; 1,572.2 for enzalutamide and placebo post-progression). These data were taken from the September 2013 data cut from the PREVAIL trial, in line with what was utilised in the TA377 submission, rather than from the June 2014 data cut which was not presented. However, the TA377 submission indicates there were minimal differences between the two data-cuts.

Table B59 Number and rates for SREs in PREVAIL (Stable Disease)

Event	Number of SREs		SRE rate	
	ENZA	PLA	ENZA	PLA
Spinal cord compression	38	21	0.033	0.042
Pathological bone fracture	41	15	0.036	0.030
Radiation to the bone	130	83	0.113	0.168
Surgery to the bone	15	9	0.013	0.018
TOTAL	224	128	0.195	0.259

Abbreviations: ENZA: enzalutamide; PLA: placebo; SRE: skeletal related event

Equivalent values from the LATITUDE trial are presented in Table 7.

- In the LATITUDE CSR, the number of spinal cord compressions were reported in Table 29, and the number of pathological fractures were reported in the table labelled “TSFAE02”.
- The number of radiation or surgery to the bone events were not reported in the CSR. As such, these have been estimated by subtracting the number of spinal cord compressions and pathological bone fractures from the total number of SREs reported in LATITUDE (n=98 in the AAP arm and n=125 in the ADT arm).
- These patients have then been allocated to either radiation to the bone or surgery to the bone, based on the ratios of these events occurring reported in PREVAIL (15/130 for AAP + ADT and 9/130 for ADT alone).

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Table 7: Total SRE events from LATITUDE

Event	Number of SREs (AAP + ADT)	Number of SREs (ADT alone
Spinal cord compression	[redacted]	[redacted]
Pathological bone fracture	[redacted]	[redacted]
Radiation to the bone	[redacted]	[redacted]
Surgery to the bone	[redacted]	[redacted]

A19. Please provide the patient numbers and durations that underline the calculation of cells E142:G174 of the *mCRPC_costs* worksheet. If possible, please also provide these patient numbers restricted to the Western EU subgroup.

A description of the analysis used to determine the patient numbers which underline the calculation of cells E142:G174 of the *mCRPC_costs* worksheet is provided in Appendix O of the submission. From this analysis, the patient numbers calculated by treatment line and by arm are given in Table 8; Table 8 also includes the patient numbers restricted to the Western EU subgroup, as requested. As explained in response to A16., Janssen do not believe undue focus should be placed on the Western EU subgroup.

Of note, to estimate the LATITUDE market shares presented in the model scenario utilising this data, any therapies that were grouped together e.g. abiraterone + radium RA 223 dichloride, were each assigned a weight of 0.5.

Table 8: Subsequent therapy regimens patient numbers: ITT population and Western EU subgroup

	Patient numbers by treatment arm (ITT population)		Patient numbers by treatment arm (Western EU subgroup)	
	AAP + ADT	ADT alone	AAP + ADT	ADT alone
Subsequent therapy regimen – first line				
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone + radium RA 223 dichloride	[redacted]	[redacted]	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Radium RA 223 dichloride	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy regimen – second line				

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Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide + radium RA 223 dichloride	[redacted]	[redacted]	[redacted]	[redacted]
Palliative care	[redacted]	[redacted]	[redacted]	[redacted]
Radium RA 223 dichloride	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy regimen – third line				
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Palliative care	[redacted]	[redacted]	[redacted]	[redacted]
Radium RA 223 dichloride	[redacted]	[redacted]	[redacted]	[redacted]

A20. Please provide the patient numbers and durations that underlie the calculation of cells G91:G98 of the *Utilities* worksheet. Please also outline if this data is restricted to mHSPC or also includes data from when patients are mCRPC.

A summary of the data used to calculate the frequency of SREs can be found in Table 23 in the LATITUDE CSR, and are also presented below.

- The SRE frequency presented in the model for AAP + ADT of 16.4% (cell "G96" in the "Utilities" sheet) is estimated by diving the reported SREs (n=98) by the patients in the AAP arm (n=597).

- The SRE frequency presented in the model for ADT alone of 20.8% (cell "G97" in the "Utilities" sheet is estimated in the same manner.

- As no data were available from LATITUDE on SRE frequency for docetaxel + ADT, the frequency of SRE was assumed to be equivalent to that of AAP + ADT.

Time to SRE was defined as the earliest of the following: clinical or pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone. The number of events were calculated from the start of the trial to the end of follow-up (IA1: median follow-up of 30.4 months); events were counted regardless of whether patients were actively receiving AAP or had discontinued therapy.

The AE frequencies (cells "G91:G93" in the "Utilities" sheet) were estimated using values from Table 27 in the LATITUDE CSR, also presented below.

- To estimate the frequency of AEs for AAP + ADT, the number of SREs (n=98) was subtracted from the number of subjects with grade 3-4 TEAEs (n=374). This

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subtraction ensured that there was no double counting of SREs in the CE model. This value (n=276) was then divided by the patients in the AAP + ADT arm (n=597).

- The AE frequency presented in the model for ADT alone of 26.9% was estimated in the same manner.

- The AE frequency for docetaxel + ADT was again assumed to be equal to the AE frequency for the AAP + ADT arm, as this was the only data available for an active therapy.

[redacted]

Table 27: Overall Safety Profile; Safety Population (Study 212082PCR3011)

TSFAE01: Overall Safety Profile; Safety Population (Study 212082PCR3011)

	AA-P	Placebo
Analysis set: safety population	597	602
Number of subjects with treatment-emergent adverse events[a]	558 (93.5%)	557 (92.5%)
Drug-related[b]	336 (56.3%)	269 (44.7%)
Number of subjects with Grade 3-4 treatment-emergent adverse event[a]	374 (62.6%)	287 (47.7%)
Drug-related[b]	162 (27.1%)	67 (11.1%)
Number of subjects with treatment-emergent serious adverse events[a]	165 (27.6%)	146 (24.3%)
Drug-related[b]	29 (4.9%)	12 (2.0%)
Grade 3-4	142 (23.8%)	116 (19.3%)
Number of subjects with treatment-emergent adverse events leading to treatment discontinuation[c]	73 (12.2%)	61 (10.1%)
Drug-related[b]	21 (3.5%)	11 (1.8%)
Number of subjects with treatment-emergent adverse events leading to death	28 (4.7%)	24 (4.0%)
Drug-related[b]	3 (0.5%)	3 (0.5%)
All deaths within 30 days of last dose	40 (6.7%)	37 (6.1%)
Adverse event	27 (4.5%)	20 (3.3%)
Death due to prostate cancer	11 (1.8%)	16 (2.7%)
Natural causes	1 (0.2%)	0
Unknown	1 (0.2%)	1 (0.2%)

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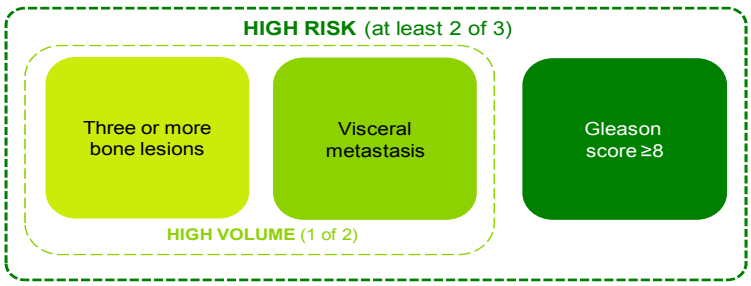
A21. For LATITUDE the company provides a post-hoc analysis of patients with high volume versus low volume of disease. Please clarify where these data come from and whether they are published or unpublished data.

A post-hoc analysis of the LATITUDE population was conducted to validate the appropriateness of the base case ITC used to inform the comparison of AAP + ADT versus docetaxel + ADT in newly diagnosed high-risk mHSPC.

Trials investigating docetaxel + ADT in mHSPC (i.e. CHAARTED and GETUG-AFU 15) used the 'high-volume' definition to ascertain which patients had more aggressive disease, and these criteria differed slightly to the 'high-risk' definition within LATITUDE. High-risk and high-volume criteria significantly overlap, as illustrated by Figure 1, and published literature has shown these definitions to be closely comparable.[3]

Figure 1: Definition of high-risk and high-volume disease



As such, a post-hoc analysis was conducted to retrospectively identify patients in the LATITUDE population who also met 'high-volume' criteria, as defined in CHAARTED and GETUG-AFU 15. Results showed both a high degree of overlap between these two definitions describing the aggressiveness of the tumour, and consistency in OS and rPFS endpoints, thus validating the appropriateness of conducting ITC with the LATITUDE ITT population.

Key results from this post-hoc analysis were published through a poster presented at the ASCO GU Congress (2018), which occurred the same week Janssen submitted to NICE. Unpublished data are still marked AIC in the submission and accompanying Appendices to protect future publication plans. As explained in response to A3., the final 'Feyerabend et al. (2018) – ASCO GU' poster is also provided in response to these clarification questions, to reassure the ERG and NICE of the veracity of evidence presented.

A22. Appendix Q page 134, Table 55: Please provide an extra column with the time to outcome for all the studies for easy comparison; currently some is given in the text only.

As requested, Table 55 from Appendix Q has been revised to include the additional column of interest and is now presented as Table 9 below.

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Table 9: mCRPC ITC: Summary of data available

Trial	Comparison	Outcome	Adjustment made for treatment switching (method)	HR	LCI	UCI	Median survival (Trial)
COU-AA-302	AAP vs. PP	OS	No	[redacted]	[redacted]	[redacted]	35.3 months
COU-AA-302	AAP vs. PP	rPFS	No	[redacted]	[redacted]	[redacted]	16.5 months
COU-AA-302	AAP vs. PP	OS	Yes (IPE)	[redacted]	[redacted]	[redacted]	Not reported
ALSYMPCA	Radium 223 vs. placebo	OS	No	[redacted]	[redacted]	[redacted]	14 months
ALSYMPCA	Radium 223 vs. placebo	rPFS*	No	[redacted]	[redacted]	[redacted]	3.6 months
PREVAIL	Enzalutamide vs. placebo	OS	No	[redacted]	[redacted]	[redacted]	32.4 months
PREVAIL	Enzalutamide vs. placebo	rPFS	No	[redacted]	[redacted]	[redacted]	Median not reached
PREVAIL	Enzalutamide vs. placebo	OS	Yes (IPCW)	[redacted]	[redacted]	[redacted]	Not reported
TAX327	Docetaxel 3wk vs. mitoxantrone	OS	No	[redacted]	[redacted]	[redacted]	18.9 months

Key: AAP, abiraterone acetate plus prednisone; HR, hazard ratio; IPCW, Inverse Probability of Censoring Weights; IPE, Iterative Parameter Estimation; LCI, lower confidence interval; OS, overall survival; PP, placebo plus prednisone; rPFS, radiographic progression free survival; UCI, upper confidence interval; vs. versus; wk, weekly.

Notes: *Based on the ALSYMPCA publication, what is taken as rPFS appears to be the time to an increase in the prostate-specific antigen (PSA) level.

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Section B: Clarification on cost-effectiveness data

B1 **PRIORITY QUESTION:** Please supply list of primary and secondary references for both the cost-effectiveness and health related quality of life (HRQL) searches.

Cost-effectiveness studies: The list provided in 'ERG B1' shows primary references with respective secondary references associated with each publication, as indicated via decimal points. Of note, this list is correct, having removed the two primary references published prior to 2005 (Nygard 2001 and Hillner 1995), as per the response to B2.

HRQL studies: The list provided in 'ERG B1' shows primary references with respective secondary references associated with each publication, as indicated via decimal points. Of note, this list is correct, having removed the five primary references published prior to (Iversen et al. 1996, Kaisary et al. 1995, Chodak et al. 1994, Tyrrell 1998, Moinpour et al. 1998), as per the response to B2.

B2 **PRIORITY QUESTION:** Please clarify date limits for searches. For cost effectiveness: Appendix G specifies searches were restricted to 2005-2017 (page 37); however, Table 22 includes several published prior to 2005. For HRQL Appendix H specifies searches were restricted to 2005-2017 (page 52); however, the identified studies in Table 29 include several published prior to 2005. Appendix H also specifies 15 studies were selected while Table 29 lists 17.

The date limits for the searches were restricted to 2005-2017. Any studies dated prior to 2005 have been included in error and should not have been presented. Indeed:

- In Appendix G (Table 22): two studies should be removed from results of the cost-effectiveness review (Nygard 2001 and Hillner 1995)

- In Appendix H (Table 29): five studies should be removed from results of the HRQL review (Iversen et al. 1996, Kaisary et al. 1995, Chodak et al. 1994, Tyrrell 1998, Moinpour et al. 1998). Accounting for these revisions, as per SLR protocol, also resolves the clarification required in Appendix H; 12 studies were selected and should be detailed in Table 29 (the original reason for this mismatch was due to the inclusion of secondary references in Table 29 that were in fact linked).

Of note, none of the studies dated prior to 2005 were utilised in the submission.

B3 **PRIORITY QUESTION:** Please clarify the following anomalies in the search strategies:

- Table 18 (Appendix G) has no date limit specified – is this the Embase & MEDLINE search used for 2015-2017 as Table 17 specifies 2005-2015?

Table 18 lists the searches carried out in Pubmed.com to identify Medline-in-Process records, where no date limits applied. The updated tables are provided as Table 17 and Table 18 should be read as mentioned below.

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Table 17: Embase and MEDLINE (via Embase.com) search strategy (Costs/resource use/cost- effectiveness)

Search no.	Search terms	No. of hits
Patient Population		
1.	'prostate cancer'/exp OR (prostate:ab,ti AND metasta*:ab,ti AND (cancer:ab,ti OR neoplas*:ab,ti OR carcinoma*:ab,ti))	179,417
Intervention or comparator		
2.	'androgen deprivation therapy'/exp OR 'anti-androgen therapy'/exp OR 'antiandrogen':ab,ti OR 'anti androgen':ab,ti OR 'anti-androgen':ab,ti OR 'androgen antagonist':ab,ti OR 'androgen dependent':ab,ti OR 'androgen-dependent':ab,ti OR 'androgen ablation':ab,ti OR 'androgen-ablation':ab,ti OR 'androgen blockade':ab,ti OR 'androgen-blockade':ab,ti OR 'androgen receptor':ab,ti OR 'androgen suppression':ab,ti OR 'luteinizing hormone':ab,ti OR 'luteinising hormone':ab,ti OR 'gonadotropin-releasing hormone':ab,ti OR 'gonadotropin releasing hormone':ab,ti OR lhrh:ab,ti OR gnrh:ab,ti OR abiraterone:ab,ti OR zytiga:ab,ti OR 'androgen deprivation':ab,ti OR adt:ab,ti OR docetaxel:ab,ti OR taxotere:ab,ti OR docecad:ab,ti OR docefrez:ab,ti OR zytax:ab,ti OR enzalutamide:ab,ti OR xtandi:ab,ti OR leuprolide:ab,ti OR leuprorelin:ab,ti OR lupron:ab,ti OR viadur:ab,ti OR eligard:ab,ti OR prostap:ab,ti OR buserelin:ab,ti OR seprefact:ab,ti OR cinnafact:ab,ti OR metrelef:ab,ti OR aminoglutethimide:ab,ti OR cytadren:ab,ti OR xtandi:ab,ti OR goserelin:ab,ti OR zoladex:ab,ti OR triptorelin:ab,ti OR decapeptyl:ab,ti OR diphereline:ab,ti OR gonapeptyl:ab,ti OR trelstar:ab,ti OR variopeptyl:ab,ti OR histrelin:ab,ti OR vantas:ab,ti OR supprelin:ab,ti OR degarelix:ab,ti OR firmagon:ab,ti OR 'antiandrogen':ab,ti OR flutamide:ab,ti OR eulexin:ab,ti OR cytomid:ab,ti OR chimax:ab,ti OR drogenil:ab,ti OR flucinom:ab,ti OR flutamin:ab,ti OR fugerel:ab,ti OR niftolide:ab,ti OR sebatrol:ab,ti OR bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR calutide:ab,ti OR kalumid:ab,ti OR nilutamide:ab,ti OR nilandron:ab,ti OR anandron:ab,ti OR estrogen:ab,ti OR oestrogen:ab,ti OR ketoconazole:ab,ti OR nizoral:ab,ti OR diethylstilbestrol:ab,ti OR ethinylestradiol:ab,ti OR cyproterone:ab,ti	280, 198
Outcomes		
3.	cost*:ab,ti OR 'economic':ab,ti OR budget*:ab,ti OR 'expenditure':ab,ti OR ('resource':ab,ti AND 'utilization':ab,ti) OR ('resource':ab,ti AND 'utilisation':ab,ti) OR ('resource':ab,ti AND 'use':ab,ti) OR ('health':ab,ti AND 'care':ab,ti AND 'utilization':ab,ti) OR ('health':ab,ti AND 'care':ab,ti AND 'utilisation':ab,ti) OR ('health':ab,ti AND 'care':ab,ti AND 'use':ab,ti) OR ('healthcare':ab,ti AND 'utilization':ab,ti) OR ('healthcare':ab,ti AND 'utilisation':ab,ti) OR ('healthcare':ab,ti AND 'use':ab,ti) OR 'economic evaluation':ab,ti OR 'cost benefit':ab,ti OR 'cost effectiveness':ab,ti OR 'cost utility':ab,ti OR 'cost minimization':ab,ti OR 'cost minimisation':ab,ti OR 'cost savings':ab,ti OR 'cost saving':ab,ti OR 'pharmaceutical economics':ab,ti OR 'budget impact':ab,ti OR 'econometric':ab,ti OR 'markov':ab,ti OR 'decision analysis':ab,ti OR 'discrete event simulation':ab,ti OR ('model':ab,ti OR 'models':ab,ti OR 'modeling':ab,ti	1,179, 057

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	OR 'modelling':ab,ti AND (cost*:ab,ti OR 'economic':ab,ti OR 'economics':ab,ti)) OR 'cost benefit analysis'/exp OR 'cost control'/exp OR 'pharmacoeconomics'/exp	
4.	#1 AND #2 AND #3	1,283
Limit to relevant publication types		
5.	('case study'/exp OR 'letter'/exp OR 'editorial'/exp) OR (review:it NOT (systematic OR meta AND analy* OR (indirect OR mixed AND 'treatment comparison'))) OR ('animal'/exp NOT 'human'/exp)	7,791,375
Combined		
6.	#4 NOT #5	960
7.	#4 NOT #5 AND [english]/lim	920
8.	English language only studies published between 2005 and 2015	610
9.	#4 NOT #5 AND [english]/lim AND [1-9-2015]/sd NOT [10-7-2017]/sd	204

Table 18: MEDLINE In-Process (via PubMed) search strategy (Costs/resource use/cost- effectiveness)

Sr. No.	Query	Hits
1.	“prostate cancer”[Mesh] OR (prostate[tiab] AND metasta*[tiab] AND (cancer[tiab] OR neoplas*[tiab] OR carcinoma*[tiab]))	24,001
2.	“androgen antagonists”[Mesh] OR “androgen receptor antagonist”[Mesh] OR “anti androgen”[tiab] OR “anti-androgen”[tiab] OR “antiandrogen”[tiab] OR “androgen antagonist”[tiab] OR “androgen dependent”[tiab] OR “androgen-dependent”[tiab] OR “androgen ablation”[tiab] OR “androgen-ablation”[tiab] OR “androgen blockade”[tiab] OR “androgen-blockade”[tiab] OR “androgen receptor”[tiab] OR “androgen suppression”[tiab] OR “luteinizing hormone”[tiab] OR “luteinising hormone”[tiab] OR “gonadotropin-releasing hormone”[tiab] OR “gonadotropin releasing hormone”[tiab] OR lhrh[tiab] OR gnrh[tiab] OR abiraterone[tiab] OR zytiga[tiab] OR “androgen deprivation”[tiab] OR adt[tiab] OR docetaxel[tiab] OR taxotere[tiab] OR docecad[tiab] OR docefrez[tiab] OR zytax[tiab] OR enzalutamide[tiab] OR leuprolide[tiab] OR leuprorelin[tiab] OR lupron[tiab] OR viadur[tiab] OR eligard[tiab] OR prostap[tiab] OR buserelin[tiab] OR seprefact[tiab] OR cinnafact[tiab] OR metrelef[tiab] OR aminoglutethimide[tiab] OR cytadren[tiab] OR xtandi[tiab] OR goserelin[tiab] OR zoladex[tiab] OR triptorelin[tiab] OR decapeptyl[tiab] OR diphereline[tiab] OR gonapeptyl[tiab] OR trelstar[tiab] OR variopeptyl[tiab] OR histrelin[tiab] OR vantas[tiab] OR supprelin[tiab] OR degarelix[tiab] OR firmagon[tiab] OR antiandrogen[tiab] OR flutamide[tiab] OR eulexin[tiab] OR cytomid[tiab] OR chimax[tiab] OR drogenil[tiab] OR flucinom[tiab] OR flutamin[tiab] OR fugerel[tiab] OR niftolide[tiab] OR sebatrol[tiab] OR bicalutamide[tiab] OR casodex[tiab] OR cosudex[tiab] OR calutide[tiab] OR kalumid[tiab] OR nilutamide[tiab] OR nilandron[tiab] OR anandron[tiab] OR estrogen[tiab] OR	223,968

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	oestrogen[tiab] OR ketoconazole[tiab] OR nizoral[tiab] OR diethylstilbestrol[tiab] OR ethinylestradiol[tiab] OR cyproterone[tiab]	
3.	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	433,864
4.	#1 AND #2 AND #3	142

- There are two line 6's. (Table 18 and Table 26 in Appendix G) The first appears to be wrong as the number of hits should not be less than line 5. Please clarify.

There are 2x line 6's because #4 and #5 are not used anywhere in the combined searches in both the tables. These searches were carried out in in Pubmed.com to identify Medline-in-Process records. The numbers are corrected in the updated Table 26 below (Table 18 was presented above).

Table 26: Embase and MEDLINE (via Pubmed.com) search strategy (HRQL/PROs/utilities)

Sr. No.	Query	Hits
1.	"prostate cancer"[Mesh] OR (prostate[tiab] AND metasta*[tiab] AND (cancer[tiab] OR neoplas*[tiab] OR carcinoma*[tiab]))	24,001
2.	"androgen antagonists"[Mesh] OR "androgen receptor antagonist"[Mesh] OR "anti androgen"[tiab] OR "anti-androgen"[tiab] OR "antiandrogen"[tiab] OR "androgen antagonist"[tiab] OR "androgen dependent"[tiab] OR "androgen-dependent"[tiab] OR "androgen ablation"[tiab] OR "androgen-ablation"[tiab] OR "androgen blockade"[tiab] OR "androgen-blockade"[tiab] OR "androgen receptor"[tiab] OR "androgen suppression"[tiab] OR "luteinizing hormone"[tiab] OR "luteinising hormone"[tiab] OR "gonadotropin-releasing hormone"[tiab] OR "gonadotropin releasing hormone"[tiab] OR lhrh[tiab] OR gnrh[tiab] OR abiraterone[tiab] OR zytiga[tiab] OR "androgen deprivation"[tiab] OR adt[tiab] OR docetaxel[tiab] OR taxotere[tiab] OR docecad[tiab] OR docefrez[tiab] OR zytax[tiab] OR enzalutamide[tiab] OR leuprolide[tiab] OR leuprorelin[tiab] OR lupron[tiab] OR viadur[tiab] OR eligard[tiab] OR prostap[tiab] OR buserelin[tiab] OR seprefact[tiab] OR cinnafact[tiab] OR metrelef[tiab] OR aminoglutethimide[tiab] OR cytadren[tiab] OR xtandi[tiab] OR goserelin[tiab] OR zoladex[tiab] OR triptorelin[tiab] OR decapeptyl[tiab] OR diphereline[tiab] OR gonapeptyl[tiab] OR trelstar[tiab] OR variopeptyl[tiab] OR histrelin[tiab] OR vantas[tiab] OR supprelin[tiab] OR degarelix[tiab] OR firmagon[tiab] OR antiandrogen[tiab] OR flutamide[tiab] OR eulexin[tiab] OR cytomid[tiab] OR chimax[tiab] OR drogenil[tiab] OR flucinom[tiab] OR flutamin[tiab] OR fugerel[tiab] OR niftolide[tiab] OR sebatrol[tiab] OR bicalutamide[tiab] OR casodex[tiab] OR cosudex[tiab] OR calutide[tiab] OR kalumid[tiab] OR nilutamide[tiab] OR nilandron[tiab] OR anandron[tiab] OR estrogen[tiab] OR	223,968

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	oestrogen[tiab] OR ketoconazole[tiab] OR nizoral[tiab] OR diethylstilbestrol[tiab] OR ethinylestradiol[tiab] OR cyproterone[tiab]	
3.	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	433,864
4.	#1 AND #2 AND #3	142

- Table 19 (Appendix G) and Table 27 (Appendix H) date limits are 2015-2017. Were NHS EED & HTA Database searched only for these years?

Table 19 and table 27 applies to searches for identification of studies in Cochrane library. Original SLR was conducted from 2005 to 2015 and an update was performed from 2015-2017. The tables are updated and provided below.

Table 19: NHS EED and HTA Database (via the Cochrane Library) search strategy

Search no.	Search terms	No. of hits
Patient population		
1.	prostate:ab,ti AND metasta*:ab,ti AND (cancer:ab,ti OR neoplas*:ab,ti OR carcinoma*:ab,ti)	2,003
2.	MeSH descriptor: [Prostatic Neoplasms] explode all trees	4,161
Intervention or comparator		
3.	'androgen deprivation therapy':ab,ti OR 'anti-androgen therapy':ab,ti OR 'antiandrogen':ab,ti OR 'anti androgen':ab,ti OR 'anti-androgen':ab,ti OR 'androgen antagonist':ab,ti OR 'androgen dependent':ab,ti OR 'androgen-dependent':ab,ti OR 'androgen ablation':ab,ti OR 'androgen-ablation':ab,ti OR 'androgen blockade':ab,ti OR 'androgen-blockade':ab,ti OR 'androgen receptor':ab,ti OR 'androgen suppression':ab,ti OR 'luteinizing hormone':ab,ti OR 'luteinising hormone':ab,ti OR 'gonadotropin-releasing hormone':ab,ti OR 'gonadotropin releasing hormone':ab,ti OR lhrh:ab,ti OR gnrh:ab,ti OR abiraterone:ab,ti OR zytiga:ab,ti OR 'androgen deprivation':ab,ti OR adt:ab,ti OR docetaxel:ab,ti OR taxotere:ab,ti OR docecad:ab,ti OR docefrez:ab,ti OR zytax:ab,ti OR enzalutamide:ab,ti OR xtandi:ab,ti OR leuprolide:ab,ti OR leuprorelin:ab,ti OR lupron:ab,ti OR viadur:ab,ti OR eligard:ab,ti OR prostap:ab,ti OR buserelin:ab,ti OR seprefact:ab,ti OR cinnafact:ab,ti OR metrelef:ab,ti OR aminoglutethimide:ab,ti OR cytadren:ab,ti OR xtandi:ab,ti OR goserelin:ab,ti OR zoladex:ab,ti OR triptorelin:ab,ti OR decapeptyl:ab,ti OR diphereline:ab,ti OR gonapeptyl:ab,ti OR trelstar:ab,ti OR variopeptyl:ab,ti OR histrelin:ab,ti OR vantas:ab,ti OR supprelin:ab,ti OR degarelix:ab,ti OR firmagon:ab,ti OR 'antiandrogen':ab,ti OR flutamide:ab,ti OR eulexin:ab,ti OR cytomid:ab,ti OR chimax:ab,ti OR drogenil:ab,ti OR flucinom:ab,ti OR flutamin:ab,ti OR fugerel:ab,ti OR niftolide:ab,ti OR sebatrol:ab,ti OR bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR calutide:ab,ti OR kalumid:ab,ti OR nilutamide:ab,ti OR nilandron:ab,ti OR anandron:ab,ti OR estrogen:ab,ti OR oestrogen:ab,ti OR ketoconazole:ab,ti OR nizoral:ab,ti OR diethylstilbestrol:ab,ti OR	18,793

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	ethinylestradiol:ab,ti OR cyproterone:ab,ti	
Combined		
4.*	(#1 OR #2) AND #3	1, 942
5.	#4, in Technology Assessments and Economic Evaluations	52
6.	#4, Publication Year from 2015 to 2017, in Technology Assessments and Economic Evaluations	6
*The results in the "Economic evaluations" category will be retrieved to obtain the results from NHS EED and the results in the "Technology assessments" category will be retrieved to obtain the results from HTA Database.		

Table 27: NHS EED and HTA Database (via the Cochrane Library) search strategy

Search no.	Search terms	No. of hits
Patient population		
1.	prostate:ab,ti AND metasta*:ab,ti AND (cancer:ab,ti OR neoplas*:ab,ti OR carcinoma*:ab,ti)	2,003
2.	MeSH descriptor: [Prostatic Neoplasms] explode all trees	4,161
Intervention or comparator		
3.	'androgen deprivation therapy':ab,ti OR 'anti-androgen therapy':ab,ti OR 'antiandrogen':ab,ti OR 'anti androgen':ab,ti OR 'anti-androgen':ab,ti OR 'androgen antagonist':ab,ti OR 'androgen dependent':ab,ti OR 'androgen-dependent':ab,ti OR 'androgen ablation':ab,ti OR 'androgen-ablation':ab,ti OR 'androgen blockade':ab,ti OR 'androgen-blockade':ab,ti OR 'androgen receptor':ab,ti OR 'androgen suppression':ab,ti OR 'luteinizing hormone':ab,ti OR 'luteinising hormone':ab,ti OR 'gonadotropin-releasing hormone':ab,ti OR 'gonadotropin releasing hormone':ab,ti OR lhrh:ab,ti OR gnrh:ab,ti OR abiraterone:ab,ti OR zytiga:ab,ti OR 'androgen deprivation':ab,ti OR adt:ab,ti OR docetaxel:ab,ti OR taxotere:ab,ti OR docecad:ab,ti OR docefrez:ab,ti OR zytax:ab,ti OR enzalutamide:ab,ti OR xtandi:ab,ti OR leuprolide:ab,ti OR leuprorelin:ab,ti OR lupron:ab,ti OR viadur:ab,ti OR eligard:ab,ti OR prostap:ab,ti OR buserelin:ab,ti OR seprefact:ab,ti OR cinnafact:ab,ti OR metrelef:ab,ti OR aminoglutethimide:ab,ti OR cytadren:ab,ti OR xtandi:ab,ti OR goserelin:ab,ti OR zoladex:ab,ti OR triptorelin:ab,ti OR decapeptyl:ab,ti OR diphereline:ab,ti OR gonapeptyl:ab,ti OR trelstar:ab,ti OR variopeptyl:ab,ti OR histrelin:ab,ti OR vantas:ab,ti OR supprelin:ab,ti OR degarelix:ab,ti OR firmagon:ab,ti OR 'antiandrogen':ab,ti OR flutamide:ab,ti OR eulexin:ab,ti OR cytomid:ab,ti OR chimax:ab,ti OR drogenil:ab,ti OR flucinom:ab,ti OR flutamin:ab,ti OR fugerel:ab,ti OR niftolide:ab,ti OR sebatrol:ab,ti OR bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR calutide:ab,ti OR kalumid:ab,ti OR nilutamide:ab,ti OR nilandron:ab,ti OR anandron:ab,ti OR estrogen:ab,ti OR oestrogen:ab,ti OR ketoconazole:ab,ti OR nizoral:ab,ti OR diethylstilbestrol:ab,ti OR ethinylestradiol:ab,ti OR cyproterone:ab,ti	18,793
Combined		
4.*	(#1 OR #2) AND #3	1, 942

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5.	#4, in Technology Assessments and Economic Evaluations	52
6.	#4, Publication Year from 2015 to 2017, in Technology Assessments and Economic Evaluations	6
*The results in the "Economic evaluations" category will be retrieved to obtain the results from NHS EED and the results in the "Technology assessments" category will be retrieved to obtain the results from HTA Database.		

- Table 25 (Appendix H) specifies date range 2005-2015. Was this search updated in 2017?

Yes, the searches were updated in July 2017 from September 2015 onwards. #7 lists the records with original searches (2005–2015) and #8 lists the records obtained during the update (2015 onwards); the updated table is presented below.

Table 10: Embase and MEDLINE (via Embase.com) search strategy (HRQL/PROs/utilities)

Search no.	Search terms	No. of hits
Patient Population		
1.	'prostate cancer'/exp OR (prostate:ab,ti AND metasta*:ab,ti AND (cancer:ab,ti OR neoplas*:ab,ti OR carcinoma*:ab,ti))	179,417
Intervention or comparator		
2.	'androgen deprivation therapy'/exp OR 'anti-androgen therapy'/exp OR 'antiandrogen':ab,ti OR 'anti androgen':ab,ti OR 'anti-androgen':ab,ti OR 'androgen antagonist':ab,ti OR 'androgen dependent':ab,ti OR 'androgen-dependent':ab,ti OR 'androgen ablation':ab,ti OR 'androgen-ablation':ab,ti OR 'androgen blockade':ab,ti OR 'androgen-blockade':ab,ti OR 'androgen receptor':ab,ti OR 'androgen suppression':ab,ti OR 'luteinizing hormone':ab,ti OR 'luteinising hormone':ab,ti OR 'gonadotropin-releasing hormone':ab,ti OR 'gonadotropin releasing hormone':ab,ti OR lhrh:ab,ti OR gnrh:ab,ti OR abiraterone:ab,ti OR zytiga:ab,ti OR 'androgen deprivation':ab,ti OR adt:ab,ti OR docetaxel:ab,ti OR taxotere:ab,ti OR docecad:ab,ti OR docefrez:ab,ti OR zytax:ab,ti OR enzalutamide:ab,ti OR xtandi:ab,ti OR leuprolide:ab,ti OR leuprorelin:ab,ti OR lupron:ab,ti OR viadur:ab,ti OR eligard:ab,ti OR prostap:ab,ti OR buserelin:ab,ti OR seprefact:ab,ti OR cinnafact:ab,ti OR metrelef:ab,ti OR aminoglutethimide:ab,ti OR cytadren:ab,ti OR xtandi:ab,ti OR goserelin:ab,ti OR zoladex:ab,ti OR triptorelin:ab,ti OR decapeptyl:ab,ti OR diphereline:ab,ti OR gonapeptyl:ab,ti OR trelstar:ab,ti OR variopeptyl:ab,ti OR histrelin:ab,ti OR vantas:ab,ti OR supprelin:ab,ti OR degarelix:ab,ti OR firmagon:ab,ti OR 'antiandrogen':ab,ti OR flutamide:ab,ti OR eulexin:ab,ti OR cytomid:ab,ti OR chimax:ab,ti OR drogenil:ab,ti OR flucinom:ab,ti OR flutamin:ab,ti OR fugerel:ab,ti OR niftolide:ab,ti OR sebatrol:ab,ti OR bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR calutide:ab,ti OR kalumid:ab,ti OR nilutamide:ab,ti OR nilandron:ab,ti OR anandron:ab,ti OR estrogen:ab,ti OR oestrogen:ab,ti OR	280,198

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	ketoconazole:ab,ti OR nizoral:ab,ti OR diethylstilbestrol:ab,ti OR ethinylestradiol:ab,ti OR cyproterone:ab,ti	
Outcomes		
3.	'quality of life'/exp OR 'qaly':ab,ti OR 'qalys':ab,ti OR 'quality adjusted life year'/exp OR 'quality adjusted life year':ab,ti OR 'quality adjusted life years':ab,ti OR 'quality of life':ab,ti OR (utilit*:ab,ti AND 'health':ab,ti) OR (utilit*:ab,ti AND scor*:ab,ti) OR (utilit*:ab,ti AND valu*:ab,ti) OR (disutilit*:ab,ti AND 'health':ab,ti) OR (disutilit*:ab,ti AND scor*:ab,ti) OR (disutilit*:ab,ti AND valu*:ab,ti) OR 'daly':ab,ti OR 'dalys':ab,ti OR 'disability adjusted life year':ab,ti OR 'disability adjusted life years':ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'eq 5d':ab,ti OR 'euroqol 5d':ab,ti OR 'eortc':ab,ti OR 'qlq':ab,ti	519,526
4.	#1 AND #2 AND #3	2,832
Limit to relevant publication types		
5.	('case study'/exp OR 'letter'/exp OR 'editorial'/exp) OR (review:it NOT (systematic OR meta AND analy* OR (indirect OR mixed AND 'treatment comparison'))) OR ('animal'/exp NOT 'human'/exp)	8,415,508
Combined		
6.	#4 NOT #5	2,154
7.	#4 NOT #5 AND [english]/lim AND 2005-2015	1,375
8.	#4 NOT #5 AND [english]/lim AND [1-9-2015]/sd NOT [10-7-2017]/sd	447

B4 Please tabulate the data of Document B Figure 12 (Mean change in EQ-5D-5L VAS and utility scores from baseline LATITUDE, ITT population), augmented with the number of EQ-5D questionnaires completed at each timepoint. Please clarify why this has many more data points through time than table 42 (Results of the descriptive analysis of EQ-5D-5L data: LATITUDE) of Appendix N. Did the regression analysis include all the data points or only the data at the timepoints given in table 42 of Appendix N? Please present table 42 of appendix N split by arm.

Table 42 from Appendix N presents the number of questionnaires utilised in the utility regression analysis, and Figure 12 from Document B presents the number of questionnaires utilised in the Chi et al 2018 publication.[4] The number of questionnaires between the utility analyses and Chi et al 2018 do not match because of differences in the two analyses.

- In the Table 42, only patients with non-missing utility values over time and observed mean utility values are presented. The utility regression utilised in the CE model does not impute values from missing questionnaires but instead only utilises observed data.

- In Chi et al 2018, the predicted mean change in utility from baseline was calculated using a regression model which included variables for treatment, cycle and treatment and cycle interaction. This model was used to predict utility values for all patients regardless of whether they completed a questionnaire or not at baseline or at specific time points during follow up. Therefore, the patient numbers presented in Chi et al.

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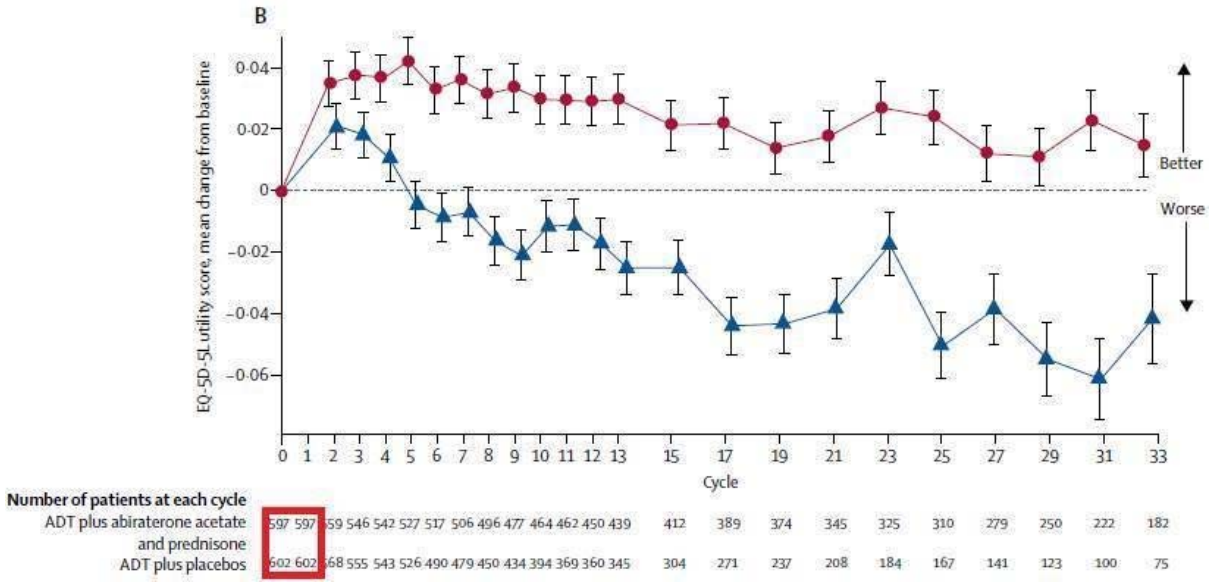
2018 represent the number of patients who were expected to complete a questionnaire in each cycle, regardless of whether they actually did or not.

The number of baseline questionnaires presented in Table 42 matches the value reported in the CSR.



[redacted]

B5 To what extent were the end of treatment and follow-up quality of life EQ-5D values included in the RMME (repeated measures mixed-effect) data set and analysed? If these were excluded from the analysis what is the reason for this?

The end of treatment and follow-up quality of life EQ-5D-5L values were included in the RMME data-set and utilised in the regression. Utilising all the available data points allowed for the best estimation of the utility regression.

B6 **PRIORITY QUESTION:** Please expand table 43 (Univariate utility regression analysis) of Appendix N to include all the variables that were examined within univariate regressions for significance at the 10% level, including those with p-values above 10%.

All the variables that were tested in univariate analysis, including their respective p-values, are presented in Table 43 of Appendix N. This included values that were found to be statistically significant and those that were not.

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B7 **PRIORITY QUESTION:** Please provide the internal report that underlies Document B Table 27 (LATITUDE utility regression results). Please augment Document B Table 27 with coefficient standard errors and p-values. Please also provide the equivalent of model 1 of Document B Table 27, with coefficient standard errors and p-values, for models which estimate:

- a single pooled coefficient for "AE (Ever)"
- a single pooled coefficient for "SRE (Ever)"
- a single pooled coefficient for "AE (Ever)" and a single pooled coefficient for "SRE (Ever)"

Please see the "ERG B7" workbook provided which presents the requested analysis. The regressions presented do the following:

Model 1.1 = Replaces the AE variables split by treatment arm for one joint AE variable (removes AE treatment interaction).

Model 1.2 = Replaces the SRE variables split by treatment arm for one joint SRE variable (removes SRE treatment interaction).

Model 1.3 = Replaces the AE variables and the SRE variables by treatment arm for one joint AE variable and one joint SRE variable (removing both treatment interactions).

Please see 'ERG B7' which presents the coefficient: estimates, standard errors, p-values, lower CI and upper CI. Regression model fit statistics (-2 Res Log Likelihood, AIC, AICC, BIC) are also presented for each model.

These three additional regression models have been incorporated in the attached abiraterone CE model. Cell "C46" on the "Controls" sheet allows the user to select the model that they wish to utilise in the CE model.

Table 11 presents the ICERs for the comparison of AAP + ADT with ADT alone and docetaxel + ADT by applying the model base-case assumptions and changing each of the utility regressions selected. The results demonstrate that the ICER remains below £30,000 in each scenario, and that when models 1.1 and 1.3 are utilised the ICERs decrease, highlighting the robustness of the results.

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Table 11: Model results using each utility regression model

Model	ICER (vs ADT alone)	ICER (vs docetaxel + ADT)
Model 1.0 (Base-case)	£23,287	£28,616
Model 1.1	£22,745	£27,230
Model 1.2	£23,266	£28,561
Model 1.3	£22,682	£27,076

Table 12 presents under the scenario where the regression coefficients for AEs and SREs are utilised in the model. This scenario differs from the base case which utilises the disutilities and rates for AE and SRE from the literature. Literature information was used in the base case in preference as there are limitations in capturing the impact of key AEs within trials, especially for patients experiencing severe AEs who often have a lower questionnaire completion rate, as highlighted in Page 136 of Document B. However, when this scenario is applied, there is little variation in the ICER as the regression model applied changes, further supporting the robustness of the base case results.

Table 12: Results

Model	ICER (vs ADT alone)	ICER (vs docetaxel + ADT)
Model 1.0 (Base-case)	£23,411	£34,332
Model 1.1	£23,653	£33,866
Model 1.2	£23,681	£34,705
Model 1.3	£24,071	£34,364

B8 **PRIORITY QUESTION:** To what extent is there statistical evidence from the regression analysis of the LATITUDE EQ-5D data that:

- the impact of having experienced an SAE was different in the AAP+ADT arm than in the ADT arm?
- the impact of having experienced an SRE was different in the AAP+ADT arm than in the ADT arm?

The base-case model does not utilise the AE and SRE coefficients from the regression analysis, but instead estimates the impact of AEs and SREs by utilising rates and disutilities for each AE and SRE from the literature. Literature information was used in the base case in preference as there are limitations in capturing the impact of key AEs within trials as patients experiencing severe AEs often have a lower questionnaire completion rate, as highlighted in Page 136 of Document B. The base-case model therefore applies the same disutility values for each AE and SRE regardless of the treatment patients receive.

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However, LATITUDE evidence suggests that the impact of having experienced an AE or SRE was different in the AAP + ADT arm than in the ADT alone arm. The utility regression analysis highlighted some difference, with the coefficient for AE being -0.031 for AAP + ADT and -0.076 for ADT alone, and the coefficient for SRE being -0.139 for AAP + ADT and -0.100 for ADT alone.

Each of the variables included in the utility regression model 1.0, which estimates treatment-specific AE and SRE coefficients, were found to be statistically significant (presented in the "ERG B7" workbook). The p-values for the AE and SRE coefficients separated by treatment arm are all well below 0.01.

B9 Please provide an Excel workbook that derives the estimates outlined in Document B table 28 (summary of utility values for cost-effectiveness analysis) using the inputs of Document B table 27 (LATITUDE utility regression results).

This table, containing all of the relevant calculations, can be found in the model on the Base-case results sheet in Cells B63 to E74.

B10 The submission mentions but does not define "*the utility value for 1L mCRPC based upon the LATITUDE data*". Please clarify how this value is derived and its value.

The utility value for 1L mCRPC is estimated from the utility regression, in line with the values presented in Document B Table 28. To estimate the utility values for 2L mCRPC and 3L mCRPC, this 1L mCRPC utility value was adjusted using utility values from the TA387 submission. This was done by firstly estimating the 1L mCRPC value using the following formula:

(p_Utilities.intercept+(p_Utilities.EQ5D.coefficient*p_Utilities.mHSPC.baselineutil)+(IF(Controls.AAPinc="Tilldeath",p_Comp1.UtilInc,0))+ p_Utilities.rPFS)

AE/SRE disutilities, as well as any treatment utility increments, were then added to the equation depending on the relevant market shares for each subsequent treatment in 2L mCRPC and 3L mCRPC. Finally, this total value was multiplied by the ratios for 2L mCRPC (0.753) and 3L mCRPC (0.602) respectively to estimate the utility values for patients in the 2L mCRPC and 3L mCRPC phases of the model.

B11 The model uses 4 utility values from TA387 (C73:C76 of the *Utilities* worksheet) but the submission does not outline how these were derived, and how they relate to the set of final quality of life values of the Appraisal Committee's preferred base case in TA387. Please present this information and comment about the plausibility of these values.

As presented below, Table 42 (page 123) in the company submission for TA387 presents the utility values that were utilised in the model. These values were utilised to calculate the relative

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utility decline from 1L to 2L mCRPC (i.e. 0.625/0.830) and from 1L mCRPC to 3L mCRPC (i.e. 0.500/0.830). In addition, the AA utility increment in mCRPC of 0.021 was applied to patients receiving AA during the 1L mCRPC phase of the model. The source of each of these values is summarised below:

- **mCRPC 1L and 2L (0.830 and 0.625):** These values were estimated from a UK-based mCRPC patient utility study. The study aimed to collect health utility values for mCRPC stratified by treatment phases. The study assumed that patients experience the same utility regardless of the treatment administered, provided they are in the same treatment phase. EQ-5D-5L values were estimated from a total sample of 163 men with mCRPC. Patients with mCRPC were classified into one of the following four subgroups reflecting treatment phases:
    - Mildly or asymptomatic after failure of ADT; chemotherapy not yet clinically indicated
    - Symptomatic after failure of ADT; chemotherapy clinically indicated but not started
    - After failure of ADT; receiving chemotherapy
    - After failure of ADT; post-chemotherapy.

- **mCRPC 3L (0.500):** This value was taken from Sandblom et al. (2004)[5] which was utilised in both the TA387 and TA259 submissions to represent the utility value of patients in their last months prior to death. These values were estimated by calculating the average observed utilities over the last eight months of life. Utilities from this study ranged from 0.58 (patients with 8–12 months of remaining survival) to 0.46 (patients with <4 months survival remaining). An average utility of 0.50 was then estimated from this study.

- **AA utility increment (mCRPC):** This value was estimated from a mapping study of COU-AA-302 utility data. In COU-AA-302, HRQL was measured using the FACT-P questionnaire. As such, the mapping algorithm described by Diels et al. (2012)[6] was used to derive EQ-5D utility values appropriate for inclusion in the economic model, as specified in the NICE reference case. Full details of this mapping study can be found in Appendix 18 of the TA387 submission.

References are included in response to these clarification questions. In utilising these values, it allowed for consistency with previous NICE submissions. Scenario analysis presented in Table 35 in Document B tested the robustness of the results when these assumptions were varied. These results showed that when the ratios for 2L and 3L mCRPC were not applied then the ICER for AAP + ADT versus ADT alone changed from £23,287 to £23,408 and for the comparison of AAP + ADT versus docetaxel + ADT the ICER changes from £28,616 to £28,851. When the AA utility increment from TA387 is excluded the ICER for AAP + ADT versus ADT alone changes from £23,287 to £23,175 and for the comparison of AAP + ADT

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versus docetaxel + ADT the ICER changes from £28,616 to £28,357. This highlights to robustness of the model results to changes in these values.

Table 42: Summary of the utility values associated with each model phase

Utilities	Value	SE (distribution)	Source
Post-ADT baseline	0.830	0.018	UK mCRPC patient utility study
AAP on-treatment utility increment	0.021	0.007	COU-AA-302 mapping study
BSC (pre-docetaxel)	0.625	0.024	UK mCRPC patient utility study
Docetaxel	0.692	0.053	UK mCRPC patient utility study
Post-docetaxel	0.700	0.027	UK mCRPC patient utility study
BSC (before death)	0.500	0.08	Sandblom et al. [154]

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone.

B12 Please confirm that all LATITUDE data used to estimate model inputs (including e.g., MRU – mHSPC rates of resource use) were collected at IA1 and that this was prior to any unblinding of LATITUDE.

Correct.

B13 With regards to the Kaplan Meier OS (pre-subsequent therapy) please define an event and how this differs from an event in the Kaplan Meier OS curve. Similarly, please define censoring events for the two curves and how these differ. Each Kaplan Meier OS curve of the model appears to have been constrained to be no more than the Kaplan Meier OS (pre-subsequent therapy) curve of the model. Please explain the rationale for this assumption.

Regarding the KM OS pre-subsequent therapy curve, death was defined as the only event for OS, while patients moving onto subsequent therapy or lost to follow-up were classed as censored.

Regarding the KM OS curve, death was defined as the only event for OS and patients lost to follow-up were censored.

The model is based on the constraint that the OS curve is never greater than the OS (pre-subsequent therapy) curve to ensure that consistent values are accounted for. The OS curve values should always be lower than the OS pre-subsequent therapy curve values as OS captures death both pre- and post-subsequent therapy, whereas the OS pre-subsequent therapy curve only captures events that occurred prior to patients receiving subsequent therapy (which would be expected to occur less frequently given that the prognosis of patients worsens when they move on to later lines of treatment). However, this constraint makes little difference to the model as when it is removed for each treatment there is only one cycle in the AAP + ADT and docetaxel + ADT arms where OS value is greater than OS (pre-subsequent therapy) value, and 3 cycles in the ADT alone arm where this is the case. The difference in each of these cycles is also minimal, with all differences being equal to less than 0.001.

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B14 The Kaplan Meier PFS curve of the model appears to have been constrained to be no more than the Kaplan Meier TTST (time to subsequent therapy) curve of the model. Please explain the rationale for this.

This constraint ensures consistency with the assumption made in the model that patients can only receive subsequent therapy after disease progression. This constraint is consistent with the transition probabilities that were estimated from the MSM analysis.

It is also consistent with the LATITUDE trial data which demonstrates that median TTST is greater than median rPFS. Radiographic progression free survival results are reported in Table 17 in the LATITUDE CSR, with a median of 33.02 months in the AAP arm and 14.78 months in the ADT arm. TTST is reported in Table 21 in the LATITUDE CSR, with the median not being reached in the AAP arm, and a reported median of 21.55 in the ADT arm.

This assumption is also consistent with the view of clinicians at the clinical advisory board who stated that time to subsequent therapy was not the most appropriate proxy for disease progression as patients will often start on subsequent therapy some time following disease progression.

B15 To avoid any possibility of ambiguity are the MSM analyses based upon the raw LATITUDE data or are they based on data that has been adjusted in some way (e.g, by IPCW)?

The MSM analyses are based on raw ITT data from LATITUDE.

Although the IPCW adjusted data is useful in demonstrating that the subsequent therapies received in the trial reduced the incremental survival benefit of AAP compared to ADT, there were issues with the analyses which meant they were inappropriate for use within the CE model. Small sample sizes across sequences of interest, limited follow-up and an imbalance in patient characteristics across switchers versus non-switchers in the current dataset, mean that these analyses lack robustness.

Secondly, the adjusted data is not utilised as the model already provides a more appropriate adjustment for the impact of subsequent therapies on survival outcomes. Indeed, the model adjusts survival estimates based on the proportion of patients who are expected to receive each subsequent therapy in UK clinical practice. This adjustment is more in line with the decision problem than the adjustments that were made in the IPCW analysis using LATITUDE IA1.

B16 **PRIORITY QUESTION:** Please provide a scenario analysis re-running the rPFS MSM analysis for 4+ months - i.e., including an additional month of data, and to 7+ months; excluding an additional two months of data to provide the equivalent of the data in cells C43:J52 of the *Efficacy_data* worksheet); if the latter provides insufficient data and fails to converge please restrict the analysis to the 6+months data.

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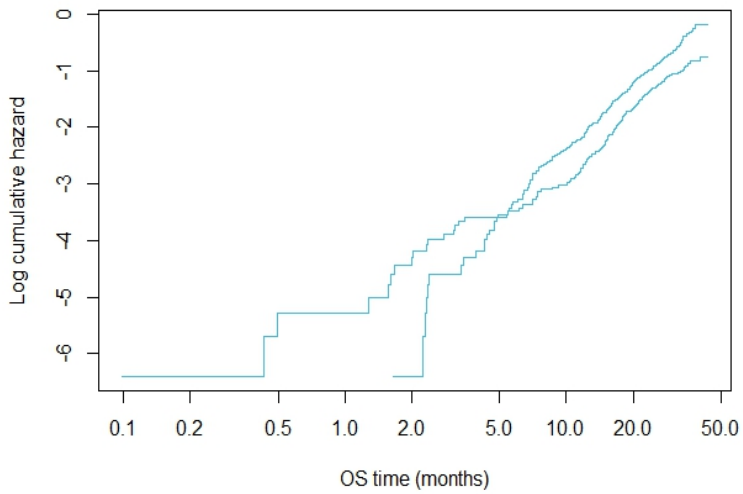
The functionality to conduct this scenario analysis for a cut-off of 4, 6 and 7 months is included in the attached CE model. The estimated transition matrices are included on the "Efficacy data" sheet.
The results for the comparison of AAP + ADT with ADT alone and docetaxel + ADT at each of the different KM cut-offs is presented in Table 13. This table highlights that the model results are robust to changes in the cut-off, with minimal changes seen in the ICERs for either comparison.

Table 13: Model results for each KM cut-off

KM cut-off	ICER (vs ADT alone)	ICER (vs docetaxel + ADT)
5 months (base-case)	£23,287	£28,616
4 months	£22,656	£27,650
6 months	£23,582	£29,404
7 months	£24,016	£30,756

The five-month cut-off was selected in the base-case analysis after an assessment of the log-cumulative hazard plots for rPFS and OS presented in in Section 3.3 in document B, which are also displayed below in Figure 2 and Figure 3. These plots show that the curves remain separate until a maximum of five months, at which point they largely become parallel. For this reason, the KM data were applied directly into the model for the first five months, after which the transition probabilities calculated through the MSM analysis were applied. This is also supported by Figures 7 and 8 presented in the Appendices which show the plots for TTD and TTST.

Figure 2: Log-cumulative hazard plots: OS



Key: OS, overall survival.

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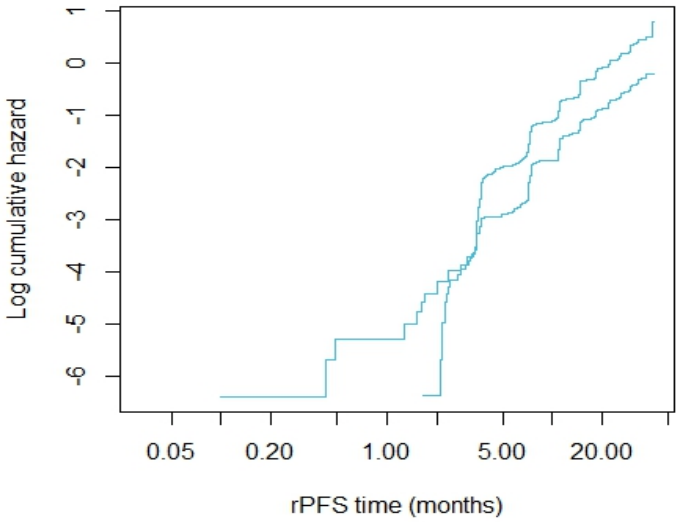
Figure 3: Log-cumulative hazard plots: rPFS



Key: rPFS, radiographic free survival.

B17 For the rPFS modelling it is not clear why the TTST Kaplan Meier curves will provide the correct probabilities for progressed patients moving into 2nd line treatment and death. Please explain the rationale behind this; e.g., the formula I8 = (1-AZ8/AZ7)*EV7 in the *KM_data* worksheet.

The movement of patients from the progressed to the mCRPC state on the "KM data" sheet is estimated using transition probabilities which are calculated in the following manner:

- Firstly, the rate with which patients in each given cycle move to the subsequent therapy or death state is estimated from the TTST curve by subtracting the TTST value in that cycle by the TTST value in the previous Cycle.
- This rate is then multiplied by the proportion of these events in a given cycle that involved patients moving to subsequent therapy and not death.
- This transition probability is then multiplied by the number of patients in the both the pre-progressed and the progressed disease states to estimate the number of patients on subsequent therapy in each cycle.

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B18 **PRIORITY QUESTION:** Please state what number of the 239 AAP+ADT patients and what number of the 354 ADT patients with an rPFS event of table 25 had had a TTST event by IA1. How were those who had had an rPFS event but had not had a TTST event by IA1 treated for the calculation of the mean treatment free interval in table 25, and what is the effect of their exclusion from this calculation? Please provide the data and the data definitions that are required for the calculation of cell C58 of the *Efficacy_data* worksheet and cell K44 of the *Transition_Matrices* worksheet. If these are Kaplan Meier data please supply them in the following format.

Please note that an error in the calculation of the treatment free interval has been identified and corrected for. For each patient with a rPFS event, their treatment free interval was previously calculated as:

$$Treatment\ free\ interval = \frac{TTST\ end\ date - rPFS\ end\ date + 1}{30.4375}$$

The TTST end date for patients who had not had a TTST event (censored for TTST) remained as it was reported in the dataset, as the last known data alive. The mean treatment free interval was then determined as the average over the 593 patients with a rPFS event to give the results in Table 14.

Table 14: Mean treatment free interval as previously calculated

	Combined	AAP + ADT	ADT alone
Number of patients with an rPFS event	593	239	354
Mean treatment free interval (months)	[redacted]	[redacted]	[redacted]
Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; rPFS, radiographic progression free survival			

This calculation has since been updated to:

$$Treatment\ free\ interval = \frac{TTSTD\ end\ date - rPFS\ end\ date}{30.4375}$$

The time to subsequent therapy or death (TTSTD) variable is set to the rPFS end date for patients with a rPFS event or the OS end date for patients with a rPFS censor event (i.e. patients had either not progressed and were hence still on treatment or they were dead), as presented in response to A15. This gave the updated mean treatment free interval results in Table 15.

Table 15: Updated mean treatment free interval

	Combined	AAP + ADT	ADT alone
Number of patients with an rPFS event	593	239	354
Mean treatment free interval (months)	[redacted]	[redacted]	[redacted]

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Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; rPFS, radiographic progression free survival

Of the 239 patients AAP+ADT with a rPFS event, 106 also had a TTST event by IA1. Of the 354 ADT alone patients with a rPFS event, 201 also had a TTST event. Patients who had had an rPFS event but had not had a TTST event were included in the calculation of the mean treatment free interval in Table 14 and Table 15. If these patients were excluded from the calculation, the effect was a reduction in the mean treatment free interval for both treatment arms, as shown in Table 16.

Table 16: Mean treatment free interval, TTST censor events excluded

	Combined	AAP + ADT	ADT alone
Number of patients with an rPFS event and a TTST event	[redacted]	[redacted]	[redacted]
Mean treatment free interval (months), excluding those without a TTST event	[redacted]	[redacted]	[redacted]
Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; rPFS, radiographic progression free survival			

The data required for the calculation of cell C58 of the Efficacy_data worksheet and cell K44 of the Transition_Matrices worksheet are provided in the 'TFI ERG B18' worksheet. Please note the 'TFI ERG B18' worksheet contains data for calculating the updated mean treatment free interval values as given in Table 15 whereas C58 of the Efficacy_data worksheet and cell K44 of the Transition_Matrices worksheet contain the previous values as in Table 14. The definitions of the variable labels used in this worksheet are given in Table 17.

This corrected value has been applied in the amended CE model that is provided and can be utilised by changing cell "C68" named "Controls.TFIfix" to "Yes".

Table 17: Data definitions

Variable	Definition
PatientID	Patient ID number
Arm	Treatment arm whereby 'PBO AA / PBO P / ADT' refers to ADT only and 'AA / P / ADT' refers to AAP+ADT
Time.rPFS	(adt - startdt + 1)/30.4375 Whereby adt and startdt refer to the date of rPFS event/censor and date of randomization, respectively.
Event.rPFS	Radiographic progression if event observed (value of 1). No radiographic progression if event not observed (censored, value of 0)
Time.TSTD	(adt - startdt + 1)/30.4375

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	Whereby adt and startdt refer to the date of event/censor and date of randomization, respectively. Where the patient had no rPFS event but did have an OS event, the adt date is the date of the OS event. Otherwise the date of the rPFS event was used.
Event.TST	"Subsequent therapy" if event is observed (value of 1). "No subsequent therapy" if event is not observed (censored, value of 0).

B19 Please provide a spreadsheet detailing how the inputs in cells E67:G70 of the *Efficacy_data* worksheet have been calculated from the values reported in table 56 of appendix Q.

The calculations which utilise the values from Table 56 of Appendix Q are all included in the CE model. The ITC results presented in cells E67:E70 are estimated by dividing "1" by the reported values in Table 56 of Appendix Q. This calculation allows for the HRs to be applied correctly in the model as the reference treatment in the ITC differs from the reference treatment in the CE model. The Lower and Upper 95% CI values are also taken from Table 56 of Appendix Q, and the same calculation where "1" is divided by these values to convert them to the appropriate form was conducted on the Parameters sheet. As Cabazitaxel was not included in the ITC, it is assumed to have the same 95% CI values as Radium-223 as this had the widest of the 95% CI values, and therefore assumed the greatest amount of uncertainty. When the active subsequent therapies were assumed to have equivalent efficacy as is assumed in the base-case analysis, then the 95% CI selected for each therapy was equal to the values for Radium-223. By using the same set of 95% CI values, it allowed for the assumption of equal efficacy to be maintained in the sensitivity analysis.

B20 **PRIORITY QUESTION:** Please supply the copy of the TA387 model that provided the inputs to cells C25:D1069 and G25:H1069 of the *1L_mCRPC_Efficacy* workbook. Please state what the model settings apply to; e.g., Janssen preferred assumptions of original TA387 submission, ERG preferred assumptions of TA387 prior to 1st AC, etc.

The model used in the TA387 submission was a Discrete Event Simulation in which the KM data from COU-AA-302 was extrapolated using the Weibull function (cells D25:1069 and H25:1069) for OS and the log-logistic function (cells C25:1069 and G25:1069) for time on treatment.

The use of Weibull functions within the model were generally accepted without warranting further discussion. The log-logistic function was used in the base case to model time on treatment for both BSC and AAP, while both a piecewise curve (log-logistic/Weibull) and Weibull extrapolation were presented in sensitivity analysis. Whilst the log-logistic function provided the best fit to observed data at IA3, the ERG challenged the appropriateness of using log-logistic for extrapolation due to its 'long-tail', which could derive clinically implausible long-term predictions.

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During the appraisal process, Janssen submitted the final analysis from COU-AA-302, as well as additional real-world evidence, to further support the appropriateness of the log-logistic extrapolation for time on treatment, since men who respond very well to AAP were seen to stay on treatment for a long time.

After comparing the KM curves from the COU-AA-302 trial with model extrapolations, the Committee agreed with the company that the log-logistic curve for time on treatment was the best fit to the trial data however, because the maximum trial follow-up with five years, there remained a degree of uncertainty around the AAP arm. Nevertheless, the Committee's preferred analysis used either a log-logistic extrapolated curve or the piecewise curve.

With regards to the extrapolation of BSC time on treatment, the Committee was concerned that neither the log-logistic distribution (used in the base case) nor the Weibull distribution (used in sensitivity analyses) provided a good fit to the final trial data, and both distributions could overestimate the time that patients would remain on BSC. The Committee noted that the piecewise curve was a closer fit to the trial data, but this was also associated with plausibility concerns. As such, the Committee concluded that, for predicting time on BSC, it preferred to use the same distribution as was used for AAP (i.e. log-logistic or piecewise).

B21 When the "*Estimate calibration factor*" box of the *Calibration* worksheet is pressed it returns a dialogue box which states: "*Solver Results: Solver could not find a feasible solution: Solver cannot find a point for which all constraints are satisfied*". Please outline how to successfully run the *run_Calibration* visual basic subroutine of the model. The combined difference of 1.138 in cell C11 of the *Calibration* worksheet with a CF of 2.616 falls to 1.099 with a CF of 2.8. Please provide an account of this. Please also clarify if when modelling using TTST within the *run_Calibration* visual basic subroutine the text. *Range("C48").Value = "Radiographic progression"* should be amended to *text .Range("C48").Value = "Time to subsequent therapy"* and the subroutine re-run, and if not why not.

Solver is utilised to estimate the calibration factor by minimising the differences between the Kaplan-Meier data and the predicted survival from the model. Due to complex nature of the problem, Solver is able to minimise the difference, but is unable to reduce the difference to zero. Therefore, the message "Solver Results: Solver could not find a feasible solution: Solver cannot find a point for which all constraints are satisfied" is not an error message but simply an acknowledgement of the inability to reduce the difference to zero.

When the calibration factor is estimating using Excel 2016 the calibration factor is equal to 2.616. When the calibration factor is manually changed from 2.616 to 2.8 then the combined difference in cell "C11" does fall to 1.099 from 1.138. However, this is because the required changes to the model settings on the "Controls" sheet needed to calculate the calibration factor cannot be made. In order to correctly estimate the calibration factor the "Controls.subs.trt.options" cell on the "Controls" sheet needs to be switched from "Clinical Practice" to "LATITUDE". This is because the calibration factor seeks to minimise the

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differences between the LATITUDE clinical trial survival data and the predicted survival from the model. For accuracy of the calculation, the predicted survival from the model must be estimated based on the subsequent therapies that patients received in the trial rather than what clinicians anticipate that they will receive in practice. When the Calibration Factor button is pressed then the model ensures that the relevant settings which impact survival are selected. When these settings are therefore selected, 2.616 is the value which minimises the combined difference in cell "C11".

B22 How did the model for TA387 estimate costs related to time on treatment with AAP and how does this differ from the approached used in this appraisal? Was an adjustment factor similar to the LATITUDE ratio given on page 127 of Document B applied? If yes, what was its value?

The costs related to time on treatment with AAP in the TA387 submission are calculated by utilising the treatment discontinuation curve from the COU-AA-302 trial. A similar approach using the MSM analysis for the treatment of mHSPC was conducted to achieve the same results using LATITUDE data (presented in Appendix P). Two models were estimated which contained "on-treatment" and "off-treatment" health states, which utilised the time to treatment discontinuation data from LATTIUDE. However, due to the small numbers of movements between some health states, these models were not able to converge, resulting in implausible transition probabilities matrices.

Therefore, to calculate treatment costs during mHSPC, a restricted means analysis was conducted (presented in Document B Section B.3.3). This involved using the TTD KM data to estimate the mean time patients spent on treatment, and dividing it by the mean time prior to disease progression, which is estimated in the same way using KM data for rPFS. This ratio was then multiplied by the number of patients in the pre-progression health state, in each cycle of the model, to estimate the proportion who were still on treatment.

For the mCRPC phase of the model, the treatment costs for AAP were taken from the TTD parametric curve used in the final base case model preferred by NICE from the TA387 submission, to retain consistency with previous decision making. Although the calibration factor estimated in the CE model only made adjustments directly to the OS curve from TA387 utilised during the mCRPC phase of the model, the TTD parametric curve was also adjusted indirectly. The adjusted TTD curve was estimated by calculating the ratio in each cycle of the unadjusted TTD and OS curves and multiplying this ratio by the calibrated OS values in each cycle (as shown in columns "K" and "O" on the "1L mCRPC Efficacy" sheet in the CE model).

B23 Please provide the data that have been used to calculate the LATITUDE unplanned MRU – mHSPC units per year estimates and outline the timeframe it applies to, why it will not attribute mCRPC resource use to the ADT arm more than to the AAP + ADT arm, and the extent to which it reflects UK clinical practice.

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As referenced in Document B, the data underpinned the unplanned MRU in mHSPC were taken from an unpublished analysis of the MRU reported in LATITUDE (Li et al. 2018). These data and methodology have now been published at the ASCO GU Congress (2018), the same week as submission. The final 'Li et al. (2018) – ASCO GU' poster is provided in response to these clarification questions, to reassure the ERG and NICE of the veracity of evidence presented.

The only data used in the CE model were the estimated rates of unplanned MRU visits that were reported while patients were actively receiving initial treatment in LATITUDE (i.e. AAP + ADT or ADT alone). As such, unplanned MRU costs reported in LATITUDE were only applied to patients who were receiving their first line mHSPC treatment.

The unplanned MRU in the mCRPC phase of the CE model is applied once patients have progressed. Since a greater proportion of patients in the ADT arm experience disease progression sooner, a higher proportion of patients in this arm are expected to start accruing unplanned MRU in mCRPC earlier than patients in the AAP + ADT arm. Of note, the unplanned MRU in the mCRPC phase was assumed to be the same, irrespective of subsequent therapy received. In answering these clarification questions, we noted the annual costs are incorrectly referenced in the CE model as one off-costs, but are in fact annual costs, and are applied as such in the model.

Medical resource use that was experienced during the STAMPEDE trial could potentially reaffirm the representativeness of these data in UK clinical practice; however, at present these data have not been released.

B24 The submission uses a number of costs of the TA387 assessment (e.g., SAE units costs and unplanned MRU – mCRPC) without showing how these have been derived or explaining what the Assessment Committee view of them was. Please provide more details of the inputs to this and their calculation. Also, what was the cost per surgery event that was applied in TA387?

The COU-AA-301 (post-chemotherapy) and COU-AA-302 (pre-chemotherapy) trials recorded MRU, as a result of unplanned events while on treatment (e.g. AEs). The unplanned MRU costs applied during the mCRPC phase of the CE model were taken from Table 56 in the TA387 submission, as shown below.

Full details of these costings can be found in the TA387 submission:

- The resource use for unplanned events while patients were receiving treatment was similar between the AAP and PP arms for the COU-AA-302 trial population.

- The unplanned event-related MRU used in the CE model of TA387 were applied as a monthly cost of £93.79 in the TA387 model base case to be more consistent with the MRU analysis result of the COU-AA-302 trial.

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The monthly unplanned MRU cost of £93.79 was converted to an annual cost of £1,125.48 in cells "C238:240" on the "MRU costs" sheet in the current CE model. Per cycle unplanned MRU costs during the mCRPC phase of the model are calculated by adjusting this annual cost to a cost which matches the cycle length of the model.

Whilst the unplanned MRU cost from the COU-AA-301 trial is also reported in the original version of Table 56, these were not used in the current CE model as patients from the COU-AA-302 trial were deemed to be clinically more aligned with the patients in the LATITUDE trial, at point of progression.

Table 56: Trial-based unplanned MRU costs per month

	Unplanned MRU cost, £	Source	Impact on application of AE cost
AAP	93.79	302 trial unplanned MRU	Already reflected in the trial unplanned MRU data; no need to consider additional AE cost
BSC (PP)	93.79	Assumed to be the same as PP arm of 302 trial	AE costs are included
BSC (pre-docetaxel)	93.79	Assumed to be the same as PP arm of 302 trial	AE costs are included
AAP, abiraterone acetate plus placebo; AE, adverse event; BSC, best supportive care; MRU, medical resource utilisation; PP, placebo plus prednisolone.			

Whilst data to inform MRU (planned and unplanned) in the TA387 submission were associated with a degree of uncertainty, variation in these parameters only had a small impact on the ICER. As such, MRU data were not discussed further and the values presented in the TA387 were accepted as reasonable clinical assumptions by the ERG and NICE Committee.

Importantly, sensitivity analysis presented in Document B consistently showed that variation in the level of MRU still had little impact on the ICER.

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Section C: Textual clarifications and additional points

C1. PRIORITY QUESTION: please provide a List of abbreviations/Glossary of terms

Abbreviation	Definition
AA	abiraterone acetate
AAP	abiraterone acetate + prednisolone
ADT	androgen deprivation therapy
AE	adverse event
AIC	Akaike information criterion
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BFI	Brief Fatigue Inventory
BIC	Bayesian information criterion
BPI-SF	Brief Pain Inventory–Short Form
BSA	body surface area
BSC	best supportive care
CAA	Commercial Access Agreement
CEAC	cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CrI	credible interval
DES	Discrete Event Simulation
DIC	deviance information criterion
DOC	docetaxel
ECOG	Eastern Cooperative Oncology Group
eMIT	electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life questionnaire
EORTC QLQ-PR25	European Organisation for Research and Treatment of Cancer Quality of Life questionnaire - prostate cancer
EPAR	European public assessment report
EQ-5D-5L	EuroQoL 5-Dimension 5-Level
FACT-P	Functional Assessment of Cancer Therapy-Prostate

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Abbreviation	Definition
FFS	failure-free survival
GCP	Good Clinical Practice
GnRH	gonadotrophin-releasing hormone
HR	hazard ratio
HRD	high-risk disease
HRQL	health-related quality of life
HVD	high-volume disease
IA	interim analysis
ICER	incremental cost-effectiveness ratio
IDMC	independent data and safety monitoring committee
IPCW	inverse probability censoring weighted
ITC	indirect treatment comparison
ITT	Intention-to-treat
IV	intravenous
KM	Kaplan–Meier
LDH	lactate dehydrogenase
LHRH	luteinising hormone releasing hormone
LVD	low-volume disease
LY	life year
LYG	life years gained
MAMS	multi-arm, multi-stage
mCRPC	metastatic castration resistant prostate cancer
mHNPC	metastatic hormone naïve prostate cancer
mHSPC	metastatic hormone sensitive prostate cancer
MIMS	Monthly Index of Medical Specialities
MRU	medical resource use
MSM	multi-state modelling
NA	not applicable
NDx	newly diagnosed
NE	not evaluable
NMA	network meta-analysis
NR	not reached

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Abbreviation	Definition
OS	overall survival
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PCWG2	Prostate Cancer Working Group 2
PFS	progression-free survival
PPS	post-progression survival
PS	performance status
PSA	probabilistic sensitivity analysis
PSA	prostate-specific antigen
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
RMME	repeated measures mixed effect
rPFS	radiographic progression-free survival
RPSFT	Rank Preserving Structural Failure Time
SA	sensitivity analysis
SAE	serious adverse event
SE	standard error
SLR	systematic literature review
SmPC	summary of product characteristics
SOC	standard of care
SRE	skeletal-related event
TEAE	treatment emergent adverse event
TFI	treatment-free interval
TTD	time to discontinuation
TTO	time trade-off
TTST	time to subsequent therapy
Tx	treatment
VAS	Visual Analogue Scale
WTP	willingness to pay

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C2. Document B page 86, Table 21: What does SA relate to?

Sensitivity analysis

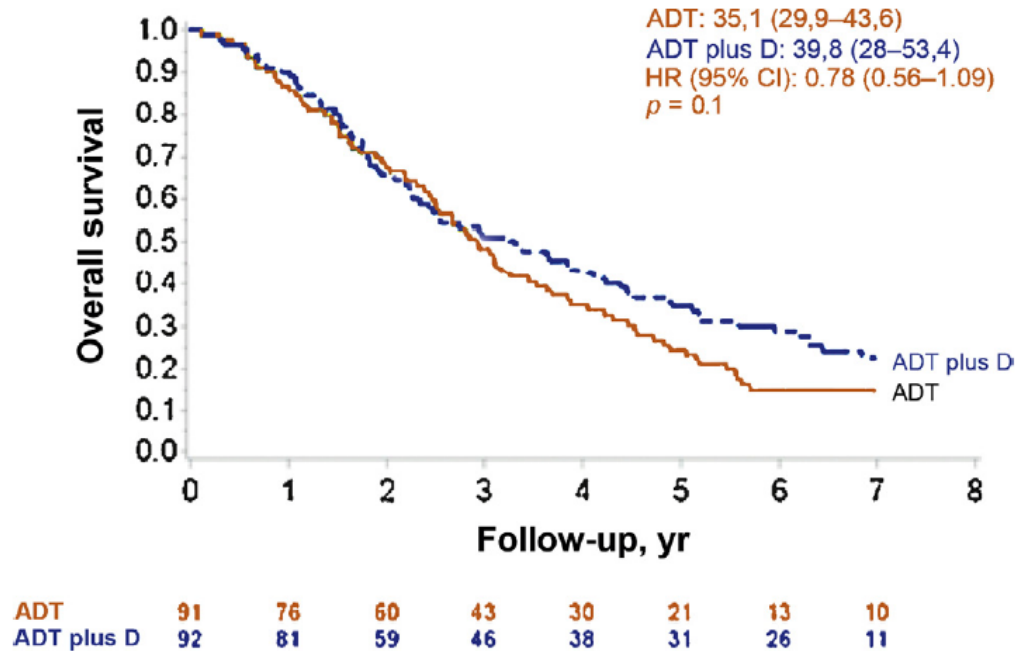
C3. Document B page 33, Figure 6 (Overview of STAMPEDE study design): Please provide a bigger and clearer image, if possible.

This has been provided in a separate document.

C4. The submission (pages 14-15) states that in recent trials patients with high volume mHSPC survived for less than 3 years. The rPFS model estimates an ADT 3-year survival of 51% and a 5 year survival of 22%. The LATITUDE KM data suggests an ADT 3 year survival of 49%. Please clarify.

The two references noted on pages 14-15 refer to the CHAARTED and GETUG-AFU 15 studies. Median OS is reported as 34.4 months[2] provided and 35.1 months[7] in these studies, respectively, in high-volume patients treated with ADT alone. Although OS rates are not reported in either reference, the KM figure from the GETUG-AFU 15 study suggest just less than 50% of patients were alive at 3-years, as presented in Figure 4.

Figure 4: Overall survival for patients with high-volume disease, GETUG-AFU 15 study



Key: ADT, androgen deprivation therapy; CI, confidence interval; D, docetaxel; HR, hazard ratio.
Source: Gravis et al. 2016

As such, data for the CHAARTED and GETUG-AFU studies, alongside survival data presented in the model, consistently report three-year OS rates ≤51%, suggesting approximately half of all patients survive for less than three years.

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Table 18: Life expectancy of patients with newly diagnosed high-risk mHSPC

RCT of Interest	Relevant patient cohort	Median OS	Source
LATITUDE	NDx, high-risk mHSPC	34.7 mo	Fizazi et al. (2017)
CHAARTED	NDx, high-volume mHSPC	34.4 mo	Sweeney et al. (2016)
GETUG-AFU 15	NDx, high-volume mHSPC	35.1 mo	Gravis et al. (2016)
Key: mHSPC, metastatic hormone-sensitive prostate cancer; NDx, newly diagnosed; OS, overall survival			

Of note, the base case analysis assumed that all patients could be suitable for chemotherapy at diagnosis, thus influencing the type of subsequent therapies that may be received after progression to mCRPC. In clinical practice, some patients who receive ADT alone, would only do so, because they are unsuitable for chemotherapy at diagnosis. These patients would be unlikely to receive therapies such as docetaxel or cabazitaxel upon progression to mCRPC and as a result would receive one less line of subsequent therapy, compared to those suitable for chemotherapy. If these patients' experience were also accounted for, estimates for life expectancy would likely decrease. Nevertheless, the current CE model works to optimise the data which are available to simulate UK clinical practice in the overall mHSPC population.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Abiraterone for treating newly diagnosed high risk metastatic hormone-naive prostate cancer [ID945]

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	Professor of Urological Oncology, The Christie and Salford Royal Hospitals Manchester
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	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 diagnosis of prostate cancer is made by Urologists and the treatment decisions, usually formulated in a weekly Urology MDT setting, are predicated on the presence or absence of metastatic disease (usually in lymph nodes or bone) at first presentation. Metastases are present in 16% of the prostate cancer population in England and Wales at the point of diagnosis (National Prostate Cancer Audit 2017 report: www.NPCA.org). When patients present in this way their prognosis is much worse than in patients presenting with high risk, clinically localised disease. A contemporary report of patients presenting in this way (James ND, Spears M, Clarke NW et European Urology 2015) showed that with conventional treatment using androgen deprivation therapy (ADT) the median time to treatment failure was 9 months, with patients with the combination of bone and lymph node metastases faring especially badly (75% mortality at 2 years with the best available modern treatment). Between 40 and 50% of prostate cancer deaths occur in this population. The prognosis of this patient population has now been improved following publication of meta-analysis data showing that Docetaxel based chemotherapy, given at the time of primary treatment with ADT, improves survival by 16 months: this has now become an international standard of care (Vale C et al Lancet Oncology). However, this treatment has toxicities, is not suitable for patients with significant co-morbidity and the average age of the patients treated in the combined trials published (eg The Stampede Trial: James ND et al Lancet December 2015) was lower than the average age of presentation in the UK by approximately 6 years. Two important trials published synchronously in the New England Journal of Medicine in July 2017 on the benefit of Abiraterone Acetate combined with ADT in primary M1 Prostate cancer (James ND et al: The Stampede Trial, Fizazi K et al: The Latitude trial). Both of these large scale randomised phase 3 trials showed clear benefit in progression free and absolute survival (37% survival improvement at 54 months in Stampede (hazard ratio 0.63), 17% at 36 months in Latitude (HR 0.62). This improvement was of a similar magnitude to that seen in the Docetaxel treated patients mentioned in the trials above, but with a lesser side effect profile and greater ease of administration (oral anti-androgen based therapy rather than cytotoxic chemotherapy). There were also important and clinically significant improvements; quality of life was enhanced and critically, there was a 55% reduction in clinically relevant skeletal related events (pathological fracture, spinal cord compression, bone pain) in both studies and a reduction in pain over the course of the disease's natural history. The results of the two trials has been combined in a further meta-analysis by the MRC clinical trials unit which is currently in press (Vale et al on behalf of the StopCaP meta-

	analysis group) which confirms the overall benefit of the this novel approach. The side effects arising from the treatment were generally modest and easy to manage clinically.
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 response seen in both the Stampede and Latitude trials was significant both in terms of progression free and absolute survival. The magnitude of improvement was similar in both trials and was larger than anything seen previously in this condition (eg reduction in PFS hazard ration 0.21 for Stampede). Furthermore, the survival and PFS benefit when the treatment was given in the hormone naïve state far exceeded that shown in large scale trials of Abiraterone Acetate when administered in the "hormone relapsed" castrate resistant setting. The combined results of the Stampede and Latitude studies confirm a 14% absolute reduction in the risk of death at 3 years (eg Stampede: median OS is 48 months in the ADT arm and median survival not been reached in the AAP arm). Clinically, both studies showed clear benefit in terms of reduced patient morbidity from progressing prostate cancer. The reduction in clinically relevant skeletal related events was similarly dramatic in both trials (eg 55% reduction in Stampede) and this was accompanied by substantial reductions in pain scores (eg 33% in Latitude). Quality of life was improved significantly as a consequence. An important difference in the two trials was that Latitude only included patients with 3 or more bone or "high risk (eg visceral) metastases whilst Stampede recruited patients with any metastases. Notwithstanding this the results of the two trials were very similar. Furthermore, there was no heterogeneity of effect when analysis the Stampede data; administration of the active agent resulted in benefit. The side effects, largely related to mild hypertension and a low rate of hepatic dysfunction was easily managed with dose reductions and short interruptions to treatment schedules. There was no evidence of neutropenia related problems, as is the case with Docetaxel where significant patient numbers have this problem (8% on the published studies but higher rates reported in "real world" populations).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Prostate cancer is a major cause of death in the UK and a significant cause of co-morbidity in patients developing the disease. Many patients presenting to urology departments are unfit for chemotherapy because of co-morbidity issues (30% of prostate cancer patients are 75 or over when they present (CRUK figures) and in this population the neutropenia rate has been reported to be as high as 20%. Added to this, there is a significant burden on health care / manpower resources for patients needing treatment with Docetaxel. This has to be given by non-urologists, adding to the cost and treatment burden for individual

	patients and health care systems. Urologists, particularly those with subspecialty expertise in Urological Oncology, are fully trained in the diagnosis and hormone based treatment of patients with this disease. The ability of this group of health care professionals to administer this treatment would be of significant benefit to patients.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Standard treatment of men presenting with metastatic prostate cancer is for them to be offered ADT plus Docetaxel provided they are fit to undergo the combined treatment. For those who are unfit for chemotherapy or those who do not wish to have the combined treatment, standard therapy is with ADT alone, usually in the form of depot injected GnRH analogue drugs.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guidelines are currently being modified in light of the recent publications of the Stampede and Latitude data (NEJM July 2017). These will be issued in the 2018 updates. Currently the most widely used ones in this regard are those produced by the European Association of Urology (www.uroweb.org) and the US based NCCN guidelines.
• 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.)	In the UK the pathway of care following diagnosis is clear in relation to treatment that should be offered. As described above, men fit for chemotherapy who wish to undergo this treatment are, after appropriate medical and specialist nurse counselling in a urology department, treated by a medical or clinical oncologist working within the Urology specialist MDT. Ideally this oncologist should have specific experience in the management of prostate cancer patients and work within a recognised department with expertise in the administration and general management of patients undergoing Taxane based chemotherapy. Once this treatment is completed the patient is then usually followed either in their original urology referral hospital or by the non-surgical urology cancer team. Patients not receiving chemotherapy are usually managed by Urologists and supporting specialist urology nursing teams in urology units with conventional ADT treatments. Subsequent therapies on failure are administered according to patterns of relapse, patient co-morbidities/frailties and geography/local resource by combined treatments / interventions by urologists, clinical/medical oncologists and palliative care teams

	according to local circumstances. In larger conurbations this is usually a balanced multi-disciplinary team but in some geographic areas, where sub-specialised manpower is a scarce resource, the burden of care lies with the urologist and palliative care teams.
• What impact would the technology have on the current pathway of care?	The proposed new therapy would have a significant impact on survival and would reduce morbidity from this disease. The therapy would also be available to many more patients who are currently ineligible for cytotoxic chemotherapy. The ability of urologists to administer the treatment, something which all sub-specialised Urologists have the ability to do, would also improve access for patients with this condition to this class of drugs.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The use of this class of drugs would change. They are currently used routinely in hormone relapse but their use in light of the current and recent evidence means that they would be used much earlier in the course of the disease. Evidence from the Stampede study (NEJM 2017) shows that subsequent use of Abiraterone in later stages of the disease will be reduced.
• How does healthcare resource use differ between the technology and current care?	Abiraterone Acetate used earlier in the course of the disease will likely mean that it is given for longer than is currently the case when it is used in later stages following hormonal relapse. However, experience with Docetaxel used in a similar way has shown that the cost/ benefit in health care analysis (James ND et al InPress) has confirmed the cost effectiveness of this approach. The drug would also be available for administration to patient by Urologists trained specifically in its use.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and under the overall supervision of cancer subspecialised Urologists and Clinical / Medical Oncologists with expertise in the management of prostate cancer.
• What investment is needed to introduce the technology? (For	The administration of Abiraterone Acetate in the hormone Naïve setting requires closer medical supervision because of the requirement to monitor hepatic function in the early stages of its use. Many departments using this agent in clinical trial settings have extensive experience of this and have set up protocols and

example, for facilities, equipment, or training.)	nurse-led clinics to accommodate this requirement. Such facilities would need to be considered for wider use.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The proposed technology would provide substantial improvements for this type of prostate cancer patient by comparison with the technologies/treatments currently available
• Do you expect the technology to increase length of life more than current care?	Yes. See above
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. See above
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients who are frail and have poor performance status may not benefit as substantially from this treatment. The majority of patients undergoing this therapy in the current trials had an ECOG performance status of 2 or better. Patients who have pre-existing hepatic dysfunction may have to be excluded.

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology will be significantly easier to administer. Abiraterone is an orally administered drug acting via the androgenic axis. This contrasts with the alternative treatment with cytotoxic chemotherapy, which can only be delivered by non-surgical urological cancer specialists in specialised units. Abiraterone can and is administered easily and safely in conventional urology departments. However, it is important to consider that urologists must have expertise / subspecialisation in uro-oncology and must be familiar with the administrative methods / management associated with this class of drugs. The facilities and nursing expertise for the monitoring of Abiraterone treated patients are already available widely in most urology departments. Patients will need regular monitoring of hepatic function in the early stages of treatment.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Some areas of the country actively discourage Urological Surgeons from prescribing novel anti-androgenic drugs (Abiraterone / Enzalutamide). This is a highly contentious issue and is seen as being inappropriate by Urologists who have been trained over many years in prostate cancer pathophysiology and treatment. This restrictive approach has limited the availability of modern treatments for patients in some areas of the UK.
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	It is likely that this technology will result in QALY related benefit for patients. However, calculations relating to this aspect of treatment at currently ongoing and to the knowledge of BAUS remain unpublished at this juncture.

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. See above
• Is the technology a 'step-change' in the management of the condition?	The technology has changed practice internationally. It is seen widely as a major advance in the treatment of this disease.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. See above
17. How do any side effects or adverse effects of the technology affect the	The side effects are modest and in the 2 published trials, easily and effectively managed. The serious side effects are much lower than those seen with the currently available cytotoxic approaches. As mentioned above, there is a requirement for closer monitoring in uro-oncology / specialist nurse-led clinics (according

management of the condition and the patient's quality of life?	to specific protocols) in the early stages of treatment. The resource requirement for this is modest and is available already in many urology departments.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. One of the 2 major trials was conducted almost exclusively in the UK (Stampede) and the other (Latitude) also included UK centres.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Substantially improved survival, progression free interval and a major reduction in clinically important complications of disease progression. These were measured as specific end-points in the two major trials in this area. Side effect profiles of treatment were modest and those effects were managed easily.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials	No

but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No
21. How do data on real-world experience compare with the trial data?	This is not currently available as this treatment indication is only recent (1st publication July 2017)
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No, but see comments above regarding administration by Urologists and patient access.
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Prostate Cancer presenting with metastases at first presentation is common and commonly lethal
- The current standard of care is ADT±Docetaxel for patients fit to receive it or ADT alone. Average time to treatment failure for ADT alone is 9 months
- Abiraterone given with ADT produces substantial improvements in progression free and actual survival in this patient group
- Serious clinical complications are reduced by up to 55% with Abiraterone/ADT treatment, pain is reduced and QoL improved
- Side effects of treatment are modest and the drug will be tolerated more widely by patients currently unsuitable for chemotherapy

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Professional organisation submission

Abiraterone for treating newly diagnosed high risk metastatic hormone-naive prostate cancer [ID945]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	British Uro-oncology Group (BUG)

3. Job title or position	**Consultant Clinical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Uro-oncology Group (BUG) was formed in 2004 to meet the needs of clinical and medical oncologists specialising in the field of urology. As the only dedicated professional association for uro-oncologists, its overriding aim is to provide a networking and support forum for discussion and exchange of research and policy ideas.
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,	The main aim of treatment for patients presenting with metastatic prostate cancer is to improve overall and failure-free survival, reduce disease associated morbidity and preserve / improve quality of life.

or prevent progression or disability.)	
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.)	A statistically significant improvement in overall survival compared with androgen deprivation therapy (ADT) alone, of similar magnitude seen in the data comparing ADT and docetaxel with ADT alone in men with hormone sensitive metastatic prostate cancer (10-15months).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is an unmet need to improve treatment for men with newly diagnosed metastatic prostate cancer who on average die of the disease within less than 5 years. As well as the need to improve life expectancy in this group of patients, we need to optimise disease related symptoms such as bone complications and improve failure free survival. Tolerable treatment side effects and convenience of delivery and monitoring need to be also optimised in this patient group.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	In January 2016, NHS England commissioned the use of docetaxel chemotherapy in hormone naïve metastatic prostate cancer. Therefore, patients presenting with hormone naïve metastatic prostate cancer are considered for docetaxel chemotherapy within 12 weeks of commencing androgren deprivation therapy (ADT). In patients where docetaxel chemotherapy is contraindicated, ADT alone is given.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guideline prostate cancer diagnosis and management (NICE guideline CG175, 2014) Clinical Commissioning Policy Statement: Docetaxel in combination with ADT for the treatment of hormone naïve metastatic prostate cancer (NHS England Ref: B15/PS/a)
• 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.)	The evidence of data from three randomised controlled trials (STAMPEDE, CHAARTED, GETUG-AFU15) have shown time to disease progression is statistically significantly larger with docetaxel and ADT compared with ADT alone. This has resulted in a defined and accepted management pathway within the prostate community of using docetaxel for good performance status patients with hormone naïve metastatic prostate cancer. This is both a nationally and internationally recognised pathway of care.
• What impact would the technology have on the current pathway of care?	Currently, patients with metastatic prostate cancer who would be eligible for the technology (abiraterone as treatment in the hormone naïve setting) are offered docetaxel, unless contraindicated. Therefore, the use of abiraterone in this setting would enable clinician and patient choice - to discuss and choose the relative use of docetaxel and abiraterone. This discussion already occurs for those patients not previously treated with abiraterone or docetaxel with metastatic castrate resistant prostate cancer.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, the abiraterone dose and administration schedule and monitoring will be the same as has been established in the metastatic castrate resistant setting (Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (2012) NICE technology appraisal 259).
• How does healthcare resource use differ	The use of docetaxel includes intravenous administration, therefore requiring medical resources (i.e. day unit facilities) for cannulation, monitoring during infusion. Generally, patients are reviewed at a pre-

between the technology and current care?	chemotherapy visit and then attend a subsequent appointment for the docetaxel infusion. Also, in some clinical practices in the UK, the prophylactic use of granulocyte colony stimulating factor is used with docetaxel chemotherapy. Within the clinical trials, chemotherapy related deaths were documented in all three randomised trials in which docetaxel was added to ADT. Abiraterone is administered orally and therefore allows for a one-stop appointment for patients (assessment and dispensing), hence easier treatment to administer logistically. Also, abiraterone has a better side effect profile than docetaxel chemotherapy.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinic. In the future, some of the monitoring associated with abiraterone such as blood pressure may be able to be performed in the community under the supervision of a specialist team.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Abiraterone is already established in clinical practice nationally in the castrate resistant metastatic setting, therefore clinical teams are familiar with the safe use and stopping rules for abiraterone. The toxicity and monitoring of abiraterone is well-established and in the reported clinical trials of using abiraterone in the hormone naïve metastatic prostate cancer patients the adverse events were in line with previous experience in the castrate resistant prostate cancer setting.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, abiraterone provides a treatment option with benefits in overall survival and failure free survival in hormone naïve prostate cancer patients with fairly few additional side effects. Abiraterone in the hormone naïve metastatic prostate cancer (LATTITUDE trial) compare favourably with those reported by patients receiving ADT and docetaxel, in whom HRQOL is not consistently improved. In the CHAARTED trial, HRQOL was worse in patients with metastatic hormone naïve prostate cancer 3 months after ADT plus docetaxel compared with ADT alone and was not improved until the 12 month time point. However, there have been no reported prospective studies directly comparing ADT plus abiraterone and prednisolone versus ADT plus docetaxel.

• Do you expect the technology to increase length of life more than current care?	In the STAMPEDE trial, the effect size reported with abiraterone is a little larger with respect to overall survival and substantially larger with respect to failure free survival than the effect size reported with early docetaxel (current care).
• Do you expect the technology to increase health-related quality of life more than current care?	Abiraterone has a better side effect profile than docetaxel and is an easier treatment to administer logistically. Also, data from the LATTITUDE study has shown statistically significant improvements compared with ADT and placebo by delaying time to worst pain intensity and pain interference, as well as worst fatigue intensity and fatigue interference, and by prolonging time to HRQOL deterioration (as per Functional Assessment of Cancer Therapy – prostate total score).
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology is for a specified patient population.
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	The technology will be easier to administer logistically than current care. Oral medication may be preferred to intravenous administration and less healthcare resource required and less intense regimen. However, the duration of treatment longer than with docetaxel. The technology does require concomitant glucocorticoid administration, and the side effects associated from this are well recognised and assessable.

example, any concomitant treatments needed, additional clinical requirements, factors 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?	Treatment should be started within 12 weeks of commencing ADT, as in the clinical trial. Treatment will be stopped at radiological, clinical or PSA progression or intolerance to abiraterone. No additional testing is required for the starting or stopping of the technology.
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?	Reduced intensity of hospital visits and resources (reduced appointments, no chemotherapy infusion).

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related not benefits and how might it improve the way that current need is met?	This technology will provide patients with a treatment shown to not only prolong life, but also lower the chance of relapse and reduce the chance of serious bone complications, with acceptable side effects and good quality of life. It will also allow patients and clinicians the ability to choose a treatment option that takes into account patient choice, comorbidities and resource as in the metastatic castrate resistant setting.
• Is the technology a 'step-change' in the management of the condition?	Yes, as the evidence surrounding this technology shows statistically significant clinical benefit with good tolerability and ease of administration.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, this technology enables a treatment option with significant clinical benefit, well tolerated, good quality of life. It offers patients a less toxic regime than that which is currently available (ie docetaxel).
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 technology has been shown to improve patient reported outcomes when compared to treatment with ADT alone. The concomitant administration of glucocorticoids and the long term effects from these need to be discussed and monitored with the patient and relevant co-morbidities reviewed.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trial data compares the addition of abiraterone to ADT in the hormone naïve metastatic prostate cancer patients with treatment of ADT alone, which at the time of the trial concept was standard of care. In January 2016 following the publication of three randomised controlled trials, docetaxel for hormone naïve metastatic prostate cancer was commissioned and this is now recognised as a standard of care in this patient population.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The trials reporting this technology encompass the priority outcome measures including overall survival, failure free survival, toxicity and quality of life.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials	No

but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	Retrospective analyses (Hussain et al. NEJM 2013, Scosyrev E et al. Cancer 2012) exploring real-world practice patterns indicate that men with newly diagnosed, metastatic, hormone sensitive prostate cancer who are not being treated in clinical trials may be nearly a decade older than those treated in clinical trials.
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to	

be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Level I evidence supporting the technology, with statistically significant overall survival, failure free survival benefit and improved overall patient reported outcome measures.
- The technology has more tolerable side effects and less resource implication than docetaxel chemotherapy.
- Based on the magnitude of clinical benefit and good tolerability, this technology should be available.
- Although there is no prospective data available comparing the combined use of ADT and docetaxel and ADT and abiraterone, the magnitude of clinical benefit and non-significant toxicity with abiraterone supports its role in hormone naïve metastatic prostate cancer patients.

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

Patient organisation submission

Abiraterone for treating newly diagnosed high risk metastatic hormone-naive prostate cancer [ID945]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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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 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Prostate Cancer UK
3. Job title or position	Policy Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do. Prostate Cancer UK has a policy that funding from pharmaceutical and medical device companies will not exceed 5% of its total annual income. During the financial year 2014/2015 donations from such organisations, expressed as a percentage of our total annual income, were less than 0.1%.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	Desk research and our own knowledge of the experiences of men. A blog post requesting people to get in touch with us with their experiences. Further evidence from people contacting our hotline or emailing our support services.
Living with the condition	
6. What is it like to live with the condition? What do carers	It is not possible to be specific about the symptoms for high-volume hormone-naïve metastatic prostate cancer, as there is limited evidence available that is specific to this sub-population of men with advanced prostate cancer. As such, the following provides evidence-based symptoms for advanced prostate cancer, which can include[i]:

experience when caring for someone with the condition?	• Fatigue. • Pain, most commonly caused by prostate cancer that has spread to the bones. • Urinary problems, this includes problems emptying the bladder, incontinence, blood in urine and kidney problems. • Bowel problems including constipation, diarrhoea, faecal urgency, faecal incontinence, pain, bowel obstruction and flatulence. • Broken bones, fractures caused by bone thinning. • Sexual problems, including reduced libido and difficult getting or keeping an erection. • Lymphoedema, primarily around the legs. • Anaemia, caused by damage to bone marrow. • Metastatic spinal cord compression, as cancer cells grow in or near the spine, which evidence suggests can occur in 1 to 12% of patients[ii]. • Hypercalcaemia, caused by calcium leaking from the bones into the blood. • Eating problems It is important to note that men are unlikely to experience all the above symptoms, as some will depend on the treatments received, while others will be the result of metastases and therefore dependent on their location. The severity of symptoms will also differ among men, while the likelihood of some of the most severe symptoms, for example Lymphoedema can be rare and vary between 1-20%[iii]. For some men, living with metastatic prostate cancer can be hard to deal with emotionally, especially as there are no current curative treatments for this stage of the disease. Symptoms and treatments can be draining and make men feel unwell. And some treatments, including hormone therapy, can make men feel more emotional and cause low moods. The pressure of advanced cancer can also put a strain on relationships. Metastatic prostate cancer and its treatments might mean that partners or family need to do more for patients, such as running the home or caring responsibilities. Additionally, the symptoms of metastatic prostate cancer and the side effects of treatments can make it difficult to work. a partner providing care might not be able to work as much either. Everyday tasks may become more difficult and respite care may be required to give carers a break.

	As the disease progressive, more palliative care and treatments will be offered. This includes palliative radiotherapy to ease bone pain, blood in urine and swollen lymph nodes
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Men with newly diagnosed metastatic prostate cancer – whether high volume or not - do not have curative treatment options available to them. They (and their carers) will weigh up the quantity of life granted by any treatment with the quality of life during that period including any side-effects or consequences of treatment. For patients with symptomatic metastases, androgen deprivation therapy (ADT) is immediately administered, both to palliate symptoms and to prevent severe complications (eg, pathologic fractures, spinal cord compression). When asymptomatic metastases are prevalent, men can take account of treatment-related side effects, which can adversely affect quality of life, but should opt for early treatment, rather than delay. There is also an option for these men to have intermittent ADT, should the side-effects become too adverse. **ADT** has until recently been the treatment for **most** patients with **metastatic** prostate cancer. Although ADT is palliative, it can normalize serum levels of prostate-specific antigen (PSA) in over 90 percent of patients and can produce objective tumour responses in 80 to 90 percent[iv]. This antitumor activity can improve quality of life by reducing bone pain as well as the rates of complications (eg, pathologic fracture, spinal cord compression, ureteral obstruction**). The** duration of response to ADT for patients with metastatic disease is highly variable, and most prostate cancer patients eventually experience disease progression despite treatment **and become hormone-refractory.** Since 2015, men who are newly diagnosed with metastatic prostate cancer can receive ADT in combination with docetaxel chemotherapy. This is a recent standard of care[v] and provides men at this stage of the disease with an additional 15 months of life[vi] compared to ADT alone. The side-effect profile[vii] of hormone therapy includes: • Impotence and/or hot flushes • Bone pain or generalised pain

	• Kidney problems or urinary tract infections The side-effect profile of docetaxel in combination with hormone therapy adds: • Infection because of weakened immune system • Low numbers of white blood cells • Diarrhoea, stomach ache, constipation, sickness • Tiredness, fever, or weakness • Breathlessness, cold/flu The side-effects associated with docetaxel were short-term and generally stopped once the 6 cycles of treatment were finished[viii]. However, some patients are contraindicated for chemotherapy and unable to receive docetaxel. Contraindications are numerous and include: • Anemia and decreased Blood Platelets • Decreased Neutrophils a type of white blood cell • Peripheral neuropathy • Fluid in the Lungs • Liver problems and abnormal liver function tests • Diarrhoea There are also some men who are too physically unfit to tolerate chemotherapy. Currently, these men must rely on ADT alone, without the additional survival benefit provided by docetaxel. For these men abiraterone, prednisone and ADT delivers to an unmet treatment need, if the hormone-sensitive metastatic prostate they have been diagnosed with is high-volume, as defined by the LATITUDE Study. *"I'm 63 and started hormone treatment in April 2017. Chemo (Doxetaxel) came next but I proved to be allergic to the chemo. I have been taking abiraterone since July 2017. My PSA is now undetectable and I experience little if any side effects. It's early days yet, but good result for me as I lead a fairly normal life."*

	Some patients can have chemotherapy but opt not to. They may not want to experience the side effects of the treatment. *"He chose not to have chemotherapy after watching his mother suffer terribly from side effects when she was treated for breast cancer."* *"It was such a relief not to have to have chemo. The side effects of chemo would have made it much tougher for me to continue to work effectively which I needed to do in order to get my business in order and in a position where it can function effectively without me."*
8. Is there an unmet need for patients with this condition?	Yes, men with hormone-naïve, high-volume metastatic prostate cancer who are contraindicated to chemotherapy or too physically weak to have it miss out on the additional 15-month survival benefit[ix] of docetaxel in combination with hormone therapy. Prostate Cancer UK believes it is critical that these men have the option of a treatment that can increase their life expectancy. Adding abiraterone to ADT can provide a 38% lower risk of death than those who receive ADT alone. The median overall survival was not yet reached in the abiraterone group when the LATITUDE trial published, but was 34.7 months in the placebo group. Abiraterone was also associated with a 53% lower risk of the cancer worsening and resulted in cancer growth being delayed by a median of 18.2 months[x]. It is disappointing, given evidence available via the abiraterone arm of STAMPEDE trial[xi] that all men with hormone-sensitive metastatic prostate cancer who are unable to have docetaxel chemotherapy will be unable to access abiraterone in combination with prednisone and ADT. They also have an unmet need and lack the potential for significantly higher rates of overall and failure-free survival than ADT alone.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Compared to hormone therapy alone, the STAMPEDE trial suggests a hazard ratio of 0.76 for docetaxel in combination with hormone therapy[xii] compared to a hazard ratio of 0.61 for abiraterone in combination with hormone therapy[xiii]. Backing up STAMPEDE's results, the LATITUDE trial shows a hazard ratio of 0.62 for abiraterone in combination with hormone therapy compared to hormone therapy alone[xiv]. An ESMO 2017 paper suggests that docetaxel in combination with ADT offers better overall survival than abiraterone combined with prednisone and ADT, while this abiraterone combination offers better failure free survival, progression free survival and symptomatic skeletal events[xv]. While, this data applies to a comparison of an overlap between two STAMPEDE trial arms containing a broader metastatic patient population than the hormone-naïve high-volume metastatic sub-population being considered by this appraisal, it does not offset the benefit to men unable to have docetaxel. Patients and their carers will appreciate the additional survival benefit granted by this treatment in comparison to their current standard of care (ADT alone). *"We honestly believe that the treatment has kept him alive and we are so grateful he was able to get the chance."* *"[The doctor] believes these drugs have prevented his stage 4 cancer from killing him so far."*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Side effects of abiraterone include[xvi]: • fluid retention which can cause swelling or bruising • high blood pressure • liver problems • low blood potassium levels leading to tiredness

- Risk of irregular heartbeat

In a study over 26 months, grade 3 to 5 adverse events were reported in 47% of patients taking abiraterone in combination with hormone therapy compared to 33% of patients taking hormone therapy alone[xvii]. In comparison, 52% of patients receiving docetaxel in combination with hormone therapy reported adverse events of grade 3 to 5. However, on docetaxel most adverse events were reported during the first six months of the trial (36% of patients) with fewer around one year after randomisation (10% of patients)[xviii].

During the STAMPEDE trial, the proportion of patients reporting worst adverse event ever as grade 3 or higher was highest with standard of care and docetaxel (288 patients [52%]). In the LATITUDE Study, several severe side effects were more common with abiraterone acetate and prednisone than placebo: high blood pressure (in 20% vs 10% of men), low potassium level (10.4% vs 1.3%), and liver enzyme abnormalities (5.5% vs 1.3%). Men and their families and/or carers may need to balance the opportunity to extend life with the potential impacts this may have on quality of life.

One further potential disadvantage is the length of treatment. Docetaxel is administered over six cycles while abiraterone is taken for 33 months. Any potential side effects of treatment will last for a shorter period for those taking docetaxel rather than abiraterone.

An additional disadvantage occurs from the trial evidence being used to appraise this technology. The LATITUDE trial has a specific patient sub-population that has been expanded upon by the abiraterone arm of STAMPEDE trial[xix]. STAMPEDE has shown that all men with hormone-sensitive metastatic prostate cancer have the potential for significantly higher rates of overall and failure-free survival than ADT alone. However, this technology only has the potential to be made available to men with hormone-sensitive, high volume metastatic prostate cancer. Prostate Cancer UK acknowledges that this constraint is the result of the licence the manufacturer has obtained, but remains concerned that the needs of sub-population of men with hormone-naïve metastatic prostate cancer, unable to have docetaxel will remain unmet.

	"Unfortunately I'm in the small minority whose liver doesn't tolerate the Abi and I'm currently off it and will have been for five weeks next Wednesday when I see my doctor to work out where we go next. Hopefully a lower dose but we have already tried that once. Despite my liver function issues I'm still really glad to have avoided chemo to date." *"He was offered the trial and started the treatment in the group having abiraterone and hormone injections in March 2012. All this time later he is doing very well and coming up to six years. Around two years into the trial he had indications his liver was being affected, had a three month break and then returned to half dose. He has had only mild symptoms like tiredness."*
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Men with hormone-naïve, high-volume metastatic prostate cancer who are contraindicated or too physically unfit for chemotherapy.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Prostate cancer is a condition that only affects the prostate, specifically men or transsexual women.

Other issues	
13. Are there any other issues that you would like the committee to consider?	The LATITUDE trial results are only for men with high-volume hormone-naïve metastatic prostate cancer. The STAMPEDE trial results include evidence on the benefit of abiraterone to all patients with hormone-naïve metastatic prostate cancer, not only those who are high volume. We understand that the submitting company were unable to get complete access to the data from the abiraterone arm of the STAMPEDE trial and so have only been able to provide sufficient evidence for high-volume hormone-naïve metastatic prostate cancer.

Key messages

- ADT in combination with docetaxel or abiraterone provides a significant survival benefit to men with hormone-naïve, metastatic prostate cancer
- Some men with hormone-naïve, high volume metastatic prostate cancer are contraindicated for chemotherapy and so unable to benefit from docetaxel, having only ADT
- Abiraterone in combination with prednisone and ADT provides men with hormone-naïve, high-volume metastatic prostate cancer who cannot have docetaxel an additional survival benefit than ADT alone

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

[i] References for each symptom available on request.
[ii] European Urology Volume 44 Issue 5 *Spinal Cord Compression in Metastatic Prostate Cancer* H Tazi et al. November 2003
[iii] Journal of Lymphoedoma Volume 5 Number 2 *Cancer-related lymphoedema in males: a literature review* Cosgriff & Gordon 2010
[iv] https://www.uptodate.com/contents/initial-systemic-therapy-for-castration-sensitive-prostate-cancer
[v] NHS England Clinical Commissioning Policy Statement: *Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer* January 2016
[vi] The Lancet Volume 387, Issue 10024, *Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial* Prof Nick James et al. March 2016
[vii] Ibid.

[viii] Ibid.
[ix] Ibid.
[x] New England Journal of Medicine *Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy* Prof Nick James et al. July 2017
[xi] Ibid.
[xii] Ibid.
[xiii] The Lancet Volume 387, Issue 10024, *Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial* Prof Nick James et al. March 2016
[xiv] New England Journal of Medicine *Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer* Fizazi k et al. July 2017
[xv] ESMO 2017: *Adding Abiraterone Acetate or Docetaxel Plus Prednisone to Standard of Care in Patients with High-Risk Prostate Cancer* September 2017
[xvi] ZYTIGA 500 mg film-coated tablets Summary of Patient Characteristics
[xvii] New England Journal of Medicine *Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy* Prof Nick James et al. July 2017
[xviii] The Lancet Volume 387, Issue 10024, *Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial* Prof Nick James et al. March 2016
[xix] New England Journal of Medicine *Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy* Prof Nick James et al. July 2017

NICE National Institute for Health and Care Excellence

Patient organisation submission

Abiraterone for treating newly diagnosed high risk metastatic hormone-naive prostate cancer [ID945]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Tackle Prostate Cancer
3. Job title or position	Trustee
4a. Brief description of the organisation (including who funds it). How many members does it have?	Tackle Prostate Cancer is the only national patient led organisation for prostate cancer patients and their families. Nationwide we have over 10,000 members and keep in touch by email and a quarterly newsletter. We have no paid employees and running costs are kept to a minimum. Our funding come fron a variety of sources, including grants from Pharma Companies and generous donations from our member organisations. Tackle is currently carrying out a major fundraising initiative called Cycle To The Moon.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**I gathered the information from researching the STAMPEDE trial by talking to the research clinicians involved and to patients. As an advanced patient I have a deep knowledge of the progress of this disease in all of its stages.** **I have received abiraterone myself, been involved with all of the abiraterone appraisal committees and fully understand the benefits and side affects of this treatment.**

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Much has changed over the last twelve years since I was diagnosed with metastatic prostate cancer. In 2005 there were no s modern treatments available and life expectancy was short. Since then, a whole raft of new therapies have thankfully transformed the outlook for advanced prostate cancer. Having said that, although life expectancy has improved, all treatments come at a cost which impacts on quality of life. 1. Fatigue (not just tiredness) is often a real problem as is "Chemo Fog", an inability to concentrate for long periods and a total loss of libido. There is always the knowledge that your current treatment will fail and what will be next on the treatment pathway. How will I cope with ever stronger therapies and will they be successful. This causes untold stress for both patients and carers. 2. Carers, who are most often wives and partners also have the same fears for their loved ones and have the added stress of watching the patient slowly deteriorate over time with a disease which they know will win in the end.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Current treatments have improved dramatically over the past few years. With the advent of abiraterone, enzalutamide, chemotherapy and radium 223 etc., there is much more in the armoury than ever used to be, but new therapies are always needed and new ways of using them.
8. Is there an unmet need for patients with this condition?	Until there is a cure, there is definitely an unmet need.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Being given abiraterone on diagnosis of advanced prostate cancer has been proven to increase life expectancy and will be very welcome to patients and carers. It will be an important new weapon in the armoury in the fight against metastatic prostate cancer. In the “abiraterone comparison” in STAMPEDE, 957 men who were randomised to receive standard of care (hormone therapy with or without radiotherapy) were compared to 960 men who were randomised to receive abiraterone plus prednisolone plus standard of care (hormone therapy with or without radiotherapy). Men in the abiraterone group had four abiraterone tablets and one prednisolone tablet a day. The proportion of men alive three years after joining the trial was 83% in the abiraterone group compared with 76% in the standard therapy group. Abiraterone also lowered the relative chance of treatment failure (measured by worsening scans or symptoms or elevated PSA level) by 71% compared to standard therapy. Abiraterone not only prolonged life, but also lowered the relative chance of relapse and reduced the relative chance of serious bone complications by 71%. At some point, most metastatic patients are likely to suffer bone complications and this fact alone would be a cause for them to welcome this new therapy. This is the most important new treatment yet devised for advanced prostate cancer. It has the advantage of using existing technology in a new and exciting way. Not only is it good for patients, but it is well within the current cost guidelines for new treatments. One important benefit is that Janssen operate a P.A.S. which would make this treatment cost less than £20,000 per QALY. Well within NICE guidelines and competitively priced against alternative treatments. It really is a win win situation.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Overall, side-effects were similar between the two groups. Worse side-effects were more common in the abiraterone group, occurring in 47% of patients compared to 33% of patients in the standard therapy group. The main unwanted side-effects occurring more frequently with abiraterone were cardiovascular problems such as hypertension; there were also more liver problems. There is also the worry that all of the advanced treatments are given at the beginning of treatment leaving nothing in reserve, but the benefits certainly outweigh the disadvantages of this
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No**
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.]	

if there are none delete highlighted rows and renumber below	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Abiraterone given on diagnosis of metastatic disease has been proven to considerably prolong survival
- Abiraterone given on diagnosis of metastatic disease has been proven to reduce treatment failure by 71% compared to standard treatment

The current PAS offered by the manufacturer equates to less than £20,000 per QALY. This makes it competitively priced against standard treatment

- The benefits for this therapy are so dramatic that it should be passed and used as soon as possible.
- Patients and carers will benefit greatly from using abiraterone in a completely novel way.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission for the NICE appraisal of abiraterone for newly diagnosed high risk metastatic hormone sensitive prostate cancer

1. The identification of high risk metastatic prostate cancer is dependent on having at least 2 of 3 criteria which reflect the behaviour of the disease: a Gleason histological score of at least 8, the presence of visceral metastases (ie non-bony and non-nodal metastases eg secondaries in the liver, lung etc) and the presence of at least 3 bone metastases on an isotope bone scan. The latter criterion is the softest in terms of implementation as the interpretation of isotope bone scans for patients with few bone metastases can be subjective. This high risk group accounts for about 50% of all comers with newly diagnosed metastatic hormone sensitive prostate cancer.
2. The current treatment pathway for newly diagnosed hormone sensitive PC consists of androgen deprivation therapy (hormone treatment) or the combination of docetaxel chemotherapy with androgen deprivation therapy. About two thirds of such patients receive ADT alone and about one third receive docetaxel plus ADT. This split of treatment choices depends on fitness for chemotherapy, visceral metastases (an adverse prognostic factor), high volume of metastatic load (another adverse prognostic factor) and patient choice. Most patients receiving chemotherapy plus ADT have adverse disease.
3. After ADT alone or ADT plus docetaxel (ie after the patient has developed castrate refractory PC), the main option is either abiraterone or enzalutamide, either used pre-chemotherapy or post chemotherapy.
4. There are separate evidence bases for the use of abiraterone plus ADT and for docetaxel plus ADT in high risk hormone sensitive PC. Both are active in patients with high volume metastatic disease and for those with visceral secondaries: the magnitude of survival benefit is similar with both combinations. Thus, one is not known to be better than the other in terms of efficacy. However, very clear differences exist in terms of toxicity and duration of treatment. Docetaxel has the main side-effects of tiredness, mucositis, taste change, nail changes, infections, neuropathy, myalgia and hair loss (unless scalp cooling is employed). Docetaxel treatment has the advantage of being completed in 4-5 months. Abiraterone has the main toxicities of tiredness, oedema, hypertension and having to take prednisolone. Abiraterone has the disadvantage of being on therapy for a median of 33 months. Oncologists will have to discuss with each patient with high risk hormone sensitive newly diagnosed PC which of 3 options are appropriate: ADT alone, abiraterone plus ADT or docetaxel plus ADT and the advantages and disadvantages of each. The patients will then be able to make an informed choice as to which is best. NHS expects the over whelming majority of poor risk patients to opt for abiraterone plus ADT as few will be unable to tolerate the combination and most will opt for abiraterone plus ADT rather than docetaxel plus ADT.

5. NHS England notes that 96% of patients in the LATITUDE trial of abiraterone plus ADT versus ADT were of ECOG performance status 0 or 1 ie these were fit patients and are likely to have tolerated the randomised treatments better than all comers will in the NHS.
6. If NICE recommends abiraterone plus ADT as 1st line systemic therapy for newly diagnosed hormone sensitive PC, then for those patients who receive such upfront abiraterone treatment, there will be no further abiraterone or enzalutamide commissioned in the later stages of the treatment pathway (ie as pre-chemotherapy or post chemotherapy for castrate –refractory PC). This is because patients will have become resistant to abiraterone by then and there is only poor efficacy for the use of enzalutamide after abiraterone. Thus NHS England will commission patients to have receive one chance to receive abiraterone in the treatment pathway.

[redacted]

May 2018

NICE National Institute for Health and Care Excellence

Patient expert statement

Prostate cancer (hormone-naive, metastatic, newly diagnosed) – abiraterone – ID945

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 conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- 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
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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	x☐ a patient with the condition? ☐ a carer of a patient with the condition?

	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☐ I don't know
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)	**x**☐ 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
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	After almost 4 years of treatment I have very few problems. I am very active, walking my dog for approx 2 hrs every day and busy around the house and garden. I also enjoy riding my motorcycle as often as possible. I don't have or need a carer.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Apart from a stomach operation in 1979 and a knee operation in1983, I have not had to call on the NHS for any serious treatment. My present treatment is excellent and my experiences of NHS treatment over the years has been excellent.
10. Is there an unmet need for patients with this condition?	?

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	For most of my working life I have worked with medical equipment, MRI, CT, Gamma cameras, etc, usually in R&D and I'm happy to still be able to contribute to the development of medicine and treatments.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I haven't experienced any disadvantages.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
15. Are there any other issues that you would like the committee to consider?	I feel well and enjoy life. I can't ask for more,
Topic-specific questions	
16. [To be added by technical team if required, after receiving	

the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

-
-

-
-
-

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.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Abiraterone for treating newly diagnosed metastatic hormone-naive prostate cancer [ID945]

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

- 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	**University Hospitals Birmingham NHS Foundation Trust**

3. Job title or position	**Professor of Clinical Oncology**
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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Abiraterone was developed as a drug for men relapsing after standard first line hormone therapy (androgen ablation therapy or ADT) with metastatic disease. In this setting it improves overall survival by 20-25% in trials that compared abiraterone + steroids to steroids alone. In absolute terms, this translates into a gain of 4-5 months overall survival. This was associated with significant palliative benefits such as a reduction in the bone complications of advanced prostate cancer. I am Chief Investigator of the STAMPEDE trial that has evaluated a range of therapies used for relapsed cancer in the newly diagnosed setting. The aim of the trial was to assess whether the proportional survival gain of therapies such as docetaxel or abiraterone was preserved when used earlier, this would translate into a much larger absolute benefit as this 20-25% gain would be on top of much longer control arm survival. We reported results from the ADT vs. ADT + abiraterone comparison in the NEJM in 2017. We demonstrated a gain in survival of 38%, which we project, would translate into an absolute gain in median overall survival of 2-3 years. This was accompanied by a reduction in significant skeletal complications of 55%.
8. 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.)	In my opinion the two gains highlighted above are both of very high importance to patients and clinicians working in the field.
9. In your view, is there an unmet need for patients and	When we commenced the STAMPEDE trial in 2004-5, survival times for men with metastatic prostate cancer were of the order of 2-3 years. The previous demonstration by the STAMPEDE (and other) trials that use of docetaxel increased projected survival to around 5 years has already been NICE approved. There have been significant improvements in relapse therapies since we began recruiting

healthcare professionals in this condition?	to the more recent abiraterone part of STAMPEDE, which probably improve the median survival now to 7 years for newly diagnosed men. To achieve this, men will need to receive either docetaxel or abiraterone as part of their initial therapy. Whether both would achieve further gains is the subject of current studies. Despite these improvements, metastatic prostate cancer remains incurable and a major cause of cancer death and morbidity in men worldwide. The upfront availability would provide an alternative life prolonging therapy for men unable or unwilling to undergo upfront chemotherapy with docetaxel. Experience from elsewhere in Europe where both are already available suggests that around 60% of newly diagnosed men fit to receive either docetaxel or abiraterone opt for abiraterone. Our own data from within STAMPEDE suggests both agents prolong survival by similar amounts but with very different side effect patterns.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	As noted above, ADT is the mainstay of therapy for newly diagnosed metastatic prostate cancer. This is lifelong and as monotherapy gives a typical survival duration of around 3-3.5 years. The upfront addition of docetaxel increases this to around 5 years and is NICE approved. Not all men are fit to receive docetaxel, but data from STAMPEDE (still recruiting to different questions and which now permits docetaxel as control therapy) shows that 90% of men entering the trial are currently receiving docetaxel. Outside the trial, where men are likely to be less fit, the proportion is certain to be lower but I do not have data on usage rates. A range of drugs is available on relapse, some of which have been shown to improve survival. These currently comprise docetaxel, cabazitaxel, abiraterone, enzalutamide and radium-223, all of which are NICE approved.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Numerous – including various NICE technology appraisals and guidelines, plus guidelines from a range of professional organisations.

• 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.)	The general elements are well defined. There is no “optimal” sequence for using the various NICE approved therapies and not all are suitable for all men with the disease.
• What impact would the technology have on the current pathway of care?	Upfront use of abiraterone would move a class of drug from one part of the pathway to another. The other elements would correspondingly reshuffle to later slots. Duration of use of abiraterone in this setting is likely to be around 36 months based on STAMPEDE compared to 12-18 months if used in relapse. Survival post relapse is shorter however as a major class of drug used in this setting is of course no longer available. This shorter post–relapse period is however still outweighed in survival terms by the upfront gain.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No – it will be used earlier and for longer.
• How does healthcare resource use differ between the technology and current care?	See above
• In what clinical setting should the technology be used? (For example,	Secondary care. It does cause clinic resource issues (as do all life prolonging therapies) and in our centre we have had to expand capacity via, for example, nurse and pharmacist based follow up and prescribing.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The drug is well established in practice. The main issue is the increased duration of therapy and survival increasing clinic loads.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – see above.
• Do you expect the technology to increase length of life more than current care?	Yes – see above
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – data published from the LATITUDE trial clearly show this. Our own data from STAMPEDE are currently being analysed. The reduction in skeletal morbidity had a significant effect on HRQOL in our recent analysis of our STAMPEDE docetaxel data (submission to NICE pending) and we expect the 55% reduction seen with abiraterone to similarly improve this metric.

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes. STAMPEDE also studied men with locally advanced but non-metastatic prostate cancer. Our data suggest proportionately bigger benefits in this group, especially in those also receiving radiotherapy (>75% improvements in time to relapse and development of metastatic spread vs. 50% in those on drug therapy only).
The use of the technology	
14. 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.)	See above – drug in widespread use but duration of care will increase.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The STAMPEDE trial used the same stop-start rules as for the drug used in the relapse setting. These are thus very familiar to clinicians in the field.
16. 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?	No
17. 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	Yes – see above

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	It mirrors a change already achieved with chemotherapy but with a completely different class of drug. Given that not all patients are willing or able to receive chemotherapy but nonetheless could receive abiraterone it represents a significant advance.
• Does the use of the technology address any particular unmet need of the patient population?	Men with metastatic prostate cancer unfit for chemotherapy but fit for abiraterone.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Main side effects are liver toxicity (up to 5%, requires regular monitoring) and cardio-vascular. These latter may become more significant with widespread off trial use in (inevitably) less fit populations. The need for regular monitoring thus needs to be stressed.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – STAMPEDE is recruiting from every oncology centre in the UK, hence both control arm and experimental arm patterns of care are representative of how we may expect care to be administered in the NHS.

• If not, how could the results be extrapolated to the UK setting?	See above
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival and symptomatic skeletal related events
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator	No

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	
22. How do data on real-world experience compare with the trial data?	Efficacy is always lower and toxicity higher. STAMPEDE however has recruited from a very broad range of centres and produced a strikingly similar survival outcome to the more selective licencing trial LATITUDE.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24.	

[To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Upfront use of abiraterone improved overall survival by 38% in STAMPEDE
- Upfront use also reduced symptomatic skeletal events by 55%
- Similar magnitude survival and skeletal benefits are also achievable with upfront chemotherapy with docetaxel but not all men are suitable for this therapy
- Abiraterone was generally well tolerated in STAMPEDE and toxicity is in line with that seen with use of the drug in the relapse setting.
- UK clinicians are very familiar with the drug but earlier use will place resource demands on clinic time.

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.

Abiraterone for treating newly diagnosed metastatic hormone-naïve 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

Ewen Cummins acted as health economist for this appraisal: critiqued and reviewed the cost-effectiveness evidence, checked and re-analysed the economic model, and carried out further sensitivity analyses. Rhona Johnston acted as programmer and modeller and contributed to the revision of the company model and helped with some of the model rebuild. Lorna Aucott 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. Clare Robertson acted as systematic reviewer: 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 and review of the clinical

effectiveness methods, checked the final report and supervised the work throughout the project.

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1 Summary

Prostate cancer is the most common male cancer in the UK, with over 46,700 people diagnosed in 2014. Approximately 18% of new cases present with metastases at first diagnosis, meaning the cancer is diagnosed too late for curative treatment to be possible as it has already spread outside the prostate gland and through the body. The term metastatic hormone sensitive prostate cancer refers to people who have not received hormone therapy or who have received hormone therapy but have not yet become resistant to treatment. Those with newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC) have a poorer prognosis than people who are first diagnosed with localised disease.

Androgen deprivation therapy (ADT) has been the standard of care in mHSPC, orchidectomy (surgical castration) and bicalutamide monotherapy are less common treatment options. Data from two recent clinical trials, CHAARTED and STAMPEDE, have shown that the addition of docetaxel (chemotherapy) to ADT for the treatment of newly diagnosed mHSPC was beneficial in terms of health outcomes, but associated with greater toxicity and potentially severe side effects. Several novel agents are now available, such as abiraterone acetate, and the order in which a patient may receive them is determined by clinical symptoms and manifestations, prior treatment, NICE recommendation and NHS policy.

1.1 Critique of the decision problem in the company submission

The company's submission considered abiraterone acetate (trade name Zytiga) with prednisone/prednisolone (AAP) plus androgen deprivation therapy (ADT) for the treatment of adults with newly diagnosed, high risk mHSPC.

The decision problem addressed in the company's submission was broadly consistent with the NICE final scope. The NICE final scope for this appraisal specified the population as adults with newly diagnosed high risk metastatic hormone-naïve prostate cancer (mHNPC), while the population addressed in the company submission is adults with newly diagnosed, high risk mHSPC. The company state that the marketing authorisation wording describes AAP as indicated for the treatment of

newly diagnosed high risk mHSPC in combination with ADT and that the terms mHNPC and newly diagnosed mHSPC are effectively the same because newly diagnosed patients are, by default, hormone naïve. The company did not consider orchidectomy and bicalutamide monotherapy as clinical experts advised that these are seldom used in the UK. The comparators presented in the company submission are ADT alone (including LHRH agonist therapy) and docetaxel (DOC) plus ADT. The company state that clinical experts provided validation that there is no difference in the type of ADT, thus justifying their approach. The company submission includes all the outcomes listed in the NICE scope and reports additional outcomes from the LATITUDE trial: progression free survival following subsequent therapy, time to symptomatic local progression, prostate cancer-specific survival, time to chronic opiate use, castration status.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence submitted by the company consist of one RCT, the LATITUDE trial (1199 participants), with supporting evidence of one further RCT, the STAMPEDE trial (1917 participants). LATITUDE is a manufacturer-sponsored, multinational, randomised, double-blind, placebo-controlled Phase III trial that investigated abiraterone acetate with prednisone/prednisolone (AAP) plus ADT (597 participants) versus ADT plus placebo (602 participants). The company consider the ADT plus placebo arm equivalent to ADT alone. The company also maintain that LATITUDE is the only RCT providing data specific to the target population of people with newly diagnosed, high-risk mHSPC. The manufacturer-sponsored STAMPEDE trial represents the largest evidence base of AAP plus ADT in early prostate cancer data relevant to UK practice but include a broader patient population than LATITUDE, and does not report data separately for high risk disease/high volume patients.

The co-primary outcomes assessed in the LATITIDE trial were overall survival (OS) and radiographic progression free survival (rPFS). OS was also the primary outcome in STAMPEDE whilst failure free survival (FFS) was the intermediate primary outcome. In the LATITUDE trial, treatment with AAP plus ADT was associated with a 38% reduction in the risk of death compared with ADT alone (HR=0.62 [95%CI: 0.51–0.76]; p<0.001).7 The overall survival rate at three years was 66% in the AAP +

ADT group and 49% in the ADT alone group. There was an imbalance in the proportion of patients who received life-extending subsequent therapies (20.9% in the AAP plus ADT arm versus 40.9% in the ADT alone arm). The company claim that this could result in the standard ITT analysis of OS underestimating the true OS benefit for AAP. Therefore, additional pre-specified OS analysis using the IPCW methodology were conducted by the company to adjust for patients who switched to other therapies. This analysis showed AAP plus ADT significantly improved survival compared to ADT alone, with an improved HR=0.48 (95% CI: 0.36–0.63; p<0.0001). Results from STAMPEDE are consistent with these results. Treatment with AAP + ADT was associated with a 39% reduction in the risk of death compared to ADT alone (HR= 0.61 [95% CI: 0.49–0.75]; p<0.0001).

In LATITUDE, treatment with AAP plus ADT significantly delayed disease progression compared with ADT alone. AAP + ADT resulted in a 53% reduction in the risk of radiographic progression or death (HR=0.47 [95% CI: 0.39–0.55]; p<0.001). At three years, 47% of patients in the AAP + ADT arm remained event-free, compared to only 21% of those in the ADT alone arm. In support of this evidence, the company present data from the metastatic (M1) subgroup of STAMPEDE, in which treatment with AAP + ADT was associated with a 69% reduction in the risk of biochemical failure, progression or death compared with ADT alone (HR=0.31 [95%CI: 0.26–0.37]; p<0.0001).

The median treatment duration in the safety population of the LATITUDE trial was 24 months in the AAP + ADT arm and 14 months in the ADT alone arm. Treatment emergent adverse events (TEAEs) were reported by a higher number of people in the AAP+ADT group than for ADT alone. The most frequently reported TEAEs in the (reported in ≥20% of patients) in either the AAP + ADT or ADT alone arm were hypertension (37% versus 22%, respectively), hypokalaemia (20% versus 4%) and back pain (18% versus 20%). Commonly reported serious adverse events (SAEs) (reported by ≥1% of patients in either the AAP + ADT or ADT alone group) included pneumonia (1.8% versus 0.3%, respectively), spinal cord compression (1.7% versus 1.8%) and urinary retention (1.5% versus 1.7%). The most frequently reported adverse events (AEs) leading to treatment discontinuation (reported in ≥1% of patients in either the AAP + ADT or ADT alone group) were spinal cord compression

(0.8% versus 1.0% of patients, respectively) and bone pain (0.5% versus 1.0%, respectively). Cases of discontinuation for hypokalaemia, hypertension and cardiac disorders were rare.

The comparison of the effectiveness of AAP with DOC for the mHSPC patient group was made using indirect treatment comparisons since no head-to-head studies currently exist in this particular patient group. For the co-primary outcomes, three RCTs were subsequently included: LATITUDE, CHAARTED (790 participants) and GETUG-AFU 15 (385 participants); the latter two using post-hoc selected sub-groups of newly diagnosed patients with high volume disease. STAMPEDE, which assessed a much broader patient group, was only included in sensitivity analyses.

The results suggest non-significant effects for OS (HR 0.92 [95% Crl 0.69-1.23]) and for rPFS (HR 0.76 [95% Crl 0.53-1.10]) albeit with Bayesian pairwise probabilities of 71.8% and 92.9%, respectively. These probabilities represent a level of certainty that AAP+ADT patients may be more likely to survive or have progression free survival using AAP+ADT compared with DOC+ADT. The company presented also a number of sensitivity analyses with varied but similar results.

Results of sensitivity analyses suggest that skeletal-related events (SRE) were similar in the indirectly comparison between AAP and DOC, [redacted] but with a Bayesian probability of [redacted] but without adequate group identification.

Two RCTs, LATITUDE and GETUG-AFU 15, fed into a Bayesian ITC for safety results, but no sensitivity analyses were reported. When the AAP+ADT group (n=597) was indirectly compared to the DOC+ADT group (n=189),

[redacted]

The Functional Assessment Cancer Therapy-Prostate (FACT-P) and Brief Pain Inventory (BPI) quality of life measures, looked at differences of change from baseline for both AAP+ADT and DOC+ADT treatment groups over four time points 3, 6, 9 and 12 months in LATITUDE (ITT) and CHAARTED (high volume disease - HVD). Sub-group analyses were conducted by the company whereby high risk disease (HRD) and HVD patients in LATITUDE were selected post-hoc. At 3 months, AAP+ADT had a significant positive and beneficial increase on FACT-P over DOC+ADT, with difference of change = 4.20 (95% CrL 1.18-7.19) and a 99.7% probability of AAP being better than DOC. AAP estimates improved further over time as did the DOC estimates (not to the same extent and never to the level of AAP), but differences between AAP and DOC were not significant by 6 months or even at 1 year. BPI results showed larger decreases in pain estimates for indirect comparisons between AAP and DOC, but the results were not significant. Pain in the DOC group increased with time whereas with AAP they remained steady if not further reduced. The sensitivity analyses were comparable for FACT-P and BPI.

In the absence of any head-to head studies, further indirect comparisons were conducted for a group of men with disease progression (for the mCRPC group with respect to the effectiveness of AAP with other treatments including DOC). These were not presented in the clinical effectiveness section of the submission but only in the cost-effectiveness section. The company used the COU_AA_302 study, which directly compared abiratone plus prednisolone with placebo plus with prednisolone, and other studies which compared different treatments with placebo or best standard care. In particular, the company focused on DOC (the TAX327 study comparing DOC to a different placebo, mitoxantrone), radium-223 (the ALSYMPCA study with prednisolone as placebo) and enzalutamide (the PREVAIL study with prednisolone as placebo). In general, the estimates show that AAP is comparable with other treatments.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

LATITUDE has provided the only evidence so far of AAP+ADT compared with ADT alone for the treatment of men with mHSPC. The ERG agree with LATITUDE results suggesting that AAP+ADT to be beneficial for the primary outcomes of OS and rPFS and for most of the secondary outcomes of safety and quality of life compared to

ADT. In terms of safety, AAP+ADT had a slight increased risk for hypertension and hypokalaemia. The results of LATITUDE are similar to those of the STAMPEDE trial. However, the STAMPEDE patient group was broader and while the company have conducted similar analyses on a *post hoc* subgroup profiled to be similar to the LATITUDE population, they rightly have not combined the results of these studies. Overall, the results from the LATITUDE trial provide evidence of benefits of AAP+ADT over ADT alone for the treatment of patients with mHSPC for the outcomes survival, progression and quality of life. The risk of some safety outcomes increased for AAP but the ERG agree that these may be well treated medically.

With no head-to-head trials assessing the effects and safety of abiratone versus the only other relevant comparator, DOC, identified for the patient group of interest, mHSPC, indirect treatment comparisons (ITC) were a sensible option. The company used a Bayesian network meta-analysis (NMA). The primary outcomes were based on three RCTs: LATITUDE, which compared AAP+ADT to ADT alone, and CHAARTED and GETUG-ARG 15, both of which compared DOC in conjunction with ADT to ADT alone. The NMA results showed no evidence of a difference in OS and rPFS between AAP+ADT and DOC+ADT, despite the many sub-group analyses using many combinations of patient groups in an attempt to mirror the LATITUDE population. The results did not vary drastically but it is not clear which might be the most reliable.

For the relapsing/progression patients, the mCRPC group, the ITC used were Bucher pairwise estimates comparing other treatments with AAP. This approach requires many independent steps and so, intuitively, seems less robust compared to the NMA above, but the ERG agree it was probably the only course of action to accommodate the lack of studies and comparison arms. Each study compared a treatment with a 'placebo' although not always the same one. The conclusion that AAP is comparable to other treatments with regard to OS and rPFS is probably reasonable.

The ITC analyses for both the mHSPC and mCRPC patient groups, have basic assumption violations of contextual heterogeneity which the company discussed in some detail and acknowledge the subsequent limitations. However, no checks were provided for statistical heterogeneity or consistency. All of these mean that clinically,

the ERG agree with the company's conclusions that AAP is at least as effective as other treatments for both newly diagnosed patients and those who have relapsed or progressed. However, the decision of which estimates to use for further modelling and interpretation should be taken with caution given the spectrum of possibilities available across different credible limits.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The company compares three mHSPC treatment arms in the economic model:

- AAP+ADT
- ADT
- DOC+ADT

This also requires the company to model the treatment sequences for when patients progress to mCRPC. Which treatments patients receive for their mCRPC is determined by which treatment they received for their mCRPC. Because the LATITUDE trial is not solely UK based the company applies mCRPC treatment proportions derived from expert opinion. These mCRPC treatment proportions have some effect upon patient outcomes, but mainly affect the estimated mCRPC costs.

The company outline that all other companies submitting in the area have adopted a partitioned survival analysis. The company model is a quite complex markov model with a 20 year time horizon. Discounting and perspectives are as per the NICE reference case. The model applies the LATITUDE Kaplan Meier OS and rPFS data for the first 5 months. The LATITUDE 5 months plus data is analysed using multi-state modelling (MSM) to provide transition probabilities for 5 months plus. The DOC+ADT curves are estimated by applying the company ITC hazard ratios to the rPFS and OS probabilities in the AAP+ADT arm.

It appears that the post progression survival is divided into 1st line mCRPC treatment, 2nd line mCRPC treatment and 3rd line treatment using mean duration data from the COU-AAP-302 trial of abiraterone for mCRPC. The model that uses this method of dividing the post progression survival is referred to as the MSM model in what follows.

The model also contains the facility to apply the mCRPC discontinuation and overall survival curves estimated by the discrete event simulation model that the company submitted for TA387. These provide estimates for 1st line mCRPC treatment with abiraterone and BSC. The curves for other active treatments are estimated by applying hazard ratios to the abiraterone curves. The curves that are applied in each arm are averages of these mCRPC curves,

weighted by the arm specific 1st line mCRPC treatment proportions. For the base case the company assumes that all active treatments are equally effective for mCRPC. This determines the duration of 1st line mCRPC treatment and mCRPC survival. The mCRPC survival after discontinuation from 1st line mCRPC treatment appears to be divided into 2nd line treatment and 3rd line treatment using mean duration data from the COU-AAP-302 trial of abiraterone for mCRPC. The model that uses this method estimating mCRPC treatment and survival is referred to as the MSM/TA387

The company argue that the LATITUDE OS data are not relevant to the UK due to different treatments for mCRPC and that it is important to model the effects of these. Mainly due to this, the company prefer the MSM/TA387 model to the MSM model.

The MSM/TA387 model that applies the mCRPC discontinuation and OS curves estimated by the TA387 model results in OS curves that are a poor fit to the LATITUDE OS Kaplan Meier curves. The company fit the MSM/TA387 model OS curves to the LATITUDE OS Kaplan Meier curves by applying an ad hoc hazard ratio of 2.62 to the OS curves estimated by the TA387 model. The TA387 model discontinuation curves have a similar compensating adjustment applied. This causes the MSM/TA387 model OS curves to be aligned with the LATITUDE OS Kaplan Meier curves.

Due to the 2.62 hazard rate adjustment, the MSM/TA387 model estimates very similar OS curves to those of the MSM model during the period of the LATITUDE trial. The models' OS curves only really diverge during the period of extrapolation.

The company undertake a repeated measures analysis of the LATITUDE EQ-5D data. This estimates a treatment effect increment of [redacted] for AAP+ADT over ADT. It also estimates quite large decrements for SAEs and SREs. The decrements for SAEs and SREs are not applied. Instead the company derive smaller decrements from the literature.

The LATITUDE data do not address what the quality of life should be in the DOC+ADT arm. The company commission a TTO study from MAPI values to estimate this relative to the ADT arm quality of life. The health state descriptor for those in the DOC+ADT arm who are receiving docetaxel treatment is worse than that

for the ADT arm. RCT trial FACT-P data supports this assumption. The health state descriptor for those in the DOC+ADT arm who have completed a course of docetaxel treatment and are now only receiving ADT is also worse than that for ADT arm. This is because they are more frequently depressed. When valued by 200 members of the UK public this results in quality of life decrements in the DOC+ADT arm for those who are receiving docetaxel treatment of [redacted] and for those who have completed their docetaxel treatment of [redacted].

Drug costs for mHSPC have treatment compliance percentages applied to them. The company estimate an [redacted] percentage for abiraterone based upon the areas under the LATITUDE AAP+ADT arm rPFS and TTD curves.

Other resource use is largely based upon expert opinion. The main difference between the arms is that DOC+ADT patients receiving docetaxel are assumed to require bone scans. No bone scans are required in either the AAP+ADT arm or the ADT arm. The frequency of bone scans increases in the DOC+ADT arm when patients have completed their course of docetaxel. The number of CT scans is also slightly higher for DOC+ADT patients who have completed their course of docetaxel than for AAP+ADT patients and ADT patients.

The company base case deterministic cost effectiveness estimates are £17,418 per QALY for AAP+ADT compared to ADT and £17,828 per QALY for AAP+ADT compared to DOC+ADT. The central probabilistic estimates are aligned with these.

A range of univariate sensitivity analyses are presented which vary inputs according to their 95% confidence limits, or if these are not available by ±10%. These find results to be sensitive to the clinical and utility inputs, due in part to these having 95% confidence limits. Results are not found to be sensitive to cost inputs, but this may be due to them largely not having 95% confidence limits.

The company also present a range of scenario analyses which find results to be sensitive to:

- the time to subsequent therapy being used as the definition of progression

- the MSM model being used, with this being coupled with the LATITUDE mCRPC treatment proportions
- a time horizon of only 5 years
- applying the abiraterone quality of life increment until death
- the DOC+ADT quality of life decrement for mHSPC patients post docetaxel treatment
- vial wastage
- applying the LATITUDE QoL regression coefficients instead of the subset of the base case
- The time point of the switch from Kaplan Meier data to MSM probabilities

Some of the company scenario analyses have cost effectiveness estimates higher than £20,000 per QALY. None have cost effectiveness estimates higher than £30,000 per QALY.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

It appears that the 1st line mCRPC costs and benefits estimates of both the MSM model and the MSM/TA387 model are not reliable. All cost effectiveness estimates may consequently not be reliable.

The company cost effectiveness estimates may be biased in favour of AAP+ADT because:

- It is questionable whether there is a quality of life decrement for those who have completed a course of docetaxel compared to those who have only ever received ADT. There are reasons and trial data to suppose there may be an increment.
- If there is a quality of life decrement for those who have completed a course of docetaxel the company commissioned TTO study that estimates this may be biased.
- The company's estimates of the quality of life decrements for docetaxel are only applied in the DOC+ADT arm, and not to docetaxel treatment for mCRPC in the AAP+ADT arm or the ADT arm.

- The company only partially apply the results of the LATITUDE QoL regression, which pushes up quality of life values to above those observed during the LATITUDE trial.
- The treatment compliance estimate for abiraterone for mHSPC seems low compared to CSR data on compliance.
- The treatment compliance estimate for docetaxel for mHSPC is not applied to the same range of costs as the compliance estimate for abiraterone.
- The treatment compliance estimates for mCRPC do not take into account that they reflect discontinuations during the relevant trials. This mainly affects mCRPC treatments in the AAP+ADT arm.
- The ERG cannot find evidence that mHSPC patients who have completed their course of docetaxel and are only receiving ADT in the DOC+ADT arm have more routine bone scans than mHSPC patients in the AAP+ADT arm.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

- The submission was generally coherent and focused on the current relevant clinical evidence.
- For the economic model, the company submission uses the LATITUDE data to estimate the probabilities.
- The LATITUDE trial provides EQ-5D data, though the quality of life values estimated from this are only partially applied.
- A good range of scenario analyses are presented by the company.

1.6.2 Weaknesses and areas of uncertainty

Clinical effectiveness

- Whilst accepting that the population in the LATITUDE trial provides the best match the target patient population in the NICE scope, the company submission is weakened by being reliant upon data from only one RCT.
- There is a concern that estimates from both of the company's ITCs using NMA for the mHSPC group and the Bucher pairwise estimates for the mCRPC patients are not be robust due to the vast contextual heterogeneity

between studies. Fixed effects models had to be run due to insufficient numbers of trials and combinations of treatment arms to strengthen the networks and evidence. Had it be possible, random effects models would have been preferred.

Cost-effectiveness

The estimates of 1st line mCRPC costs and benefits may not be reliable. These are central to the cost effectiveness estimates as they provide cost offsets to the abiraterone mHSPC treatment costs. All the cost effectiveness estimates may not be reliable.

The company prefer the MSM/TA387 model over the MSM model. Due to the *ad hoc* 2.62 hazard ratio this is in large part an elaborate non-statistical method of fitting curves to the LATITUDE Kaplan Meier OS curves. The fitting of the MSM/TA387 model OS curves to the LATITUDE Kaplan Meier OS curves also seems to largely negate the reason for adopting the MSM/TA387 modelling approach.

If curves are to be fitted to the LATITUDE Kaplan Meier OS curves it may be better to use the usual well-established statistical methods, which would also allow time varying probabilities to be explored.

There may be procedural issues around using the model outputs of a previous submission as axiomatic inputs to the model of a subsequent submission. Approval of abiraterone for mCRPC prior to chemotherapy during TA387 also does not imply that the model outputs of TA387 were necessarily viewed by the Committee as reliable estimates of the most probable mCRPC OS and discontinuation curves.

The Committee for this appraisal may be more equipoise between the MSM model and the MSM/TA387 model than the company. The most important difference between them is the amount of time they model patients spending on 1st line, 2nd line and 3rd line mCRPC treatment. Alternatively, the Committee may prefer a partitioned survival analysis, or a presentation of parameterised curves that are fitted statistically to the LATITUDE rPFS and OS data by way of model validation.

There is uncertainty about what 1st line mCRPC treatments proportions should be applied subsequent to AAP+ADT, ADT and DOC+ADT treatment for mHSPC. It is also not clear whether NICE approval of abiraterone for mHSPC would over time lead to mHSPC patients receiving more than one novel agent for their metastatic prostate cancer. These proportions are likely to become more important if the models' estimates of 1st line mCRPC treatments' costs and benefits are corrected.

The company do not submit any scenario analyses that limit the extrapolation of the treatment effect, as suggested in the NICE methods guide section 5.1.16.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG make a number of revisions to the company model. The detail of these is presented in section 5.4. The main ERG revisions are:

- Applying the full LATITUDE quality of life regression so that the quality of life values reflect those observed during the trial:
- Not applying the company quality of life decrement for those who have completed a course of docetaxel for mHSPC. The ERG consider the evidence presented by the company for this as thin. There is RCT data which may suggest there is actually an increment.
- Applying a compliance estimate for mHSPC abiraterone costs based upon compliance data in the clinical study report. The company estimate derived from the LATITUDE rPFS and TTD curves seems too low, particularly towards the end of these curves.
- Equalising the frequency of bone scans for those who have completed a course of docetaxel for mHSPC with those receiving abiraterone for mHSPC in the AAP+ADT arm.

Each of these changes has a reasonable impact upon the cost effectiveness estimates.

The results summarised below take into account the abiraterone commercial access agreement but do not take into account the enzalutamide, cabazitaxel or radium-223 patient access schemes. The ERG provides a separate cPAS Appendix that takes into account the enzalutamide, cabazitaxel or radium-223 patient access schemes.

When using the MSM/TA387 model the ERG's changes taken together worsen the cost effectiveness estimates from £17,418 per QALY to £17,992 per QALY for the comparison of AAP+ADT with ADT and from £17,828 per QALY to £31,439 per QALY for the comparison of AAP+ADT with DOC+ADT.

When using the MSM model the ERG's changes taken together worsen the cost effectiveness estimates from £20,438 per QALY to £20,855 per QALY for the comparison of AAP+ADT with ADT and from £26,909 per QALY to £41,697 per QALY for the comparison of AAP+ADT with DOC+ADT.

The probabilistic estimates are aligned with these deterministic estimates.

The ERG provide a range of sensitivity and scenario analyses:

- Applying the LATITUDE Kaplan Meier data for a longer period worsens the cost effectiveness estimates.
- Assuming that DOC+ADT patients who progress have the same probability of receiving treatment for mCRPC as those in the AAP+ADT arm worsens the cost effectiveness estimate.
- Differentiating 1st line mCRPC treatments' effectiveness has little effect. However, assuming that patients prefer enzalutamide rather than abiraterone for 1st line mCRPC treatment improves the cost effectiveness estimates. Both costs and QALYs are affected due to enzalutamide not being associated with a quality of life treatment effect increment compared to ADT, whereas abiraterone is.
- Quality of life increments and decrements for ADT (post DOC+ADT) have the predictable effects.
- Not applying the LATITUDE QoL regression in full but deriving SAE and SRE decrements from values in the literature improves the cost effectiveness estimates considerably.
- Applying the company mHSPC abiraterone compliance percentage improves the cost effectiveness estimates.
- Applying the company bone scan frequencies for DOC+ADT improves the cost effectiveness estimates considerably.

2 Background

2.1 Critique of company's description of underlying health problems

The company's description of prostate cancer and newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC) in terms of prevalence, symptoms and complications appears generally accurate and appropriate to the decision problem. Prostate cancer is the most common male cancer in the UK, with over 46,700 people diagnosed in 2014.[1] Approximately 18% of new cases present with metastases at first diagnosis, meaning the cancer is diagnosed too late for curative treatment to be possible as it has already spread outside the prostate gland and through the body.[1] The term metastatic hormone sensitive prostate cancer refers to people who have not received hormone therapy or have received hormone therapy but have not yet become resistant to treatment. Those with newly diagnosed mHSPC have a poorer prognosis than people who are first diagnosed with localised disease.[2, 3] Localised prostate cancer has an expected survival of at least five years after diagnosis, while only 30% of those with metastatic disease are expected to reach five-year survival.[4] The outlook for those classed as 'high-risk' at diagnosis is even worse, with life expectancy generally less than three years on conventional hormone therapy.[5-7] This is because high-risk disease is aggressive and is likely to advance more quickly.

High-risk disease is defined as having two of the following three poor prognostic factors: a Gleason score of ≥8 (describing the aggressiveness of the tumour), the presence of ≥3 lesions on a bone scan, or the presence of visceral metastases (both describing the extent of tumour spread).[4] Approximately 50% of men with newly diagnosed mHSPC are likely to have high-risk prognostic factors at diagnosis, amounting to approximately 4400 cases each year (Incidence statistics, Janssen Research & Decelopment, 2018).[1, 8] 'High-volume' is a concept previously used in mHSPC research (i.e. the CHAARTED and GETUG-AFU 15 studies) which is of similar severity to high-risk disease (three or more bone lesions and visceral metastasis) but without a specified Gleason score. As well as impacting survival, quicker progression to metastatic castrate resistant prostate cancer (mCRPC) is associated with further reduced health-related quality of life (HRQL), increased healthcare costs and greater medical resource use (MRU), affecting both patients and

the wider NHS.[9, 10] Symptoms can be highly debilitating and distressing. Over half of advanced prostate cancer patients suffer from pain, fatigue, drowsiness and bone pain. Up to 75% of people with advanced prostate cancer develop bone disease that can result in skeletal-related events (SREs) including spinal cord compression and pathological fracture,[11] both of which are associated with loss of mobility and further impaired HRQOL.[12] Patients with high-volume disease report worse HRQOL compared to men with low-volume disease as measured by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. Diagnosis of advanced prostate cancer also carries a psychological burden. Compared with localised disease, those with advanced prostate cancer report less vitality and energy, as well as poorer social and emotional wellbeing.[13]

2.2 Critique of company's overview of current service provision

The ERG believe the company's description of current service provision for newly diagnosed mHSPC is correct.

The ultimate aims of treating newly diagnosed mHSPC are to delay disease progression (and thus extend the time to developing mCRPC), maintain HRQOL and prolong survival.[14] Prostate cancer is an androgen-dependent disease, and inhibition of testosterone is a key initial treatment strategy. Androgen deprivation therapy (ADT) has been the standard of care (SOC) in mHSPC and it is still used as monotherapy to treat 50–60% of these people in the UK.[15-17] As noted in the company submission, orchidectomy (surgical castration) and bicalutamide monotherapy are less common treatment options.(Advisory Board Report, Janssen Research & Development, 2017).[18]Although most men initially respond to ADT, the vast majority develop progressive disease within one to two years.[19] Data from the CHAARTED and STAMPEDE studies have shown that giving docetaxel (chemotherapy) in addition to ADT to men with newly diagnosed mHSPC (i.e. before they have become resistant to hormone therapy) was beneficial for health outcomes. Although unlicensed in this setting, NHS England have released a clinical commissioning policy to support the use of docetaxel with ADT in newly diagnosed mHSPC in response because of its reported survival benefits,[20, 21] and new recommendations for the use of docetaxel in addition to ADT have been implemented in most guidelines published by the urological and oncological societies.[7] Whilst ADT alone does not

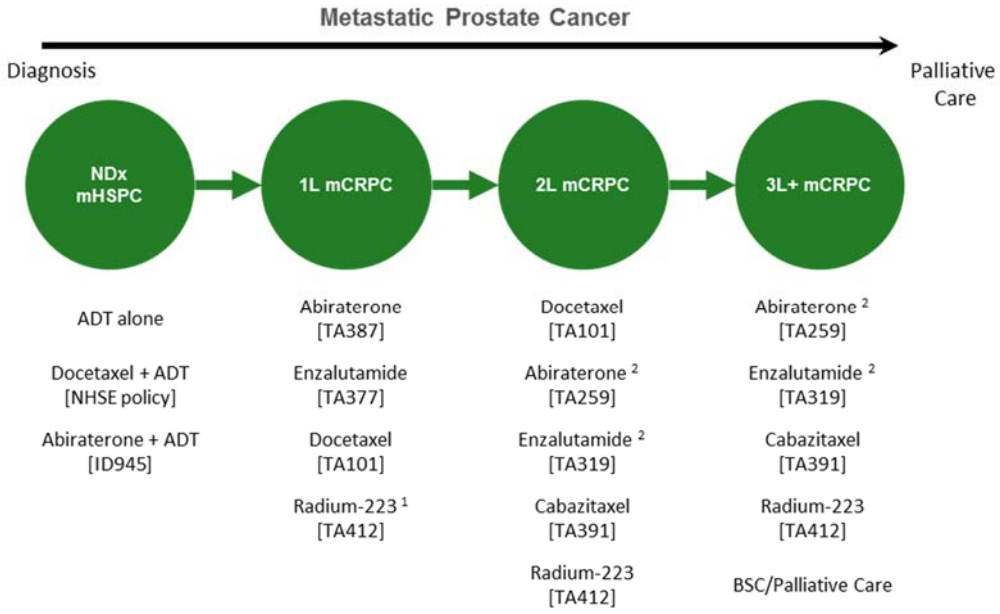
elicit comparable survival benefits, the addition of docetaxel is associated with greater toxicity and potentially severe side effects. Similarly, 20% of patients are considered clinically unsuitable for docetaxel and other psychological, social and economic factors influence an individual's suitability for treatment; such as the presence of a carer or loved one for support, proximity to chemotherapy clinics, emotional capacity to endure the toxicity of chemotherapy and religious beliefs that can prevent uptake of chemotherapy due to the alcohol content in docetaxel. As a result, some patients in the UK prefer to delay chemotherapy and would choose to receive ADT alone and, as stated in the company submission, this compromises their survival in the absence of any alternative life-prolonging therapy. Limitations of docetaxel and ADT treatment are presented in Table 1, reproduced from the Company submission, document B, Table 3 on page 17.

Table 1 Limitation of current treatment

Treatment	Limitations
Docetaxel	• Docetaxel (plus ADT) for the treatment of prostate cancer is commonly associated with numerous AEs[22] including: – Grade 4 neutropenia as well as other grade 3/4 blood and lymphatic system disorders such as anaemia, febrile neutropenia and thrombocytopenia. – Grade 3/4 gastrointestinal disorders, including nausea, diarrhoea and vomiting. – Grade 3/4 neuropathy, alopecia and fatigue • Docetaxel-associated grade 3/4 toxicities are shown to have detrimental effects on patients' QoL.[23] – One patient has described being "*unable to carry out daily chores like tidying up*" and another could "*hardly walk due to groin pain*".[24] – Docetaxel also impacts social interaction, psychological and emotional wellbeing. – The morbidity associated with docetaxel can incur significant AE costs whilst compromising the effectiveness of treatment due to resulting dose reductions and discontinuations.[25] • Docetaxel is not suitable for use in all patients, due to clinical prognostic factors (such as ECOG PS and comorbidities) as well as patient preferences[26, 27] • Docetaxel can negatively impact on carers, despite their efforts to stay positive and provide support; some have specifically

Treatment	Limitations
	mentioned the emotional impact of witnessing a family member or friend battle the disease.[24] – According to the Burden Scale for Family Caregivers Tool, 79% of caregivers for men undergoing docetaxel reported they wished they could *"run away from their current situation*", and 58% were worried about their future. • Increased use of docetaxel in mHSPC could deplete the number of chemotherapy services available for NHS patients with other cancers.
ADT alone	• Despite initial response to ADT, most patients progress to mCRPC within one to two years.[19] – Progression to mCRPC is associated with substantial burden on patients directly, and on wider society indirectly. – Patients with mCRPC have worse vitality, social functioning and mental health and more pain compared to patients with mHSPC.[9] – mCRPC is also associated with longer inpatient stays and greater number of prescriptions for outpatient drugs, all leading to increased healthcare costs.[10] • Patients with metastatic prostate cancer treated with ADT alone have life expectancy of less than four years; further reduced to less than three for patients with high-risk disease.[21, 28]
Key: ADT, androgen deprivation therapy; AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group Performance Status; mCRPC, metastatic castrate resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; NHS, National Health Service; OS, overall survival; QoL, quality of life.	

The care pathway for newly diagnosed metastatic disease has evolved and treatment can now be considered in terms of sequential lines of therapy, i.e. first-line treatment for mHSPC followed by a sequence of suitable regimens (first line [1L], second line [2L], etc.) for mCRPC. Several novel agents are now available and the order in which a patient may receive them is determined by prior treatment, NICE recommendation and NHS policy. The clinical pathway of care provided is reproduced from the company submission (document B, figure 4 on page 19) and presented as Figure 1. A summary of the current NICE guidelines for the treatment of metastatic prostate cancer is presented in Table 2.



Key: ADT, androgen deprivation therapy; BSC, best supportive care; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NDx, newly diagnosed; NHSE, National Health Service England.
Notes: [1], If docetaxel is contraindicated or not suitable; [2], Use of abiraterone or enzalutamide in mCRPC is dependent on the prior use of docetaxel and/or prior abiraterone or enzalutamide, as per respective NICE guidance

Figure 1 Clinical pathway of care for metastatic prostate cancer in NHS England and the Company's proposed positioning for AAP

Table 2 Current NICE guidelines for the treatment of metastatic prostate cancer

Therapy	Population	Summary of NICE guidance	NICE technology appraisal or clinical guidance number
Androgen deprivation therapy (ADT)	Metastatic prostate cancer	For people who are willing to accept the adverse impact on overall survival and gynaecomastia in the hope of retaining sexual function, offer anti-androgen monotherapy with bicalutamide 150mg. Begin ADT and stop bicalutamide treatment in people who do not maintain satisfactory sexual function.	CG175[29]
Abiraterone	Castration-resistant metastatic prostate cancer previously treated with docetaxel	Abiraterone, in combination with prednisone or prednisolone, is recommended only if: • the disease has progressed on or after one docetaxel-containing chemotherapy regimen and • the manufacturer provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England	TA259[30]
	Metastatic hormone-relapsed prostate cancer	Abiraterone in combination with prednisone or prednisolone is recommended, within its marketing authorisation, as an option for treating metastatic hornone-relapsed prostate cancer: • in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated • only when the company provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England	TA387[31]

Docetaxel	Hormone-refractory metastatic prostate cancer	Docetaxel is recommended, within its licensed indications, as a treatment option for hormone-refractory prostate cancer only in their Karnofsky performance-status score is 60% or more. It is recommended that treatment with docetaxel should be stopped: • at the completion of planned treatment of up to 10 cycles or • if severe adverse events occur or • in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies. Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.	TA101[32]
Enzalutamide	Metastatic hormone-relapsed prostate cancer, before chemotherapy is indicated	Enzalutamide is recommended, within its marketing authorisation,: • in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated • when the company provides it with the discount agreed in the patient access scheme	TA377[33]
	Metastatic hormone-relapsed prostate cancer previously treated with docetaxel	Enzalutamide is recommended, within its marketing authorisation, an option for treating metastatic hormone relapsed prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy, only if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.	TA316[34]
Cabazitaxel	Hormone-relapsed metastatic prostate cancer treated with docetaxel	Cabazitaxel in combination with prednisone or prednisolone is recommended in people with metastatic hormone-relapsed prostate cancer, whose disease has progressed during or after docetaxel if: • the person has an ECOG performance status of 0 or 1 • the person has had 225 mg/m^2 or more of docetaxel	TA391[35]

		• treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first) In addition, cabazitaxel is recommended only if: • the company provides cabazitaxel with the discount in the patient access scheme agreed with the Department of Health, and • NHS Trusts purchase cabazitaxel in accordance with the commercial access agreement between the company and NHS England, either - pre-prepared intravenous-infusion bags, or - in vials, at a reduced price that includes a further discount reflecting the average cost of waste per patient	
Radium-223 dichloride	Hormone-relapsed prostate cancer with bone metastases	Radium-223 dichloride is recommended as an option for treating hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases in adults only if: • they have had docetaxel or • docetaxel is contraindicated or is not suitable The drug is only recommended if the company provides the discount agreed in the patient access scheme	TA412[36]
Best supportive care/palliative care	Metastatic prostate cancer	Personal preferences for palliative care should be discussed as early as possible with people with metastatic prostate cancer and their partners and carers. Treatment and care plans should be tailored accordingly.	CG175[29]

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 newly diagnosed high risk metastatic hormone-naïve prostate cancer (mHNPC). The population addressed in the company submission is adults with newly diagnosed, high risk mHSPC. The company state that the marketing authorisation wording describes AAP as indicated for the treatment of newly diagnosed high risk mHSPC in combination with ADT. The company further state that terms mHNPC and newly diagnosed mHSPC are effectively the same because, if a patient is newly diagnosed they are, by default, hormone naïve.

3.2 Intervention

The intervention in both the NICE final scope and the company submission is abiraterone acetate (trade name Zytiga) with prednisone/prednisolone (AAP) plus androgen deprivation therapy (ADT). AAP is currently authorised in more than 100 countries worldwide for the treatment of mCRPC.[37] AAP decreases serum testosterone to undetectable levels when given with LHRH analogues.

The company provides details of abiraterone acetate in Table 2 of the submission (document B, page 11) and is reproduced by the ERG in this report as Table 3 below.

Table 3 Technology being appraised

UK approved name and brand name	**Abiraterone acetate (Zytiga®)**
Mechanism of action	Abiraterone acetate (AA) is converted *in vivo,* to abiraterone, a potent androgen biosynthesis inhibitor that selectively inhibits the enzyme 17α-hydroxylase (CYP17). CYP17 catalyses the conversion of pregnenolone and progesterone into the testosterone precursors dehydroepiandrosterone (DHEA) and androstenedion[38] CYP17 inhibition also results in increased mineralocorticoid production by the adrenal glands via a feedback loop which culminates in increased adrenocorticotropic hormone (ACTH) secretion. By inhibiting the production of both DHEA and androstenedione, AA blocks androgen biosynthesis at all sites in the body, including the testes, adrenal glands and prostatic tumour. Treatment with AA decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH agonists (or orchidectomy)[39, 40]
Marketing authorisation/CE mark status	Positive Committee for Medicinal Products for Human Use (CHMP) opinion was received on 12th October 2017. Marketing authorisation was subsequently granted on 20th November 2017.6
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Abiraterone acetate is indicated with prednisone or prednisolone for: the treatment of newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC) in adults in combination with androgen deprivation therapy (ADT) the treatment of metastatic castration-resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated the treatment of mCRPC in adults whose disease has progressed on or after a docetaxel-based chemotherapy regimen.[38]
Method of administration and dosage	AA is administered orally at a recommended dose of 1,000mg (two 500mg tablets) as a single daily dose in combination with 5mg prednisolone daily for mHSPC and 10mg daily for mCRPC.[38]
Additional tests or investigations	Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter, until treatment discontinuation. Blood pressure, serum potassium and fluid retention should be monitored monthly. During treatment of patients with significant risk for congestive heart failure, blood pressure, serum potassium fluid retention, and other signs and symptoms of congestive heart failure should be monitored every two weeks for three months, then monthly thereafter and abnormalities corrected.
List price and average cost of a course of treatment	The NHS list price of AA 500mg tablets x 56 = £2,735.00. Treatment with AA is continued until disease progression. The median duration of treatment in men with newly diagnosed high-risk mHSPC is 24 months.[41]

	Drug cost [list price]	£2,735 [28 days]
	Packs per year	365/28 = 13
	Drug cost per patient per year*	£35,652.68
	*Maximum drug cost presented, assuming all patients who are initiated on abiraterone acetate stay on treatment for a full year.	
Patient access scheme (if applicable)	Abiraterone acetate is available to NHS customers through a confidential Commercial Access Arrangement (CAA) with NHS England. This CAA will extend to cover the use of AAP + ADT in patients with newly diagnosed high-risk mHSPC. [redacted]	
Key: AA, abiraterone acetate; CYP17, 17α-hydroxylase; DHEA, dehydroepiandrosterone; EPAR, European Public Assessment Report; LHRH, luteinising-hormone-releasing hormone; PAS, patient access scheme; SPC, summary of product characteristics.		

3.2.1 Safety

Abiraterone acetate (AA) may cause hypertension, hypokalaemia, fluid retention and cardiac failure due to increased mineralocorticoid levels. Caution is required in treating patients whose underlying medical conditions might be compromised by these contraindications (e.g. cardiac glycosides, severe renal impairment, heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia).

It is recommended that potassium levels are maintained at ≥ 4.0 mM in patients with pre-existing hypokalaemia or those that develop hypokalaemia whilst being treated with AA.[38] For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment with AA should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline.[38]

For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]), treatment should be withheld immediately. Re-treatment following return of liver function tests to baseline may be given at a reduced dose of 500 mg (two tablets) once daily and serum transaminases should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, treatment should be discontinued. If patients develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy, treatment should be discontinued and patients should not be re-treated.[38]

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment but there are no data for the safety or efficacy of multiple does of AA in patients with moderate to severe hepatic impairment. It is, therefore, advised that AA is used cautiously in patients with moderate impairment and not used in patients with severe impairment.[38]

AA should be used with caution in patients with a history of cardiovascular disease and treatment should be discontinued if there is a clinically significant decrease in cardiac function. Decreased bone density may occur in people with metastatic advanced prostate cancer and the use of AA in combination with a glucocorticoid could increase this effect. Caution is also recommended in patients concomitantly treated with medicinal products known to be associated with myopathy/rhabdomyolysis. Sexual dysfunction and anaemia may occur in patients with mCRPC, including those undergoing treatment with AA.

3.2.2 Adverse reactions

The company provided details of adverse reactions observed during clinical studies and post-marketing experience in Table 1 of Appendix C, and reproduced by the ERG below. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4 Adverse reactions identified in clinical studies and post-marketing

System Organ Class	Adverse reaction and frequency
Infections and infestations	very common: urinary tract infection common: sepsis
Endocrine disorders	uncommon: adrenal insufficiency
Metabolism and nutrition disorders	very common: hypokalaemia common: hypertriglyceridaemia
Cardiac disorders	common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia uncommon: arrhythmia not known: myocardial infarction, QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	very common: hypertension
Respiratory, thoracic and mediastinal disorders	rare: allergic alveolitis[a]
Gastrointestinal disorders	very common: diarrhoea common: dyspepsia
Hepatobiliary disorders	very common: alanine aminotransferase increased and/or aspartate aminotransferase increased [b] rare: hepatitis fulminant, acute hepatic failure
Skin and subcutaneous tissue disorders	common: rash
Musculoskeletal and connective tissue disorders	uncommon: myopathy, rhabdomyolysis
Renal and urinary disorders	common: haematuria

General disorders and administration site conditions	very common: oedema peripheral
Injury, poisoning and procedural complications	common: fractures**

* Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased
** Fractures includes osteoporosis and all fractures with the exception of pathological fractures
[a] Spontaneous reports from post-marketing experience
[b] Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST d hepatic function abnormal.

3.3 Comparators

The NICE final scope specifies the comparators as ADT alone (including orchidectomy, luteinising hormone-releasing hormone [LHRH] agonist therapy or monotherapy with bicalutamide) and docetaxel + ADT. The comparators considered by the company differ from the NICE scope. The company state that clinical experts advised that both orchidectomy and bicalutamide monotherapy are seldom used in the UK and the company, consequently, chose to not include these comparators in their submission. The comparators presented in the company submission are ADT alone (including LHRH agonist therapy) and docetaxel + ADT. The company state that clinical experts provided validation that there is no difference in the type of ADT, thus justifying their approach. The ERG clinical expert agrees that orchidectomy and bicalutamide monotherapy are seldom used in NHS clinical practice and that it is appropriate to remove these as comparators for AAP + ADT.

3.4 Outcomes

The outcomes stated in the NICE final scope are: overall survival (OS), progression free survival (PFS), prostate specific antigen (PSA) response, adverse effects of treatment and HRQOL. The company submission includes all the outcomes listed in the NICE scope and reports additional outcomes from the LATITUDE trial: PFS following subsequent therapy (PFS2), time to symptomatic local progression, prostate cancer-specific survival, time to chronic opiate use, castration status.

3.5 Other relevant factors

The company present several factors, substantiated by UK clinical experts, that could prevent a person with newly diagnosed high-risk mHSPC from undertaking treatment

with docetaxel + ADT for reasons beyond clinical prognostic factors. These include but are not limited to:

- The presence of a carer or loved one for support, both for attending chemotherapy clinics and managing potential side effects
- Where a man lives, be it isolated or accessible by public transport to attend chemotherapy clinics, with or without a carer
- The emotional state required to endure the toxicity of chemotherapy, which is often understated
- Religious beliefs that can prevent a man from pursuing chemotherapy due to the alcohol content in docetaxel
- Being unwilling to undertake treatment

It is therefore essential that psychological, social and economic factors are considered so that clinicians and patients can make an informed judgement regarding which treatment is best suited to an individual patient.

Table 5 Comparison of NICE final scope and decision problem addressed by the company

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with newly diagnosed high risk metastatic hormone-naïve prostate cancer (mHNPC)	Adults with newly diagnosed, high-risk, mHSPC.	As per the marketing authorisation wording: AAP is indicated for the treatment of newly diagnosed high-risk mHSPC in adult men in combination with ADT. While the LATITUDE trial used the term mHNPC, this is effectively the same as newly diagnosed mHSPC because (by default) if a patient is newly diagnosed, they are hormone naïve.
Intervention	AAP + ADT	AAP + ADT	N/A
Comparator(s)	ADT alone (including orchidectomy, luteinising hormone-releasing hormone [LHRH] agonist therapy or monotherapy with bicalutamide) Docetaxel + ADT	ADT alone (including LHRH agonist therapy) Docetaxel + ADT	Orchidectomy was not included because clinical experts advised this is seldom used in the UK.(Advisory Board Report, Janssen, 2017) Bicalutamide monotherapy was not included either for the same reasons. (Advisory Board Report, Janssen, 2017) Clinical experts validated there to be no difference in the type of ADT hence justifying this approach.
Outcomes	OS PFS PSA response Adverse effects of treatment HRQL	OS PFS PSA response Adverse effects of treatment HRQL	Additional outcomes are also detailed in **Error! Reference source not found.**
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.	Pairwise ICERs were presented against ADT alone and docetaxel + ADT	The source of evidence is different for the comparison versus ADT alone (i.e. LATITUDE head-to-head data) and the comparison versus docetaxel + ADT (i.e. Bayesian ITC) therefore cannot be combined into incremental analysis.

	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.	Adhering to the reference case, a lifetime horizon was used.	N/A
	Costs will be considered from an NHS and Personal Social Services perspective.	The reference case has been adhered to.	N/A
	The availability of any commercial access agreement for the intervention and treatments included in the economic analyses will be taken into account.	Adhering to the reference case, the CAA for AAP has been applied in all economic analysis (as detailed in **Error! Reference source not found.**)	Confidential patient access schemes which apply to relevant subsequent comparator therapies are not included in these analyses as Janssen are not privy to such information.
Key: HRQL, health-related quality of life; N/A, not applicable; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PSA, prostate specific antigen.			

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Literature searching

The company submission provides full details of the searches that were undertaken to identify the included studies for the clinical effectiveness review. The major relevant databases were searched: MEDLINE. MEDLINE In-Process, EMBASE and CENTRAL for RCTs and DARE for systematic reviews. The searches were undertaken in September 2015 and updated in July 2017. The searches were restricted to reports published after 2005 and in the English language

In addition, the company searched conference proceedings from six major relevant organisations for the last four years. References of identified evidence syntheses were also scrutinised for additional publications.

The search strategies are documented in full in Appendix D and are reproducible. However, the company conducted the searches using the EMBASE.com platform, which is not accessible to the ERG. The MEDLINE and EMBASE searches combined three search facets using the Boolean operator AND: prostate cancer; abiraterone or any comparator; and RCT study design. The search of MEDLINE In-Process via Pubmed, CENTRAL and DARE excluded the study design facet, 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.

The company review, however, included three company-authored reports that were published after the last search date. Following a clarification question from the ERG, the company responded that the 2018 sources are company-owned publications, which were considered relevant for inclusion, despite being outside of the pre-specified search dates, as they contain data relevant to the key outcomes reported in the LATITUDE trial[42-44]. It should be noted, however, that any relevant comparator studies published after the last search date would not have been identified.

The company submission originally included studies published prior to 2005 but in response to the ERG request for clarification, the company removed these studies from the report.

4.1.2 Inclusion criteria

The company conducted a systematic review to assess the clinical effectiveness of AAP plus ADT. The company provided details of their inclusion criteria, shown in Table 6 below. A total of 16 studies met all the inclusion criteria and were ultimately included in the company's systematic review. Of these, only the LATITUDE trial[41] was considered to match the patient population indicated in the company submission and this forms the primary evidence base of the submission. Two additional trials (CHAARTED and GETUG-AFU 15) were included in the indirect treatment comparison (with one further trial included in sensitivity analyses - STAMPEDE). Of the 16 included studies, the most commonly investigated intervention (either as intervention of interest or comparator) was conventional ADT, which was evaluated in all but five studies. Abiraterone was investigated in two studies (LATITUDE and STAMPEDE).[41, 45]

Table 6 Inclusion and exclusion criteria for the systematic review of clinical effectiveness (reproduced from Table 4, Appendix D of the company submission)

Category	Inclusion criteria	Exclusion criteria
Population	Men (aged 18 years and over) with high risk/high-volume mHSPC	Publications reporting on patient populations in the following categories: Females Children Healthy volunteers Patients with only non-cancerous prostate disease (such as benign prostatic hyperplasia) Patients with malignancies other than prostate cancer Patients with localised/locally advanced prostate cancer Metastatic prostate cancer patients who have progressed on endocrine manipulation for their disease
Interventions	Studies to be considered eligible for inclusion in the review will have reported on at least one of the following treatments: Abiraterone acetate (Zytiga®) Enzalutamide (Xtandi®) Conventional ADT drugs: Luteinising hormone-releasing hormone agonists Buserelin Histrelin Goserelin Leuprorelin Triptorelin Luteinising hormone-releasing hormone antagonists/gonadotropin releasing hormone Degarelix	Publications that do not report data specific to treatment using abiraterone acetate, ADT, docetaxel and enzalutamide

Category	Inclusion criteria	Exclusion criteria
	Anti-androgens Bicalutamide Flutamide Nilutamide Cyproterone Androgen blocker Aminoglutethimide Ketoconazole Chemotherapy Docetaxel Surgery Bilateral orchiectomy	
Comparators	No limits will be applied for comparators	N/A
Outcomes	The review will be limited to publications that report on the following outcomes: Clinical effectiveness Clinical safety	Publications that only report data on the following types of outcomes: Narrative publications, non-systematic reviews, case studies, case reports, editorials PK/PD HRQL and related PROs Cost and resource use ICERs, QALYs and other cost-effectiveness outcomes
Study type	The review will be limited to publications of studies with the following designs: RCTs	Publications of studies with the following designs: Animal studies *In vitro*/*ex vivo* studies Gene expression/protein expression studies Prospective non-randomised controlled interventional studies Prospective longitudinal observational studies

Category	Inclusion criteria	Exclusion criteria
		Retrospective longitudinal observational studies Cross-sectional studies Economic models and trial-based economic analyses Systematic reviews and meta-analyses of RCTs[a]
Time limit	Sept 2015 through to present	Studies published before 2015
Language	English language	Non-English language

Key: ADT, androgen deprivation therapy; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; mHNPC, metastatic hormone-naïve prostate cancer (also called castrate-sensitive, hormone-dependent, or hormone-sensitive prostate cancer); N/A, not applicable; PK/PD, pharmacokinetics/pharmacodynamics; PROs, patient reported outcomes; QALY, quality-adjusted life year; RCT, randomised controlled trial.
Notes: [a], Systematic reviews and meta-analyses of RCTs will be included and flagged. Bibliographies of these systematic reviews will be screened to check if literature searches have missed any potentially relevant studies

4.1.3 Critique of data extraction

The company state that two reviewers independently screened titles and abstracts identified by the literature searches. Secondary screening of full text articles was also independently conducted by two reviewers, although it is unclear whether these were the same reviewers who screened titles and abstracts. During the study selection any uncertainties between the two reviewers were checked by a senior reviewer. Data were extracted using a pre-specified template by one independent reviewer and validated by a second senior reviewer. The ERG consider the methods used by the company to be appropriate.

4.1.4 Quality assessment

Quality assessment was conducted for every included full text publication by the company using the National Institute of Health and Care Excellence (NICE) quality assessment tool, based on the Centre for Reviews and Dissemination (CRD) guidance.[46] The company reported the results of their quality assessment for the trials included in the indirect treatment comparison. These are presented in Table 7. The

ERG mainly agree with the company's results. The company did not provide an overall risk of bias for the STAMPEDE trial. The ERG judge this trial to be at unclear risk of bias due to the high risk scoring for performance bias.

Table 7 Summary of quality assessment for the RCTs included in the indirect treatment comparison (reproduced from Table 11, Appendix D of the company submission)

Study	Selection bias	Performance bias	Attrition bias	Detection bias	Overall risk
LATITUDE[41]	Unclear	Low risk	Low risk	Low risk	Low risk
CHAARTED[21]	High risk	High risk	Low risk	Low risk	High risk
GETUG AFU-15[28]	Low risk	Low risk	Low risk	Unclear	Low risk
STAMPEDE[45]	Low risk	High risk	Low risk	Low risk	

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the CRD criteria. Results are presented in Table 8.

Table 8 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 provide evidence for the effectiveness of AAP plus ADT from two RCTs: LATITUDE and STAMPEDE. LATITUDE[41] is a manufacturer-sponsored, multinational, randomised, double-blind, placebo-controlled Phase III trial that investigated AAP plus ADT versus ADT plus placebos (hereafter referred to as, and

considered equal to, ADT alone) in people with newly diagnosed, high-risk mHSPC. This is the only trial providing data specific to the target (i.e., licensed) population of interest, and thus is the primary evidence source for the company submission. The manufacturer-sponsored STAMPEDE study[45] represents the largest evidence base of data specific to UK clinical practice for AAP + ADT in early prostate cancer but include a broader patient population than LATITUDE and does not report data separately for HRD/HVD patients. Due to these limitations, data from the STAMPEDE trial are referenced as supportive evidence only in the company submission.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Characteristics and critique of the trials included in the systematic review of clinical effectiveness

As stated previously in section 4.1.5, the main evidence for the company submission is taken from the LATITUDE trial[41] with supporting evidence presented from the STAMPEDE trial[45]. A summary description of these two trials is presented in Table 9.

Table 9 Summary of the two RCTs presented in the review of clinical effectiveness (reproduced from Table 4, Document B of the company submission)

Study	LATITUDE (NCT01715285)[41]	STAMPEDE (NCT00268476)[45]
Study design	A manufacturer-sponsored, multinational, randomised, double-blind, placebo-controlled Phase III trial.	An investigator-sponsored, multinational (UK dominant), multi-arm multi-stage platform design incorporating a seamless Phase II/III component.
Population	Newly diagnosed high-risk mHSPC.[a] [High-risk is defined as having 2 of the following: Gleason score of ≥8, the presence of ≥3 lesions on a bone scan, or the presence of visceral metastases]	Prostate cancer that was newly diagnosed and metastatic, node-positive, or high-risk localised or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features.
Intervention(s)	AA 1,000mg daily oral dose (given once daily as four 250mg tablets) plus prednisolone 5mg daily plus ADT (LHRH agonist or orchidectomy). Selection of the LHRH agonist was at the investigator's discretion, and dosing was consistent with the respective product labelling. Patients could also have opted to undergo surgical castration in lieu of receiving ADT by LHRH analogue.	• Docetaxel + ADT 75mg/m^2 IV on Day 1 plus prednisolone 5mg BID for 21 days Q3W for a maximum of six cycles • AA 1000mg (4x 250mg) daily oral dose plus prednisolone 5mg daily plus ADT Permitted methods of ADT included bilateral orchidectomy, LHRH agonists or antagonists, dual androgen blockade, or other methods discussed with the STAMPEDE trial team. The planned duration of ADT +/- AA was 2 years in non-metastatic patients and until disease progression in metastatic patients.
Comparator(s)	ADT alone (LHRH agonist or orchidectomy). Selection of the LHRH agonist was at the investigator's discretion, and dosing was consistent with the respective product labelling. Patients could also have opted to undergo surgical castration in lieu of receiving ADT by LHRH agonist.	ADT alone. Permitted methods of ADT included bilateral orchidectomy, LHRH agonists or antagonists, dual androgen blockade, or other methods discussed with the STAMPEDE trial team. The planned duration of ADT was 2 years in non-metastatic patients and until disease progression in metastatic patients.
Supports marketing authorisation	Yes	No
Used in the economic model	Yes	Yes, for sensitivity analysis only

Study	LATITUDE (NCT01715285)[41]	STAMPEDE (NCT00268476)[45]
Rationale for use/non-use in the model	Pivotal trial supporting this indication.	Provides supportive randomised data of the benefits of AAP + ADT; however, this is not specific to the population of interest in this submission.
Reported outcomes specified in the decision problem	• OS (co-primary endpoint) • rPFS (co-primary endpoint) • Time to next SRE[b] • Time to PSA progression (Prostate Cancer Working Group 2 criteria) • Time to subsequent therapy for prostate cancer • Time to initiation of chemotherapy • Time to pain progression • Safety, including time to treatment discontinuation • HRQL, including BPI-SF, FACT-P, BFI and **EQ-5D-5L**	• OS (primary endpoint) • FFS (intermediate primary endpoint) • Safety • Symptomatic skeletal events • PFS • PSA-specific survival • HRQL, including EQ-5D and EORTC QLQ-C30 with the prostate-specific module QLQ PR25[c]
All other reported outcomes	• PSA response rate • PFS following subsequent therapy (PFS2) • Time to symptomatic local progression • Prostate cancer-specific survival • Time to chronic opiate use • Castration status	N/A

Key: AA, abiraterone acetate; ADT, androgen deprivation therapy; BFI, Brief Fatigue Inventory; BID, twice daily; BPI-SF, Brief Pain Inventory-Short Form; EQ-5D-5L, EuroQoL; FACT-P, Functional Assessment of Cancer Therapy – Prostate; FFS, failure-free survival; HRQL, health-related quality of life; IV, intravenous; LHRH, luteinising hormone releasing hormone; mHSPC, metastatic hormone sensitive prostate cancer; N/A, not applicable; OS, overall survival; PFS, progression-free survival; PSA, prostate specific antigen; rPFS, radiographic progression-free survival; SRE, skeletal-related event; Q3W, every 3 weeks.
Notes:[a], Patients could have received up to 3 months treatment with ADT prior to randomisation; [b], economic model uses SRE rates; [c], HRQL data have not yet been published from the STAMPEDE study.

The baseline demographics and disease characteristics were well-balanced across treatment groups in the LATITUDE trial and are shown in Table 10. The majority of patients (>95%) had a Gleason score ≥8 and ≥3 bone lesions (96% in the AAP plus ADT group, 95% in the ADT alone group). Post-hoc analysis showed that 487 patients (82%) in the AAP plus ADT group and 468 patients (78%) in the ADT alone group had 'high-volume' disease, defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis (as per CHAARTED and GETUG-AFU 15 studies, discussed further in section 4.3). The extent of disease was similar between groups, as was median PSA level (25ng/mL in the AAP plus ADT group and 23ng/mL in the ADT alone group), demonstrating that patients with high-risk and high-volume disease are closely comparable.

There was comparable distribution in the use of hormonal therapy, surgery or radiotherapy across treatment groups. Most patients received prior hormonal therapy, comprising predominantly of a gonadotrophin-releasing hormone (GnRH) analogue (75%) and first generation anti-androgens (62%). A smaller percentage of patients had undergone an orchidectomy (12%). Although this is higher than what is usually seen in UK clinical practice, the company state there is no clinical difference between orchidectomy and LHRH, and the form of ADT would not impact the effect of AAP.

Table 10 Baseline characteristics of the LATITUDE intention to treat population (reproduced from Table 6, Document B of the company submission)

	AAP + ADT (n=597)	**ADT Alone (n=602)**
Age, median years (range)	68 (38–89)	67 (33–92)
Median PSA level before ADT, ng/mL (range)	25.4 (0–8,775.9)	23.1 (0.1–8,889.6)
ECOG PS, n (%)	0: 326 (54.6) 1: 245 (41.0) 2: 26 (4.4)	0: 331 (55.0) 1: 255 (42.4) 2: 16 (2.7)
Gleason score at initial diagnosis, n (%)	<7: 4 (0.7) 7: 9 (2) ≥8: 584 (98)	<7: 1 (0.2) 7: 15 (2) ≥8: 586 (97)
Baseline pain score (BPI-SF Item 3), n (%)	N: 570 0–1: 284 (50) 2–3: 123 (22) ≥4: 163 (29)	N: 579 0–1: 288 (50) 2–3: 137 (24) ≥4: 154 (27)

	AAP + ADT (n=597)	ADT Alone (n=602)
≥3 bone metastases at screening, n (%)	586 (98.2)	585 (97.2)
High-risk at screening, n (%)	597 (100)	601 (100)
Gleason score ≥8 + ≥3 bone lesions	573 (96)	569 (95)
Gleason score ≥8 + measurable visceral disease	82 (14)	87 (14)
≥3 bone lesions + measurable visceral disease	84 (14)	85 (14)
Gleason score ≥8 + ≥3 bone lesions + measurable visceral disease	71 (12)	70 (12)
Extent of disease, n (%)	596 (100)	600 (100)
Bone	580 (97)	585 (98)
Liver	32 (5)	30 (5)
Lungs	73 (12)	72 (12)
Node	283 (47)	287 (48)
Prostate mass	151 (25)	154 (26)
Viscera	18 (3)	13 (2)
Soft Tissue	9 (2)	15 (3)
Other	2 (0.3)	0
Bone lesions at screening, n (%)		
0	6 (1.0)	7 (1.2)
1–2	5 (0.8)	10 (1.7)
3–10	202 (33.8)	208 (34.6)
11–20	109 (18.3)	97 (16.1)
>20	275 (46.1)	280 (46.5)
Previous prostate cancer therapy, n (%)	560 (94)	560 (93)
Radiotherapy	19 (3)	26 (4)
Hormonal	559 (96)	558 (93)
GnRH agonists/antagonists[a]	449 (75)	450 (75)
Orchidectomy[a]	73 (12)	71 (12)
First-generation androgen receptor agonists	373 (62)	371 (62)
Other	7 (1)	10 (2)
Time from GnRH agonist/antagonist to first dose of study drug, median months (range)	1.08 (0.1–3.0)	1.08 (0.1–3.5)
[Post-hoc] High-volume disease, n (%)	487 (81.5)	468 (77.7)

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; BPI-SF, Brief Pain Inventory – Short Form; ECOG, Eastern Cooperative Oncology Group; GnRH, gonadotropin-releasing hormone; ITT, intention-to-treat; PS, performance status; PSA, prostate specific antigen.
Notes: [a], within 3 months prior to randomisation.
Source: Fizazi et al. 2017[41] LATITUDE CSR, 2017 Fizazi et al. 2018[44]

Table 11 presents a summary of results for the key outcomes for disease progression and overall survival for both LATITUDE and STAMPEDE.

Table 11 Summary of co-primary endpoints of the trials included in the systematic review of clinical effectiveness (reproduced from Table 9, Document B of the company submission)

Study	**LATITUDE** [ITT]		**STAMPEDE** [Arm G vs. Arm A]		**STAMPEDE** [Arm G vs. Arm C]	
Treatment	AAP + ADT	ADT alone [a]	AAP + ADT	ADT alone [a]	AAP + ADT	Docetaxel + ADT
ITT	597	602	960	957	377	189
Metastatic (%)	597 (100)	602 (100)	500 (52.1)	502 (52.5)	227 (60.2)	115 (60.8)
Patient population	NDx high-risk mHSPC		mHSPC			
Data cut	31-Oct-16		10-Feb-17		04-Mar-17	
Median follow-up	30.4 months		40 months		48 months	
Progression-free survival						
	Radiographic PFS		**PFS** [b]			
Events (%)	239 (40.0)	354 (58.8)	173 (34.6)	301 (60.0)	94 (41.4)	62 (53.9)
Median	33	14.8	-	-	-	-
[95% CI]	29.57-NE	14.69-18.27	-	-	-	-
HR	0.47		0.43		0.69	
[95% CI]	0.39-0.55		0.36-0.52		0.50-0.95	
p-value	<0.0001		-		0.02	
Failure-free Survival [c]						
HR	-	-	0.31		0.56	
[95% CI]	-	-	0.26-0.37		0.42-0.75	
p-value	-	-	-		<0.001	
Overall Survival						
Events (%)	169 (28.3)	237 (39.4)	150 (30.0)	218 (43.4)	89 (39.2)	38 (33.0)
Median	NE	34.7	-	-	-	-
[95% CI]	NR-NR	33.05-NR	-	-	-	-
HR	0.62		0.61		1.13	
[95% CI]	[0.51-0.76]		0.49-0.75		0.77-1.66	
p-value	<0.0001		0.195×10^{-7}		0.53	

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; DOT, duration of treatment; HR, hazard ratio; IQR, inter-quartile range; ITT, intent to treat; m1, metastatic; mHSPC, metastatic hormone sensitive prostate cancer; NDx, newly diagnosed; NR, not reached; OS, overall survival; rPFS, radiographic progression-free survival; PSA, prostate-specific androgen; SRE, skeletal-related events; Tx, treatment.
Notes: [a], Placebos + ADT; [b], PFS defined as radiologic or clinical progression or death from prostate cancer, [c], FFS defined as radiologic, clinical, PSA progression or death from prostate cancer
Source: Fizazi et al. 2017[41] LATITUDE CSR, 2017; James et al. 2017 [45]Sydes et al. 2017[47] Rydzewska et al. 2017[48]

Progression-free survival

For progression-free survival (PFS), treatment with AAP + ADT significantly delayed disease progression in patients with newly diagnosed high-risk mHSPC when compared with ADT alone in the LATITUDE trial. Treatment with AAP + ADT resulted in a 53% reduction in the risk of radiographic progression or death (HR=0.47 [95% CI: 0.39–0.55]; p<0.001). At three years, 47% of patients in the AAP + ADT arm remained event-free, compared to only 21% of those in the ADT alone arm.

While STAMPEDE did not consider PFS, the company argue that the outcome failure free survival (FFS) is considered to be generally comparable by the clinical community. In the metastatic (M1) subgroup of STAMPEDE, treatment with AAP + ADT was associated with a 69% reduction in the risk of biochemical failure, progression or death compared with ADT alone (HR=0.31 [95%CI: 0.26–0.37]; p<0.0001). Although the M1 subgroup is broader than the licensed indication for abiraterone, the company state that results for this comparable endpoint of FFS provide strong supporting evidence for the benefit of AAP + ADT over ADT in prolonging time to disease progression. Whilst the post-hoc analysis from STAMPEDE comparing AAP + ADT with docetaxel + ADT was not pre-specified, and thus not statistically powered to detect clinical differences in treatment, results for the M1 subgroup showed treatment with AAP + ADT was associated with a 44% reduction in the risk of biochemical failure, progression or death (HR=0.56 [95% CI: 0.42–0.75]; p<0.001)

Overall survival

In the LATITUDE trial, treatment with AAP + ADT was associated with a 38% reduction in the risk of death compared with ADT alone (HR=0.62 [95%CI: 0.51–0.76]; p<0.001).7 The overall survival rate at three years was 66% in the AAP plus ADT group and 49% in the ADT alone group. There was an imbalance in the proportion of patients who received life-extending subsequent therapies (20.9% in the AAP plus ADT arm vs. 40.9% in the ADT alone arm), which could result in the standard ITT analysis of OS underestimating the true OS benefit for AAP. Therefore, additional pre-specified OS analysis using the IPCW methodology was conducted to adjust for patients who switched to other therapies. This analysis showed AAP plus ADT significantly improved survival compared to ADT alone, with an improved

HR=0.48 (95% CI: 0.36–0.63; p<0.0001). Results from STAMPEDE are consistent with these results. Treatment with AAP + ADT was associated with a 39% reduction in the risk of death compared to ADT alone (HR= 0.61 [95% CI: 0.49–0.75]; p<0.0001).

Health-related quality of life

Patients' responses to the Visual Analogue Scale (VAS) and their health utility scores were significantly improved (p<0.05) when treated with AAP + ADT in LATITUDE and time to HRQL degradation was significantly by 4 to 6 months (15%), as measured by the Functional Assessment of Cancer Therapy – Prostate (FACT-P) total score, as well as consistently delaying worsening of pain-related symptoms by 24%. The worsening of physical wellbeing on treatment with AAP + ADT was also delayed by 25%, allowing patients to experience a longer time before their physical condition got worse. Significant improvements, as measured by the Brief Fatigue Inventory (BFI) in fatigue were also observed with AAP + ADT treatment. Median time to pain progression, measured by the BPI short form, was not reached for patients who received AAP + ADT and was 16.6 months for patients who received ADT alone, demonstrating a significant delay until pain progression (HR=0.70 [95% CI: 0.583–0.829], p<0.0001). These data indicate a 31% reduction in the risk of pain progression. The 36-month event-free rate was 55.5% for AAP + ADT versus 37.9% for ADT alone.

Secondary endpoints

Table 12 presents the summary of secondary endpoints for the LATITUDE trial.

Table 12 Summary of secondary endpoints for the LATITUDE intention to treat population (reproduced from Table 11, Document B of the company submission)

	AAP + ADT (n=597)	ADT alone (n=602)
Time to pain progression		
Events, n (%)	233 (39.0)	289 (48.0)
Median months (95% CI)	NR (36.5, NR)	16.6 (11.1, 24.0)
HR (95% CI) [p-value]	0.70 (0.58–0.83) [<0.001]	
Time to subsequent prostate cancer therapy		
Events, n (%)	191 (32.0)	322 (53.5)
Median months (95% CI)	NR ([redacted])	21.6 ([redacted])
HR (95% CI) [p-value]	0.42 (0.35–0.50) [<0.001]	
Time to life-extending subsequent therapy for prostate cancer		
Events, n (%)	125 (20.9)	246 (40.9)
Median months (95% CI)	[redacted]	[redacted]
HR (95% CI) [p-value]	[redacted]	
Time to initiation of chemotherapy		
Events, n (%)	109 (18.3)	191 (31.7)
Median months (95% CI)	NR ([redacted])	38.9 ([redacted])
HR (95% CI) [p-value]	0.44 (0.35–0.56) [<0.001]	
Time to PSA progression		
Events, n (%)	241 (40.4)	434 (72.1)
Median months (95% CI)	33.2 (27.6, NR)	7.4 (7.2, 9.2)
HR (95% CI) [p-value]	0.30 (0.26–0.35) [<0.001]	
Time to next SRE		
Events, n (%)	[redacted]	[redacted]
Median months (95% CI)	NR (NR, NR)	NR (NR,NR)
HR (95% CI) [p-value]	0.70 (0.54–0.92) [0.009]	

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not reached; PSA, prostate specific antigen; SRE, skeletal-related event.
Source: Fizazi et al. 2017[41] LATITUDE CSR, 2017 European Public Assessment Report[37].

In the LATITUDE trial, treatment with AAP+ADT significantly reduced the time to subsequent therapy for prostate cancer. The median time to subsequent therapy was not reached in the AAP + ADT group, it was 21.6 months for the ADT group (HR=0.415 [95%CI: 0.346–0.497], p<0.0001). Twice as many ADT alone patients required life-extending subsequent therapy (either docetaxel, enzalutamide, cabazitaxel, radium-233 or AAP) compared with those who received AAP+ADT (40.9% versus 20.9% respectively). The median time to life-extending subsequent therapy was not reached in the AAP + ADT group and was 29.5 months in the ADT

group (HR=0.37 [95%CI: 0.29–0.45]; p<0.0001). Of those who received life-extending subsequent therapy at any time, docetaxel was the most common treatment after AAP+ADT or ADT alone (17.8% and 31.1%, respectively).

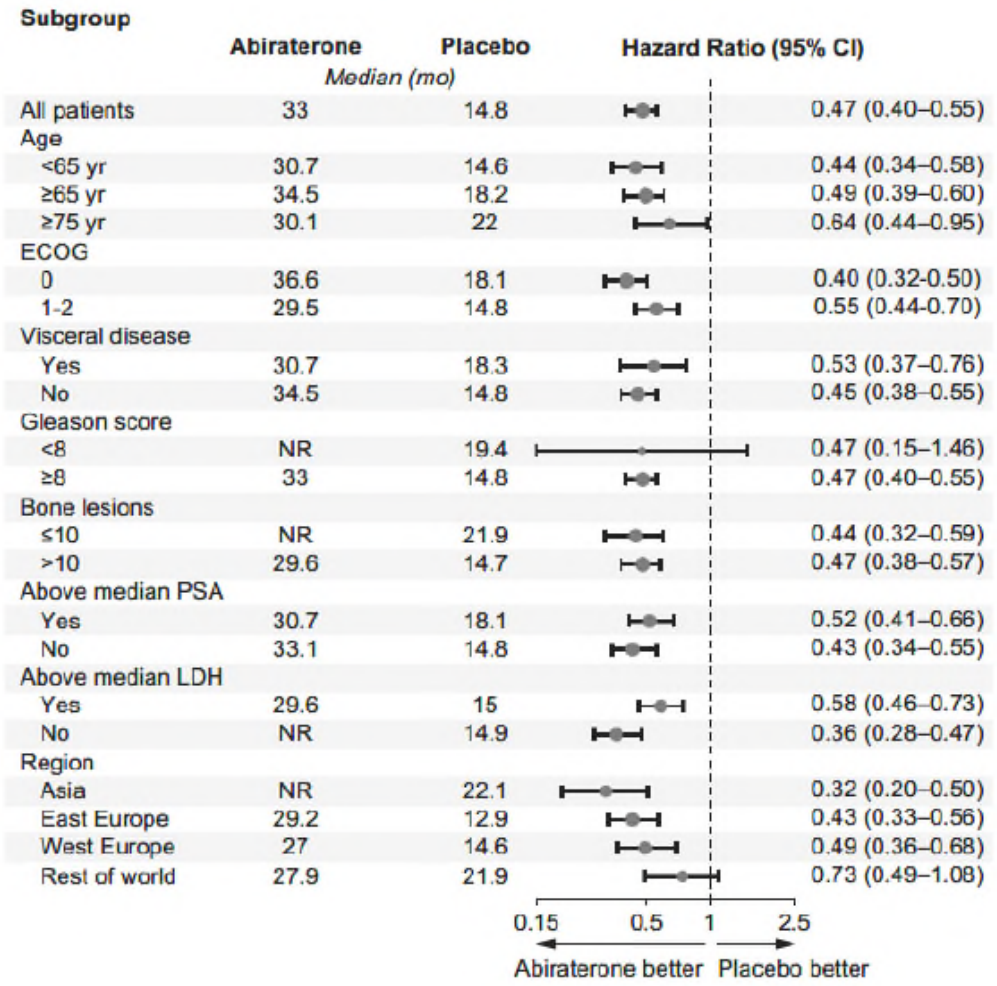
The median time to initiation of chemotherapy was not reached in the AAP + ADT group and 38.9 months in the ADT group. This translated to a 56% reduction in risk for initiating chemotherapy.

Time to PSA progression in the LATITUDE trial was defined as a 25% increase in PSA from baseline, and an increase in absolute value of 2ng/mL or more, after 12 weeks of treatment. The median time to PSA progression was 33 months in the AAP + ADT arm compared to 7 months in the ADT alone arm (HR=0.30 [95% CI: 0.26–0.35]; p<0.0001).

Treatment with AAP + ADT significantly reduced the risk of SREs by 30% (HR=0.70 [95%CI: 0.539,0.916], p=0.0086), although median time to SRE was not reported in either arm. However, it should be noted that this analysis was based on data for a small number of events, and the results should be interpreted with caution.

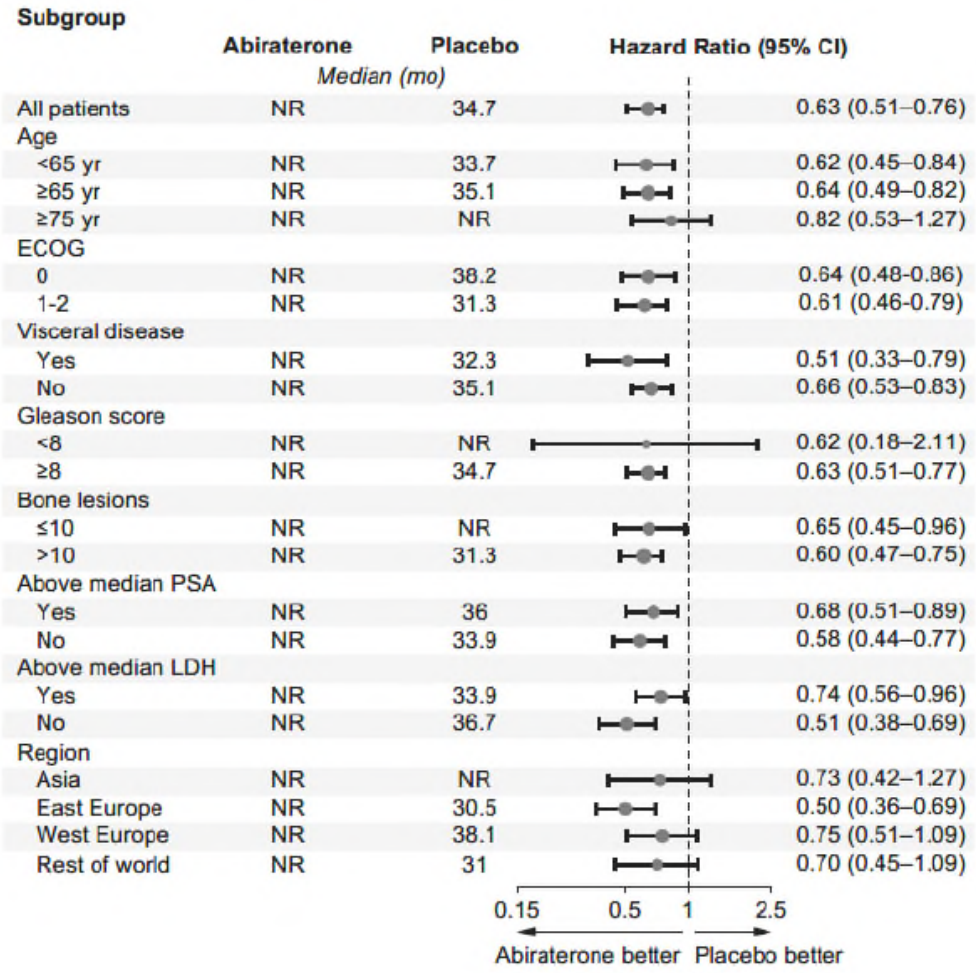
Deaths due to prostate cancer occurred less frequently in the AAP + ADT group compared to the ADT alone group (20.4% vs. 32.3%, respectively). This resulted in a statistically significant improvement in prostate cancer-specific survival for the AAP + ADT group compared to the ADT alone group (HR=0.55 [95% CI: 0.44, 0.69]; p<0.0001)

LATITUDE subgroup analyses are presented in Figures 2 and 3.



Key: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; LDH, lactate dehydrogenase; mo, months; NR, not reached; PSA, prostate specific antigen; rPFS, radiographic progression-free survival.
Source: Fizazi et al. 2017[41]

Figure 2 Subgroup analysis of radiographic progression free survival from the LATITUDE intention to treat population (reproduced from Figure 21, Document B of the company submission)



Key: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; LDH, lactate dehydrogenase; mo, months; NR, not reached; OS, overall survival; PSA, prostate specific antigen.
Source: Fizazi et al. 2017[41]

Figure 3 Subgroup analyses of overall survival from the LATITUDE intention to treat population (reproduced from Figure 22, Document B of the company submission)

Details of a meta-analyses of LATITUDE and STAMPEDE overall survival and disease progression data, which was independently conducted by Rydzewska et al.,[48] are presented in Table 13. Results of these analyses show a significant survival benefit of AAP + ADT versus ADT alone (HR=0.62 [95%CI: 0.53–0.71]; p=0.55 x 10-[10]) and a consistently significant benefit of AAP + ADT versus ADT was demonstrated for disease progression (HR=0.45 [95%CI: 0.40–0.51]; p=0.66 x10-[36]). The company note that STAMPEDE M1 subgroup is broader than the licensed indication for

abiraterone in mHSPC, these data should only be considered as strong supporting evidence of AAP's clinical effectiveness, with the direct evidence from LATITUDE being the most appropriate source to inform the economic modelling in the licensed population.

Table 13 Meta-analyses of AAP+ADT versus ADT alone for the outcomes overall survival and disease progression (reproduced from Table 16, Document B of the company submission)

OS			
	Direct Evidence: AAP+ADT vs. ADT	**Direct Evidence: AAP+ADT vs. ADT**	**Meta-Analysis: AAP+ADT vs. ADT**
Trial Name	LATITUDE	STAMPEDE	Rydzewska et al. 2017[48]
Population	ITT	M1	
HR [95% CrI]	0.62 [0.51, 0.76]	0.61 [0.49, 0.75]	0.62 [0.53, 0.71]
Disease progression (i.e. rPFS or PFS)[a]			
	Direct Evidence: AAP+ADT vs. ADT	**Direct Evidence: AAP+ADT vs. ADT**	**Meta-Analysis: AAP+ADT vs. ADT**
Trial Name	LATITUDE	STAMPEDE	Rydzewska et al. 2017[48]
Population	ITT	M1	
HR [95% CrI]	0.47 [0.39, 0.55]	0.43 [0.36, 0.52]	0.45 [0.40, 0.51]
Key: AAP, abiraterone acetate prednisone/prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; CrI, credible interval; HR, hazard ratio; ITT, intent to treat; M1, metastatic; OS, overall survival; rPFS, radiographic progression-free survival. **Notes:** [a], PFS=radiological or clinical progression-free survival			

Adverse reactions

Treatment exposure

The median treatment duration in the safety population of the LATITUDE trial was 24 months in the AAP + ADT arm and 14 months in the ADT alone arm.[41] [redacted] A total of 91.8% of patients in the AAP + ADT group and 86.0% of patients in the ADT alone group received ≥6 cycles of study drug; 54.5% and 29.7% of patients, respectively, received ≥24 cycles.

Dose reductions were reported for [redacted]% of patients treated with AAP + ADT and [redacted]% of patients treated with ADT alone, while dose interruptions were reported for

[redacted]% and [redacted]% of patients, respectively. A [redacted] percentage of patients in the AAP + ADT group had dose interruptions of prednisolone due to AEs compared with the ADT group ([redacted]% vs. [redacted]%). A [redacted] percentage of patients in each treatment group ([redacted]% AAP + ADT and [redacted]% ADT alone) had additional prednisolone prescribed by the investigator for more than two weeks to manage drug-related toxicity pertaining to insufficient control of mineralocorticoid effects.
The company report that data on treatment duration reported in STAMPEDE are not comparable to data reported in LATITUDE.

Summary safety data

A summary of treatment emergent adverse events (TEAEs) is presented in Tables 14 and 15. TEAEs were reported by a higher number of people in the AAP+ADT group than for ADT alone. The most frequently reported TEAEs in the LATITUDE trial (preferred terms reported in ≥20% of patients) in either the AAP + ADT or ADT alone arm were hypertension (37% versus 22%, respectively), hypokalaemia (20% versus 4%) and back pain (18% versus 20%). Commonly reported SAEs (≥1% of patients in either the AAP + ADT or ADT alone group) included pneumonia (1.8% versus 0.3%, respectively), spinal cord compression (1.7% versus 1.8%) and urinary retention (1.5% versus 1.7%). The most frequently reported AEs leading to treatment discontinuation (reported in ≥1% of patients in either the AAP + ADT or ADT alone group) were spinal cord compression (0.8% versus 1.0% of patients, respectively) and bone pain (0.5% versus 1.0%, respectively). Cases of discontinuation for hypokalaemia, hypertension and cardiac disorders were rare. A post-hoc analysis of safety data for LATITUDE patients with HVD was consistent with the intention to treat population. This post hoc group had a similar baseline characteristics profile to those of the ITT.

Table 14 Summary of adverse reactions in the LATITUDE safety population (reproduced from Table 13, Document B of the company submission)

	LATITUDE	
	AAP + ADT (n=597)	**ADT alone (n=602)**
Any TEAE, n (%)	558 (93.5)	557 (92.5)
Drug-related	336 (56.3)	269 (44.7)
Any serious TEAE, n (%)	165 (27.6)	146 (24.3)
Drug-related	29 (4.9)	12 (2.0)
Grade 3–4 TEAE, n (%)	374 (62.6)	287 (47.7)
Drug-related	162 (27.1)	67 (11.1)
Discontinuation due to TEAE, n (%)	73 (12.0)	61 (10.1)
Drug-related	21 (3.5)	11 (1.8)
Death due to TEAE, n (%)	28 (4.7)	24 (4.0)
Drug-related	3 (0.5)	3 (0.5)

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; TEAE, treatment-emergent adverse event.
Source: Fizazi et al. 2017[41] European Public Assessment Report[37]

Table 15 Treatment emergent Grade 3-4 adverse events reported in at least 1% of patients in the LATITUDE safety population (reproduced from Table 14, Document B of the company submission)

	AAP + ADT (n=597)			ADT Alone (n=602)		
	Total	**Grade 3**	**Grade 4**	**Total**	**Grade 3**	**Grade 4**
Any TEAE, n (%)	374 (62.6)	342 (57.3)	32 (5.4)	287 (47.7)	265 (44.0)	22 (3.7)
Vascular disorders	127 (21.3)	126 (21.1)	1 (0.2)	65 (10.8)	64 (10.6)	1 (0.2)
Hypertension	121 (20.3)	121 (20.3)	0	60 (10.0)	59 (9.8)	1 (0.2)
Cardiac disorder						
Any	74 (12)	15 (3)	5 (1)	47 (8)	6 (1)	0
Atrial fibrillation	8 (1)	2 (<1)	0	2 (<1)	1 (<1)	0
Metabolism and nutrition disorders	98 (16.4)	90 (15.1)	8 (1.3)	42 (7.0)	39 (6.5)	3 (0.5)
Hypokalaemia	62 (10.4)	57 (9.5)	5 (0.8)	8 (1.3)	7 (1.2)	1 (0.2)
Hyperglycaemia	27 (4.5)	26 (4.4)	1 (0.2)	18 (3.0)	18 (3.0)	0
Hyperkalaemia	7 (1.2)	5 (0.8)	2 (0.3)	9 (1.5)	9 (1.5)	0
Investigations	69 (11.6)	62 (10.4)	7 (1.2)	47 (7.8)	45 (7.5)	2 (0.3)
ALT increase	33 (5.5)	31 (5.2)	2 (0.3)	8 (1.3)	8 (1.3)	0
AST increase	26 (4.4)	25 (4.2)	1 (0.2)	9 (1.5)	9 (1.5)	0
LDH increase	11 (1.8)	10 (1.7)	1 (0.2)	9 (1.5)	9 (1.5)	0
Weight increase	6 (1.0)	6 (1.0)	0	6 (1.0)	6 (1.0)	0
Musculoskeletal and connective tissue disorders	55 (9.2)	55 (9.2)	0	72 (12.0)	72 (12.0)	0
Bone pain	20 (3.4)	20 (3.4)	0	17 (2.8)	17 (2.8)	0
Back pain	14 (2.3)	14 (2.3)	0	19 (3.2)	19 (3.2)	0
Pain in extremity	7 (1.2)	7 (1.2)	0	12 (2.0)	12 (2.0)	0

	AAP + ADT (n=597)			ADT Alone (n=602)		
	Total	**Grade 3**	**Grade 4**	**Total**	**Grade 3**	**Grade 4**
Arthralgia	6 (1.0)	6 (1.0)	0	15 (2.5)	15 (2.5)	0
Musculoskeletal pain	4 (0.7)	4 (0.7)	0	6 (1.0)	6 (1.0)	0
Muscular weakness	3 (0.5)	3 (0.5)	0	7 (1.2)	7 (1.2)	0
Nervous system disorders	35 (5.9)	32 (5.4)	3 (0.5)	35 (5.8)	31 (5.1)	4 (0.7)
Spinal cord compression	12 (2.0)	12 (2.0)	0	10 (1.7)	7 (1.2)	3 (0.5)
Infections and infestations	31 (5.2)	29 (4.9)	2 (0.3)	19 (3.2)	17 (2.8)	2 (0.3)
Pneumonia	10 (1.7)	9 (1.5)	1 (0.2)	3 (0.5)	3 (0.5)	0
Urinary tract infection	6 (1.0)	6 (1.0)	0	5 (0.8)	5 (0.8)	0
Renal and urinary disorders	30 (5.0)	29 (4.9)	1 (0.2)	29 (4.8)	28 (4.7)	1 (0.2)
Urinary retention	10 (1.7)	10 (1.7)	0	8 (1.3)	8 (1.3)	0
Haematuria	6 (1.0)	6 (1.0)	0	3 (0.5)	3 (0.5)	0
Blood and lymphatic system disorders	26 (4.4)	21 (3.5)	5 (0.8)	35 (5.8)	33 (5.5)	2 (0.3)
Anaemia	15 (2.5)	12 (2.0)	3 (0.5)	27 (4.5)	26 (4.3)	1 (0.2)
General disorders and administration site conditions	26 (4.4)	26 (4.4)	0	39 (6.5)	37 (6.1)	2 (0.3)
Fatigue	10 (1.7)	10 (1.7)	0	14 (2.3)	14 (2.3)	0
Asthenia	4 (0.7)	4 (0.7)	0	7 (1.2)	7 (1.2)	0
General physical health deterioration	4 (0.7)	4 (0.7)	0	6 (1.0)	6 (1.0)	0

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; LDH, lactate dehydrogenase; TEAE, treatment-emergent adverse events.
Source: Fizazi et al. 2017[41] European Public Assessment Report[37]

No new safety signals were identified in the LATITUDE trial compared to those already characterised through the use of AAP in mCRPC, has across the two established licensed indications. AAP + ADT was well tolerated, with a comparable incidence of TEAEs to ADT alone. In line with its known safety profile, the most frequently reported Grade 3 or 4 TEAEs were mineralocorticoid-associated AEs.7 However, all events were medically manageable, only rarely required treatment discontinuation and seldom led to serious consequences. The safety results from LATITUDE are further supported by the STAMPEDE trial which also demonstrated that AAP + ADT was well tolerated, with a comparable incidence of Grade 3 to 5 AEs to ADT alone in patients with metastatic and non-metastatic prostate cancer. Table 16 presents a summary of Grade 3-4 adverse events reported in STAMPEDE.

Neutropenia and febrile neutropenia were more frequent after treatment with docetaxel (13% and 17%, respectively), compared to AAP (1% for both outcomes). Hypertension and hypokalaemia were reported more frequently by patients treated with AAP + ADT, compared to that observed in the LATITUDE trial. Treatment discontinuation due to AEs with AAP + ADT was similar in LATITUDE and STAMPEDE, and was also comparable with respect to ADT alone (10%). Of note, data on the occurrence of AEs by pre-specified metastatic subgroups were not provided

Table 16 Grade 3-5 adverse events reported in the STAMPEDE safety population (reproduced from Table 15, Document B of the company submission)

	AAP + ADT vs. ADT alone		AAP + ADT vs. docetaxel + ADT	
	AAP + ADT (n=948)	ADT alone (n=960)	AAP + ADT (n=373)	ADT + Doc (n=172)
AE, n (%)				
Endocrine disorders	129 (14)	133 (14)	49 (13)	15 (9)
Febrile neutropenia	-	-	3 (1)	29 (17)
Neutropenia	-	-	4 (1)	22 (13)
Cardiovascular disorders	92 (10)	41 (4)	32 (9)	6 (3)
Hypertension	44 (5)	13 (1)	-	-
MI	10 (1)	9 (1)	-	-
Cardiac dysrhythmia	14 (1)	2 (<1)	-	-
Musculoskeletal disorders	68 (7)	46 (5)	33 (9)	9 (5)
Gastrointestinal disorders	49 (5)	40 (4)	28 (8)	9 (5)
Hepatic disorders	70 (7)	12 (1)	32 (9)	1 (1)
Increased ALT levels	53 (6)	4 (<1)	-	-
Increased AST levels	10 (1)	2 (<1)	-	-
General disorders	45 (5)	29 (3)	21 (6)	18 (10)
Fatigue	21 (2)	15 (2)	-	-
Oedema	5 (1)	0	-	-
Respiratory disorders	44 (5)	23 (2)	11 (3)	12 (7)
Dyspnoea	18 (2)	7 (1)	-	-
Laboratory abnormalities	34 (4)	21 (2)	11 (3)	9 (5)
Hypokalaemia	12 (1)	3 (<1)	-	-

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Doc, docetaxel; MI, myocardial infarction.
Source: James et al. 2017[45]; Sydes et al. 2017[47]

4.2.2 Critique of statistical techniques used in trial

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

The company presented results of an indirect treatment comparison (ITC). The company reported their criteria for considering whether the trials included in the

systematic review of effectiveness were eligible for inclusion in the ITC. The criteria were reported were that the trials:

- Contributed data to the ITC of AAP + ADT versus ADT + docetaxel
- Reported comparable outcomes of interest
- Were sufficiently comparable with regards to study design, treatment and patient-level characteristics.

A total of three of the 16 trials (LATITUDE, CHAARTED and GETUG-AFU 15)[21, 28, 41] were included in the global base case network and one additional trial (STAMPEDE) was included in sensitivity analyses. Both CHAARTED and GETUG-AFU 15 were phase 3, open-label RCTs. As described earlier, LATITUDE was a phase 3, double-blind RCT and STAMPEDE was a multi-arm, multi-stage phase 2/3 trial. The company state that trials that did not report data separately for HRD/HVD populations were excluded from the ITC. The STAMPEDE trial was, therefore, excluded as the trial did not report data separately for HRD/HVD patients, but was included in sensitivity analyses due to the clinical importance of this large scale trial. The ERG agree that the STAMPEDE trial does not provide sufficiently comparable data for the considered patient population to be included in the ITC.

The four trials included in the ITC were linked in a network via a standard ADT arm based on the assumption that the ADT/standard of care arms were all similar. The company state that clinical opinion confirmed that differences in docetaxel administration would not have a significant impact on outcomes and the company, therefore, determined that the docetaxel arms of the trials were similar. Details of the interventions evaluated by the trials included in the ITC are presented in Table 17. The company state that the population enrolled in the LATITIDE trial is closest to the HVD *de novo* population considered in the company submission. All patients in the LATITIUDE trial had HRD determined by patients having at least two of the following: Gleason score $\geq$8; presence of $\geq$3 lesions on a bone scan; presence of measurable visceral (excluding lymph node disease) metastasis.

Table 18 presents baseline demographics and disease characteristics of participants from the RCTs included in the ITC. In general, participant and disease characteristics

were fairly well balanced with the exception of prostate specific antigen (PSA) level before ADT, Gleason score and Eastern Cooperative Oncology Group (ECOG) performance status (the STAMPEDE trial reported World Health Organisation [WHO] performance status instead of ECOG).

Table 17 Summary characteristics of the interventions evaluated in the trials included in the company's indirect treatment comparison (reproduced from Tables 5 and 6, Appendix D of company's submission)

Name of trial	Intervention	Comparator	Population abbreviation	Population description
CHAARTED[21]	ADT: LHRH receptor agonist or an LHRH receptor antagonist or orchidectomy; anti-androgens were given at the investigators' decision.	ADT + docetaxel: Docetaxel was given as 75mg/m^2 every 3 weeks for a maximum of six cycles.	ITT HVD NDx HVD	Patients with HVD as well as those with LVD, and patients with NDx disease as well as those with prior local treatments Patients with NDx metastatic HVD AND patients who had received prior local treatments Patients with NDx metastatic HVD
GETUG-AFU 15[28]	ADT: LHRH receptor agonist alone or combined with non-steroidal anti-androgens, or orchiectomy	ADT + docetaxel: Docetaxel was given as 75mg/m^2 every 3 weeks for a maximum of nine cycles.	ITT HVD NDx HVD	Patients with HVD as well as those with LVD, and patients with NDx disease as well as those with prior local treatments Patients with NDx metastatic HVD AND patients who had received prior local treatments Patients with NDx metastatic HVD
LATITUDE[41]	LHRH or surgical castration + placebo	AAP + ADT: AA was given as 1,000mg daily (once daily as four 250mg tablets), while prednisolone was given as 5mg daily.	NDx HRD ITT NDx HVD&HRD	Patients with NDx disease; all patients have HRD Patients with NDx HVD and HRD
STAMPEDE[45]	SoC: Hormone therapy for at least 2 years with gonadotropin-releasing hormone agonists or antagonists or, only between 2006 and 2011 for patients with non-metastatic disease, oral anti-androgens alone. Orchiectomy was an allowable alternative to drug therapy. Patients received orchiectomy, LHRH-based therapy, or bicalutamide (anti-androgen)	SoC + docetaxel: Docetaxel was given as 75mg/m^2 every 3 weeks for a maximum of six cycles. AAP + SoC: AA was given as 1,000mg daily (once daily as four 250mg tablets), while prednisolone was given as 5mg daily.	M1	Patients with NDx metastatic disease; HRD or HVD status of patients is unknown
Key: AA, abiraterone acetate; ADT, androgen deprivation therapy; AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; LHRH, luteinising hormone releasing hormone; SoC, standard of care. HRD, high risk disease; HVD, high-volume disease; ITT, intent-to-treat; LVD, low volume disease; M1, metastatic; NDx, newly diagnosed				

Table 18 Baseline characteristics of the participants of the RCTs included in the company's indirect treatment comparison (reproduced from Table 8, Appendix D of the company's submission)

Study	Treatment	Sample size, n	Baseline characteristics				
			Age, median years	PSA level before ADT, median (range)	ECOG PS, n (%)	Gleason score at diagnosis, n (%)	Metastases at diagnosis, n (%)
LATITUDE[41]	AAP + ADT	597	68	• 25.4	• 0: 326 (54.6) • 1: 245 (41.0) • 2: 26 (4.4)	<7: 4 (0.7) 7: 9 (2) ≥8: 584 (98)	597 (100)
	ADT alone	602	67	• 23.1	• 0: 331 (55.0) • 1: 255 (42.4) • 2: 16 (2.7)	<7: 1 (0.2) 7: 15 (2) ≥8: 586 (97)	602 (100)
CHAARTED[21]	ADT + Doc	397	64	50.9	0: 277 (69.8) 1: 114 (28.7) 2: 6 (1.5)	4–6: 21 (5.3) 7: 96 (24.2) 8–10: 241 (60.7) Unknown: 39 (9.8)	Low: 134 (33.8) High: 263 (66.2)[a]
	ADT alone	393	63	52.1	0: 272 (69.2) 1: 115 (29.3) 2: 6 (1.5)	4–6: 21 (5.3) 7: 83 (21.1) 8–10: 243 (61.8) Unknown: 46 (11.7)	Low: 143 (36.4) High: 66 (16.8)[a]
GETUG AFU-15[28]	ADT + Doc	192	63	26.7	0: 181 (99) 1–2: 2 (1)	<7: 84 (45) ≥8: 103 (55)	128 (67)
	ADT alone	193	64	25.8	0: 176 (96) 1–2: 7 (4)	<7: 78 (41) ≥8: 113 (59)	144 (76)
STAMPEDE[45]	AAP + ADT	960	67	51	0: 745 (78) 1/2: 215 (22)[b]	≤7: 221 (23) 8–10: 715 (74) Unknown: 24 (2)	500 (53)

Study	Treatment	Sample size, n	Baseline characteristics				
			Age, median years	PSA level before ADT, median (range)	ECOG PS, n (%)	Gleason score at diagnosis, n (%)	Metastases at diagnosis, n (%)
	ADT alone	957	67	56	0: 744 (78) 1/2: 213 (22)[b]	≤7: 223 (23) 8–10: 721 (75) Unknown: 13 (1)	502 (53)
	AAP + ADT	377	67	56	0: 79%[b]	Not Reported	60%
	ADT + Doc	189				Not Reported	
	ADT + Doc	592	65	70	0: 461 (78) 1+: 131 (22)[b]	≤7: 110 (19) 8–10: 436 (74) Unknown: 46 (8)	362 (61)
	ADT alone	1,184	65	67	0: 922 (78) 1+: 262 (22)[b]	≤7: 282 (24) 8–10: 810 (68) Unknown: 92 (8)	724 (61)

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; Doc, docetaxel; ECOG, Eastern Cooperative Oncology Group; MAMS, multi arm multi stage; PS, performance status PSA, prostate specific antigen.

Notes: a, volume of metastases; b, WHO performance status.

Outcome definitions differed across the trials. GETUG-AFU 15 used Response Evaluation Criteria for Solid Tumors (RECIST) version 1.0, while LATITUDE used RECISIT 1.1 definitions for radiographic progression-free survival (rPFS). Progression-free survival (PFS), failure-free survival (FFS), time to clinical progression and time to castration resistant prostate cancer (CRPC) were only available for one trial each. All trials reported overall survival (OS) and used similar definitions. Summary details of the primary outcomes are presented in Table 19.

Table 19 Summary of primary outcomes reported by the RCTs included in the company's indirect treatment comparison (reproduced from Table 9, Appendix D of the company's submission)

Outcome	CHAARTED	GETUG-AFU 15	LATITUDE	STAMPEDE
OS	Time between randomisation and death from any cause	Time between randomisation and death from any cause	Time between randomisation and death from any cause	Time between randomisation and death from any cause
rPFS	Not reported	Time from randomisation to the occurrence of radiographic progression or death from any cause (based on RECIST 1.0)	Time from randomisation to the occurrence of radiographic progression or death from any cause (based on PCWG2 and RECIST 1.1)	Not reported
FFS	Not reported	Not reported	Not reported	Time to first evidence of at least one of: • Biochemical failure • Progression either locally, in lymph nodes, or in distant metastases • Death from prostate cancer
Time to CRPC (biochemical, symptomatic or radiographic)	Time to documented clinical or serologic progression with a testosterone level of less than 50ng per decilitre	Not reported	Not reported	Not reported

Outcome	CHAARTED	GETUG-AFU 15	LATITUDE	STAMPEDE
Time to clinical progression (symptomatic or radiographic)	Time from randomisation to: • Increasing symptoms of bone metastases • Progression according to the RECIST 1.0 • Clinical deterioration due to cancer according to the investigator's opinion	Not reported	Not reported	Not reported
Key: CRPC, castration-resistant prostate cancer; FFS, failure-free survival; OS, overall survival; PCWG2, Prostate Cancer Working Group 2; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; rPFS, radiographic progression-free survival.				

The proportions of people receiving subsequent treatment in the included trials are presented in Table 20.

Table 20 Proportions of people receiving subsequent treatment after relapse/progression

Treatment	LATITUDE[a]		STAMPEDE[b]		CHAARTED[c]		GETUG-AFU 15[d]	
	ADT + Placebo (n=469)	ADT + AAP (n=314)	ADT (n=535)	ADT + AAP (n=248)	ADT (n=287)	ADT + Docetaxel (n=238)	ADT (n=149)	ADT + Docetaxel *
Abiraterone acetate	53 (11%)	10 (3%)	120 (22%)	8 (3%)			36 (24%)	33
Cabazitaxel	30 (6%)	11 (4%)	28 (5%)	15 (6%)	37 (13%)	57 (24%)	15 (10%)	16
Docetaxel	187 (40%)	106 (34%)	200 (37%)	115 (46%)	137 (48%)	54 (23%)	127 (85%)	
Enzalutamide	76 (16%)	30 (10%)	138 (26%)	25 (10%)			12 (8%)	15
Radium-223	27 (6%)	11 (4%)	24 (4%)	19 (8%)				
Abiraterone and/or enzalutamide					104 (36%)	105 (44%)		

a. Data from Fizazi 2017[41]– Percentages are calculated from the numbers of people who discontinued treatment and were eligible for subsequent therapy
b. Data from James 2017[45] – percentages calculated from the numbers with progression
c. Data from Sweeney 2015[21] – percentages are calculated from those with serological progression/clinical progression. Numbers for clinical progression only are ADT 228 and ADT+D 180.
d. Data from Gravis 2016[28] – * the paper reports 27/149 treated for progressive disease in the ADT arm. Unclear how many patients were treated for progression in the ADT+D arm.

Statistical comparison of AAP versus docetaxel (DOC) for the primary outcomes OS and rPFS was only possible using ITC methods. The patient populations of two RTCs, CHAARTED (790 participants) and GETUG-AFU 15 (385 participants), which compared DOC +ADT with ADT alone using post-hoc selected sub-groups of newly diagnosed patients with high volume disease (HVD), were considered to be comparable with those in LATITUDE. The company used Bayesian network meta-analyses with fixed effects to find the indirect results of AAP+ADT versus DOC+ADT. The results suggest non-significant effects for OS (HR 0.92, 95% CrL 0.69-1.23) and rPFS (HR 0.76, 95% CrL 0.53-1.10) presented in Table 21 but with Bayesian probabilities of 71.8% and 92.9%, respectively, suggesting AAP+ADT is a better life prolonging treatment option. Various sensitivity analyses examined the effect of post-hoc selection of the HVD patients rather than the high risk disease (HRD) group of LATITUDE; the inclusion of the M1 group from STAMPEDE (for both AAP+ADT and DOC+ADT) and the inclusion of those treated prior to current treatment or not. The results of the sensitivity analyses varied but there was a consistent trend in favour of AAP+ADT.

Results of sensitivity analyses of time to skeletal-related events (SRE) were similar in the indirect comparison between AAP+ADT and DOC+ADT, [redacted] but with a Bayesian pairwise probability of [redacted].

Only two RCTs, LATITUDE (AAP+ADT versus ADT) and GETUG-AFU 15 (DOC+ADT versus ADT, presumably newly diagnosed HVD patients) could be included into an ITC for the assessment of secondary outcome measures of safety. No sensitivity analyses were reported. When the AAP+ADT group (n=597) was indirectly compared to the DOC+ADT group (n=189), [redacted] However, AAP+ADT was found [redacted]

Table 21 Base case results and sensitivity analyses results of Bayesian ITC (Synthesised from Tables 18 and 19 from Document B, pages 80-81)

Outcome for original and various sensitivity analyses		AAP + ADT vs. ADT alone			ADT alone vs. docetaxel + ADT			AAP + ADT vs. dox + ADT	ITC	
		LATITUDE		STAMPEDE	CHAARTED	GETUG-AFU 15	STAMPEDE	STAMPEDE	AAP + ADT vs. docetaxel + ADT	
		ITT	HV *post-hoc*	M1	NDx HV	NDx HV	M1	M1	HR (95% CrI)	P_{AA-Doc}
OS (95 % CI)	MAIN	**x**			**X**	**x**			**0.92 (0.69,**	**71.8**
	sa	x		x	X	x	x	x	0.91 (0.76,	84.5
	sa		x		X	x			0.85 (0.63,	86.7
	sa		x	x	X	x	x	x	[redacted]	[redacted]
	sa	x			x[d]	x[d]			[redacted]	[redacted]
	sa								[redacted]	[redacted]
rPFS (95% CI)	MAIN	**x**			**X**	**x**			**0.76 (0.53,**	**92.9**
	sa	x			x[d]	x[d]			0.71 (0.49, 1.02)	96.8 %

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; dox, docetaxel; HR, hazard ratio; HV, high-volume; ITT, intent-to-treat; M1, metastatic disease; NDx, newly diagnosed; OS, overall survival; rPFS, radiographic progression-free survival; SA, sensitivity analysis.

Notes: $PA_{A>Doc}$, Bayesian pairwise probability for ADT+AAP being more effective compared with ADT+DOC; [a], Definitions of rPFS differed across trials; [b], Time to CRPC data; [c], FFS data, [d] included prior treated

The Functional Assessment of Cancer Therapy-Prostate (FACT-P) and the Brief Pain Inventory (BPI) quality of life measures, looked at differences of change from baseline for both AAP+ADT and DOC+ADT treatment groups over four time points 3, 6, 9 and 12 months from the LATITUDE (ITT) and CHAARTED (HVD) studies. Here another variation of sub-group analyses were conducted whereby HRD together with HVD patients in LATITUDE were selected post-hoc. At 3 months, AAP+ADT had a significant positive and beneficial increase on FACT-P over DOC+ADT, with difference of change being 4.20 (95% CrL 1.18-7.19) and the probability of the AAP patients having better quality of life to DOC being 99.7%. AAP estimates improved further over time as did the DOC estimates but not to the same extent and never to the level of AAP, although differences between AAP and DOC were not significant by 6 months or even at 1 year. BPI results showed larger decreases in pain estimates for indirect comparisons between AAP+ADT and DOC+ADT, but the results were not significant. Pain in the DOC+ADT group increased with time whereas with

AAP+ADT initially improved and then remained steady if not further reduced. The sensitivity analyses were comparable for FACT-P and BPI.

With regard to the effectiveness of AAP+ADT compared with other treatments including DOC+ADT, further indirect comparisons were conducted by the company for people with disease progression to metastatic castration resistant prostate cancer (mCRPC) although these were not presented in the clinical effectiveness section of the submission. Again, no direct head-to-head trial comparing abiratone to docetaxel was identified indicating the need for an ITC. On this occasion the company used Buchers pairwise comparisons using four trials: COU_AA_302, which compared abiratone with prednisolone as placebo; TAX327, which compared docetaxel with a mitoxantrone as placebo; ALSYMPCA, which compared radium-223 with prednisolone as placebo; and PREVAIL, which compared enzalutamide with prednisolone as placebo. Thus, each compared a treatment (AAP, radium-223, enzalutamide and docetaxel) to a 'similar' control and assessed OS. For rPFS the other co-primary outcome, only three trials could be connected, COU-AA-302, ALSYMPCA and PREVAIL. The submission focuses on the positive AAP results and the high Bayesian probabilities, see Table 22 below for the ERG replication of results [redacted].

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

Abiratone compared with docetaxel for the treatment of mHSPC or mHNPC patients

With no direct head-to-head comparison of abiratone to docetaxel available the ERG agree that this gap could be bridged using and Indirect Treatment Comparison (ITC) and that the Bayesian Network Meta-Analysis (NMA) was appropriate. The company may have considered doing a Matching-Adjusted Indirect Comparisons (MAIC) instead where those in each study who fulfil the required target population and baseline characteristics are matched. However, this approach requires having the data for individuals from al the included studies and the matching often means that many of the observations are not comparable and are dropped and the results lack robustness because of poor sample size. NMA is a reasonable option.

The ERG replicated the NMA results using WinBUGS14 (50,000 burn-in and 100,000 iterations) with reference to examples and programs from NICE DSU Technical Support

Document 2.[49] The company submission used 50,000 run-in iteration phase and a 50,000 iteration phase for parameter estimation. Throughout, the company have use fixed effect models. Random effect models may have been preferred and conducted where possible by the ERG but most were not resolvable probably due to the limited number of studies.

Replication of results presented in Table 18 Document B for OS and rPFS
OS: the trials compared were LATITUDE ITT (30.4 mo), CHAARTED (newly diagnosed HVD sub-group 53.7 mo) and GETUG-AFU 15 (newly diagnosed HVD subgroup 43 mo). The ERG considered the fixed effects as per company model but also attempted a random effects model. The programmes for each may be found in DSU Document 2 Example 7a and 7b. Our findings show the fixed effects to be similar to the company submission (OS between AAP+ADT versus docetaxel+ADT, HR= 0.920, 95% CrL 0.689-1.22). The random effects model resulted in an HR of 0.894, 95% CrL: 0.258, 2.979, so slightly more benefit to the AAP+ADT but very wide credible limits (CrL). The other various sub-group analyses were also replicated using a fixed effects model. Depending on the groups used the estimate varied between 0.63 up to 1.23, which is between all the credible limits.

rPFS: the trials with relevant data for this outcome were LATITUDE ITT and GETUG-AFU 15 (newly diagnosed HVD subgroup) and again the ERG replicated ITC results [fixed effects model] for the assessment of AAP+ADT versus DOC+ADT were similar to those reported in the company submission (HR= 0.770, 95% CrL: 0.538-1.11). **Note:** random effects model did not resolve, which is to be expected with just 2 studies for 3 treatments, and thus too many parameters to estimate.

Verification of secondary outcome comparisons between trials and other treatments
Several safety and HRQL measures were compared across the trials and treatments. The ERG performed 'trial comparisons' for all of these, using the program in DSU Example 3b:
For the safety measures, comparisons between the HRs were performed using 'trial arms' and the same programs as for OS and rPRS above but on the OR's rather than HR's. This was because the binary data over time within each group used by the company were not provided. Nevertheless, the company estimates were comparable to those of the ERG (see Table 22 below).

or the HRQL measures, the company took an 'arm comparison' approach; however, the company submission only gave differences of mean changes and relevant CIs. Arm comparisons require actual mean changes from baseline for each arm in each trial, along with their relevant precision measure - but such information was not available. A referenced paper only had the same summary[a] estimates (without CIs) but again did not provide mean changes. As a result, while the point HR estimates are similar for the trial comparison approach, some CrLs differ to those in the submission.

Table 22 Safety and HRQL results - Bayesian ITC (Reconstruction of Tables 20 and 21; pages 83-86; Document B)

Saftey: LAITUDE and GetUG-AFU 15					**HRQL§: LAITUDE and CHAARTERED**			
Trial comparison					**Trial rather than Arm comparison**			
AAP+ADT vs ADT alone versus DOC+ADP vs ADT alone					AAP+ADT vs ADT alone versus DOC+ADP vs ADT alone			
Recalculation of Table 20 in Document B					**Recalculation of Table 21 in Document B**			
OR	**HR**	**CrL 2.5%**	**CrL 97.5%**		**Differences***	**HR**	**CrL 2.5%**	**CrL 97.5%**
Anaemia	0.065	0.036	0.118		**FACT-P** 3mo	4.196	[redacted]	[redacted]
Hot Flush	3.763	2.216	6.400		6 mo	2.487	[redacted]	[redacted]
AST	0.529	0.263	1.067		9 mo	3.067	-0.112	6.250
Constipation	0.158	0.068	0.372		12mo	2.347	-0.877	5.576
ALT	0.606	0.317	1.162		**BPI** 3 mo	-0.150[1]	[redacted]	[redacted]
Odema	0.144	0.063	0.330		6 mo	-0.761	[redacted]	[redacted]
					9 mo	-0.851	[redacted]	[redacted]
					12 mo	-0.451	[redacted]	[redacted]

§ The company also performed analysis for the HRQL measure using non ITT patients in LAITUDE who were classed as the post hoc HVD group also reported for the CHAARTED trial. The ERG did not repeat here since there was no valid reason why this considered useful here was not for other outcomes.

[a] NOTE: The reference by Feyerabend[43] shows BPI at 3 months has a difference of the mean changes for CHAARTED HVD as 44, in line with the others in that column, but in the submission this was presented as -.01.

Validity of the NMA approach for the comparison abiratone versus docetaxel

There were a number of key differences between the different trials incorporated into the NMAs above. These were:

- Differing target patient groups making ITT comparisons impossible, with respect to:
  - Being newly diagnose, and /or primary progressive
  - High Volume and High Risk – The company make some attempt to justify these are the same –but even within LATITUDE, while there were commonalities, the sub-groups did not entirely match
- Variable ADT doses in the control arm and with different definitions
- Variable docetaxel doses
- Different patterns of subsequent therapies during follow-up
- Varying previous therapies (recall some were not newly diagnosed)
- Reporting variations
- Different definitions of how to measure rPFS
- Length of studies

Since the company felt they had to compare DOC with AAP the resulting estimates are of interest albeit with huge reservations for taking them forward into the economic modelling given the degree of clinical heterogeneity highlighted above. In addition to the conceptual heterogeneity, no account of statistical heterogeneity, consistency or fit were reported in the main submission documents. If inconsistent, the results for the same treatment combinations via different routes will differ to another. Some fit statistics were provided, but not consistently nor commented on. These limitations could impact on the economic modelling and such estimates will require caution and various scenarios to reflect these concerns.

Comparison of abiratone with other treatments for patients with disease progression

The evidence of progression into mCRPC (castration resistant) is given in Appendix Q of the company submission. The company recognised that the observed heterogeneity between trials was not ideal (Appendix Q5 page 137). In particular, there was some notable clinical heterogeneity between trials including a range of differences in patient baseline characteristics. These include:

- Controls being different (although company suggest these are comparable!)
- Follow up times (i.e., survival or progression) differing from 21 to 36 months

- Some trials adjust for treatment switching (an inevitable problem) and different methods are used for this adjustment, IPE and IPCW
- Differing definitions of rPFS
- Various previous therapies
- Baseline characteristics differing between trials (only the below are admitted to)
  - Populations targeted
  - Levels of PSA

Despite these inconsistencies, comparisons of AAP+ADT versus other drugs for this patient group were needed to carry forward into any cost analyses. Rather than gaining more evidence, the company attempted indirect estimates. This time the company considered a different method to NMA (used for the mHNPC/mHSPC patient group); they chose Bucher pairwise estimates which are simple to perform and easy to understand and known to work best on "triangle structures" as is the case here. What these do not allow is for better efficiency by each trial control group being 'pooled'. The ERG understand why this approach was chosen; the company were anxious about doing a complete network analysis because of the above heterogeneity issues. The ERG agree with the company's choice. In addition, attempts to run complete NMA models by the ERG did not converge. The suggested pairwise separate comparisons was probably the only viable option even though it does not address the heterogeneity concerns highlighted above and brings issues of robustness in to question. The result was eight separate combinations. The ERG have replicated these and confirm that they are as the submission suggest (page 136 Appendix Q Table 56) but would like to reiterate that they cannot be thought of as anything but as indicators and not as robust estimates. The results are given in Table 23 below.

The interpretation of the results given by the company requires some attention.
OS: the company state that AAP+ADT has slightly lower risks, if the adjustments for treatment switching are applied. Given that not all the trials adopt a treatment switching adjustment, this strategy has to be questioned – unless there are good reasons for treatment switching to be more valid in these trials over the others (why should some be adjusted and other not). Taking the results as they stand, [redacted] suggesting that AAP will be at least as equivalent to DOC – the company however only reflect on the Bayesian probabilities. As a precautionary the ERG suggest that ongoing

economic models be based on scenarios reflecting the credible intervals around these estimates.

Table 23 ITC between AAP and other treatment in the mCRPC patient group (The ERG replicated the Bucher estimates based on Table 55 leading to Table 56 of the Appendices document)

			Each trial results			ITC results		
			HR	Low	Upper	HR	LCL	UCL
OS	AAP+Radium	COU-AA-302	0.806	0.697	0.931	[redacted]		
		ALSYMPCA	0.745	0.562	0.987			
ipe -treat swtich	AAP+Radium*	COU-AA-302	0.741	0.6	0.882	[redacted]		
		ALSYMPCA	0.745	0.562	0.987			
	AAP+Enz	COU-AA-302	0.806	0.697	0.931	[redacted]		
		PREVAIL	0.77	0.67	0.88			
ipe -treat switch AND ipcw -treat switch	AAP+ENZ **	COU-AA-302	0.741	0.6	0.882	[redacted]		
		PREVAIL	0.66	0.57	0.77			
	APP+doc	COU-AA-302	0.806	0.697	0.931	[redacted]		
		TAX327	0.76	0.62	0.94			
ipe -treat switch	AAP+Doc*	COU-AA-302	0.741	0.6	0.882	[redacted]		
		TAX327	0.76	0.62	0.94			
rPFS	AAP vs. PP	COU-AA-302	0.52	0.45	0.61	[redacted]		
Def^{n} different	Radium 223 vs. placebo	ALSYMPCA	0.64	0.54	0.77			
	AAP vs. PP	COU-AA-302	0.52	0.45	0.61	[redacted]		
	Enzalutamide vs. placebo	PREVAIL	0.19	0.15	0.23			

rPFS: The company do not seem to fully interpret the results in their submission, focusing only on positive AAP results and the high Bayesian probabilities. [redacted]

As for OS, scenarios reflecting the credible intervals are advocated for any further economic modelling.

Overall, the company conclude that abiratone to be at least equivalent to other treatments based on these analyses, on a sensitivity analysis including STAMPEDE data and on two

previous not truly comparable systematic reviews[50, 51] for both the mHSPC and the mCRPC patient popultions. The ERG would agree this to be fair provided further claims are not made.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG was largely able to verify the company's NMA results for the mHSPC patient group using either the programs supplied in Appendix D1 pages 29-31 or comparable programs from NICE Decision Support Unit (DSU) TSD 2[49] when pertinent data were not available. Similarly the ERG confirmed the ITC results using the Bucher's approach.

4.6 Conclusions of the clinical effectiveness section

The ERG are satisfied that the methods used to conduct the systematic review of clinical effectiveness are appropriate.

The submission presents results from the LATITUDE study providing evidence of the benefits of AAP over ADT for the treatment of men with mHSPC. The benefit found in LATITUDE is evident for the primary outcomes of overall survival and progression measured by rPFS and extends to the secondary outcomes for safety and quality of life. The results of LATITUDE are similar to those from the STAMPEDE study. However, the STAMPEDE patient group was broader and while the company have conducted similar analyses on a post hoc subgroup meant to be similar to the LATITUDE population, they rightly have not combined them in any further analyses.

Less reliable are the company results of AAP compared to other treatments, predominately docetaxel. With no head-to-head studies available, these were compared using indirect methods. The company chose NMA at this stage, which the ERG agree, was sensible. When conducting the NMA the company used the recommended WinBUGS program from the NICE DSU TSD 2.[49] They were restricted to only fixed effects models because of the lack of studies and links between treatment groups. Further concerns are the many aspects of heterogeneity between the studies, all recognised by the company. So while the ERG confirm the results provided showing abiraterone to be at least equivalent to docetaxel, there is a concern that estimates from these results will not be robust. There were no checks of statistical heterogeneity or consistency commented on. As such any economic modelling on these estimates will require caution and various scenarios to reflect these concerns.

The company also attempted to assess the use of AAP+ADT for patient with disease progression (mCRPC) again compared with other subsequent treatments. Here they concentrate on docetaxel, radium-223 and enzalutamide. The more robust method of NMA was not conducted and instead the company used Bucher pairwise comparisons. While NMA are more useful when making choices between multiple alternatives, the ERG confirm that NMA models did not converge probably due to the limited number of studies and data so that Bucher estimates were a reasonable alternative. For this patient group too, the estimates show abiraterone to be comparable with other treatments. However, since checks of statistical heterogeneity or fit were not provided and as before the conceptual heterogeneity (e.g., differences in study populations, study setting, follow-up procedures, outcome measures) were extensive caution for further economic modelling is warranted.

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 State objective of cost effectiveness review. Provide description of manufacturers search strategy and comment on whether the search strategy was appropriate. If the manufacturer did not perform a systematic review, was this appropriate?

Reports of cost effectiveness were sought by the company by searching MEDLINE AND EMBASE (via Embase.com), MEDLINE In-Process (vis Pubmed), NHS Economics Evaluation Database (NHS EED) and HTA Database (via Cochrane Library) and Econlit (via Ebsco) in September 2015 and updated in July 2017. The searches were restricted to studies published between 2005 and 2017.

The search strategies are documented in full in Appendix G and are reproducible however the company conducted the MEDLINE and EMBASE searches using the EMBASE.com platform which is not accessible to the ERG.

The MEDLINE and EMBASE searches combined three search facets using the Boolean operator AND: prostate cancer; abiraterone or comparator; and economic/cost terms.
The search strategies were considered fit for purpose, including both relevant controlled vocabulary and text terms with appropriate used of the Boolean operators. However, the ERG identified errors which were clarified by the company as documentation errors:
Date ranges: Table 17 (Embase and MEDLINE) imposed date range 2005-2015 while Table 19 (NHS EED and HTA Database) was restricted to 2015-2017. The company confirmed that all searches were run initially in 2015 with a start date of 2005, and then updated in 2017. The company removed pre-2005 studies, which had initially been included in the review of cost-effectiveness.

Table 18: The company confirmed that the heading should have been MEDLINE In process (via Pubmed).

Modifications to final set:Errors were identified by the ERG in Table 18 (lines 5-6) and Table 19 (lines 5-8). The company provided the corrected search strategies.

5.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

Inclusion criteria for the cost-effectiveness review are shown in Table 24

Table 24 Inclusion and exclusion criteria for the systematic review of cost-effectiveness, reproduced from Table 16, Appendix G of the company submission

Category	Inclusion criteria	Exclusion criteria	Exclusion code
Population	Men (aged 18 years and over) with mHSPC	Publications reporting on patient populations in the following categories • Females • Children • Healthy volunteers • Non-cancerous prostate disease (such as benign prostatic hyperplasia) • Cancer other than prostate • Localised/locally advanced prostate cancer patients • Metastatic prostate cancer patients who have progressed on endocrine manipulation for their disease	Population not of interest
Interventions	Abiraterone acetate, ADT, docetaxel and enzalutamide	Publications that do not report data specific to treatment using abiraterone acetate, ADT, docetaxel and enzalutamide	Intervention not of interest
Comparisons	No restriction based on treatment comparisons reported/not reported	N/A	N/A
Outcomes	The review will be limited to publications that report on the following outcomes: • Direct costs • Indirect costs • Other healthcare resource use • ICERs, QALYs, and other cost- effectiveness outcomes	Publications that only report data on the following types of outcomes: • Pharmacokinetics/pharmacodynamics • Clinical efficacy • Clinical safety • HRQL and related PROs • Epidemiological outcomes	Relevant outcomes unreported
Date	2005–2017, inclusive	Publications published before 2005	Date
Duplicate	N/A	Publications that are duplicates of other publications in the search yield	Duplicate
Publication types	N/A	Publications of the following types: • Narrative publications • Non-systematic reviews • Case studies • Case reports Editorials	Publication type not of interest
Other criteria	Only English language articles/conference abstracts will be included	Journal articles and conference abstracts without English full-text	Non-English

Key: ADT, androgen deprivation therapy; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; mHSPC, metastatic hormone-sensitive prostate cancer (also called castrate-sensitive, hormone-dependent, or hormone-naive prostate cancer); N/A, not applicable; PRO, patient-reported outcome; QALY, quality adjusted life-year; RCT, randomised controlled trial

Inclusion criteria for the HRQOL review match those for the clinical effectiveness review, with the exception of the criteria shown in Table 25. The review identified 26 publications from 15 studies (all RCTs) reporting on HRQOL, patient reported outcomes (PROs) or utilities derived from disease-specific and generic PRO instruments. Studies by Jolly 2010[52] and Patrick-Miller 2016[53] were used in the ERG's critique of the company's economic model.

Table 25 Inclusion and exclusion criteria for the systematic review of HRQOL (reproduced from Table 24, Appendix D of the company submission)

Category	Inclusion criteria	Exclusion criteria	Exclusion code
Outcomes	The review will be limited to publications that report on the following outcomes: HRQL and related PROs QALYs Utilities	Publications that only report data on the following types of outcomes: Pharmacokinetics/pharmacodynamics Clinical efficacy Clinical safety Cost and resource use Epidemiological outcomes ICERs and other cost-effectiveness outcomes	Relevant outcomes unreported
Study designs	The review will be limited to publications of studies with the following designs: Prospective non-randomised controlled interventional studies Prospective longitudinal observational studies Retrospective longitudinal observational studies Cross-sectional studies RCTs	Publications of studies with the following designs: Animal studies In vitro/ex vivo studies Gene expression/protein expression studies Economic models and trial-based economic analyses	Study design not of interest
Date	2005 – 2017, inclusive	Publications published before 2005	Date
Duplicate	N/A	Publications that are duplicates of other publications in the search yield	Duplicate

Category	Inclusion criteria	Exclusion criteria	Exclusion code
Publication types	N/A	Publications of the following types: Narrative publications Non-systematic reviews Case studies Case reports Editorials	Publication type not of interest
Other criteria	Only English language articles/conference abstracts will be included	Journal articles and conference abstracts without English full-text	Non-English
Key: Abbreviations: N/A, not applicable; PRO, patient-reported outcome; QALY, quality adjusted life-year; RCT, randomised controlled trial.			

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 <u>most important</u> cost effectiveness studies.

In response to a clarification request by the ERG, the company provided the list of studies included in the cost-effectiveness review, which is reproduced as Table 26 below.

Table 26 Studies included in the company's systematic review of cost-effectiveness, reproduced from the company's response to ERG clarification B1

	Reference
1	Penson DF, Ramsey S, Veenstra D, Clarke L, Gandhi S, Hirsch M. The cost-effectiveness of combined androgen blockade with bicalutamide and luteinizing hormone releasing hormone agonist in men with metastatic prostate cancer. J Urol. 2005;174(2):547-52; discussion 52.
2	Ramsey S, Veenstra D, Clarke L, Gandhi S, Hirsch M, Penson D. Is combined androgen blockade with bicalutamide cost-effective compared with combined androgen blockade with flutamide? Urology. 2005;66(4):835-9.
3	Chau A, de Lemos M, Pickles T, Blood P, Kovacic L, Abadi S, et al. Use of combined androgen blockade for advanced prostate cancer in British Columbia. Journal of Oncology Pharmacy Practice. 2010;16(2):121-6.
4	Iannazzo S, Pradelli L, Carsi M, Perachino M. Cost-effectiveness analysis of LHRH agonists in the treatment of metastatic prostate cancer in Italy. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(1):80-9.
5	Grabner M, Onukwugha E, Jain R, Mullins CD. Racial variation in the cost-effectiveness of chemotherapy for prostate cancer. The American journal of managed care. 2011;17(5 Spec No):e151-9.
6	Lu L, Peters J, Roome C, Stein K. Cost-effectiveness analysis of degarelix for advanced hormone-dependent prostate cancer. BJU international. 2012;109(8):1183-92.
7	Lee D, Porter J, Gladwell D, Brereton N, Nielsen SK. A cost-utility analysis of degarelix in the treatment of advanced hormone-dependent prostate cancer in the United Kingdom. Journal of medical economics. 2014;17(4):233-47.
10	Zheng HR, Wen F, Wu YF, Wheeler JRC, Li Q. Cost-effectiveness analysis of additional docetaxel for metastatic hormone-sensitive prostate cancer treated with androgen-deprivation therapy from a Chinese perspective. European journal of cancer care. 2017;26(6).

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.

A key parameter for the cost effectiveness modelling is the quality of life decrement for those in the DOC+ADT arm once they have completed their course of docetaxel: ADT (post DOC+ADT). The company derives this value from a company commissioned TTO study that compares DOC+ADT with ADT. The health state descriptors of the TTO study have been supplied at the request of the ERG. They may be biased.

Appendix H of the submission presents the details of the company systematic review of quality of life studies and associated data extraction. This is not particularly accessible and does not present the conclusions of the studies from which data have been extracted. The presentation of the results of the company systematic review of quality of life studies within the main body of the submission is insufficient for an assessment of the reasonableness of the health state descriptors of the company commissioned TTO study.

The company systematic review of quality of life studies identifies two mHPSC studies with RCT trial data for a comparison of the quality of life of DOC+ADT with ADT. One uses the EORTC-QLQ-C30 questionnaire.[52] It concludes that while DOC+ADT is associated with an initial deterioration, at 12 months there is no difference in overall quality of life between DOC+ADT and ADT. The other[53] uses the FACT-P questionnaire. It concludes that both arms resulted in some increased symptoms over time, but DOC+ADT not only provided a survival benefit but also preserved a better quality of life for mHSCP patients for longer than ADT alone. The FACT-P total score analysed with a mixed effects model estimated a net difference between the arms at baseline of -1.00 (p=0.43) in favour of ADT, with this falling further in favour of ADT to -3.09 (p=0.02) at 3 months but improving steadily thereafter to reach 2.85 (p=0.04) at 12 months in favour of DOC+ADT. This is written up in more detail in the 2018 paper by Morgans et al.[54]

The recent 2018 paper by Morgans et al[54] analyse quality of life among an RCT of DOC+ADT (n=397) compared to ADT for mHSPC (n=393). Quality of life was assessed at baseline and 3 monthly to 12 months using FACT-P, FACT-Taxane, Functional Assessment of Chronic Illness Therapy-Fatigue and the Brief Pain Inventory with the data being analysed using a mixed effect model. FACT-P completion rates were high at 90%, 86%, 83%, 78% and 77% at the five timepoints, non-completions being roughly equally split between those not given the form by staff and for unknown reasons. DOC+ADT FACT-P scores were

significantly lower at 3 months (-3.09, p=0.02) but significantly higher at 12 months compared to ADT (+2.85, p=0.04). But differences did not exceed the minimum clinically meaningful change at any time point, which was taken to be a change of 6 to 10 points. Both arms reported significantly poorer FACT-Taxane scores compered to baseline. Brief pain inventory scores were similar between the arms. The authors conclude that "*Although ADT+D was associated with statistically worse QOL at 3months, QOL was better at 12months for ADT+D patients than for ADT patients. Both arms reported a similar minimally changed QOL over time, suggesting that ADT+D is not associated with a greater long-term negative impact on QOL*".

[redacted]The company do not reference minimum clinically meaningful changes and conclude that "*Results of the ITC showed treatment with AAP+ADT was associated with notable benefits in HRQL compared to DOC+ADT. These benefits were observed from three months and sustained for at least one year after treatment*".

A crude reading of the company ITC and the results of Morgans et al[54] suggests that the 12 month FACT-P improvement from AAP+ADT compared to ADT is roughly double that of the improvement from DOC+ADT compared to ADT.

The model requires estimates for quality of life increments or decrements relative to ADT for patients in rPFS. For rPFS specific estimates of FACT-P changes there may be some confounding between both AAP+ADT and ADT and DOC+ADT and ADT in the RCT data due to more progression with ADT than with either AAP+ADT or DOC+ADT.

However, given the greater rPFS superiority for AAP+ADT over ADT compared to DOC+ADT over ADT, any such confounding might be expected to benefit AAP+ADT more than DOC+ADT. Yet, it cannot be unambiguously stated that the literature concludes that FACT-P changes for those remaining in rPFS are better among AAP+ADT patients than among ADT (post DOC+ADT) patients, or that they are better among ADT (post DOC+ADT) patients than among ADT patients.

The company have not explored the possibility of mapping from FACT-P to quality of life using the LATITUDE data as a possible means of exploring estimates based upon RCT data for AAP+ADT, DOC+ADT and ADT (post DOC+ADT) relative to ADT. It is also unclear to the ERG whether any of the three FACT-P mapping functions identified in the HERC mapping studies database[55] could help to inform this.

In the opinion of the ERG, the RCTs' quality of life data cast doubt on the company TTO study health state descriptors which assume that the quality of life among ADT (post DOC+ADT) patients is unambiguously worse than the quality of life among ADT patients. The evidence presented by the company for this unambiguous assumption also seems quite thin.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Table 27 NICE reference case checklist

Attribute	**Reference case and TA Methods guidance**	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	The model compares: • AAP+ADT • ADT • DOC+ADT
Patient group	As per NICE scope. "*Adults with newly diagnosed high risk metastatic hormone-naïve prostate cancer*".	In part. The data taken from LATITUDE reflects the patient population, and is analysed using multi state modelling (MSM) to derive the main transition probability matrices (TPMs) of the model. But for the company base case the outputs of the TA387[31] DES

		model for mCRPC are used as inputs. This is a poor fit due to the TA387[31] patients having a better prognosis than mHSPC patients who progress to mCRPC. The company compensates for this by applying an ad hoc hazard ratio of 2.62 to the survival probabilities derived from the TA387 model outputs.[31]
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Yes. Cost-utility.
Time horizon	Sufficient to capture differences in costs and outcomes	20 years. This is effectively a lifetime horizon.
Synthesis of evidence on outcomes	Systematic review	Yes. A systematic review and indirect treatment comparison is undertaken for mHSPC and for mCRPC.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	The LATITUDE quality of life data is EQ-5D-5L.
Benefit valuation	Time-trade off or standard gamble	Time trade off.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	The LATITUDE EQ-5D -5L data is cross walked to EQ-5D-3L using the van Hout et al[56] algorithm which the company describes as being recommended by the DSU. The ERG assumes this is valued using the UK social tariff, but omitted to ask this during clarification. The company has commissioned a stand-alone TTO study that estimates how much worse the quality of life for those in the

		DOC+ADT arm is compared to those in the ADT arm.
Discount rate	An annual rate of 3.5% on both costs 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 outputs of the TA387[31] model that are used as inputs to the MSM/TA387 model of the base case are not treated probabilistically.
Sensitivity analysis		A range of univariate sensitivity analyses and scenario analyses are presented by the company. No scenario analyses limiting the duration of effect as per section 5.1.16 of the NICE methods guide are provided.

The company outline that all other companies submitting in the area have adopted a partitioned survival analysis. The company model is a quite complex Markov model. It is also unusual in having the option of applying the curves outputted by discrete event simulation model of TA387 for mCRPC as, in a sense, axiomatic inputs to the current model.

The model that is based upon the MSM analysis of the LATITUDE data augmented with clinical data from the COU-AA-302 trial will be referred to as the MSM model. The model that is based upon the MSM analysis of the LATITUDE data that also uses the output of TA387 DES model as inputs will be referred to as the MSM/TA387 model.[31] The company chooses the MSM/TA387 model for its base case.[31]

The ERG raise a number of issues with the current company model. The ERG is particularly concerned about the handling of the costs and benefits of 1st line treatment for mCRPC among patients who have progressed from their mHSPC. These are central to the cost effectiveness estimates because for AAP+ADT they provide net cost offsets to the mHSPC abiraterone drug costs.

The ERG have not attempted to address its concerns about the handling of 1st line mCRPC costs and benefits. To do so requires extensive remodelling to the extent that the major part of the model would be an ERG model rather than a company model. Moreover, it is not responsibility of the ERG to conduct such extensive remodelling.

There are some minor issues which do not much affect the current cost effectiveness estimates. These are only briefly alluded to in order to highlight the issues to the company. The issues are more simply understood through the ERG revised company model, which contains full cell referencing.

The company base case relies upon rPFS as the definition of progression. The company model also contains an option to define progression as time to subsequent therapy. The company place relatively little stress on this option. Given time constraints the ERG have not much reviewed it and has not rebuilt the model underlying it. The cost effectiveness estimates of the model that uses time to subsequent therapy as the measure of progression are more favourable for AAP+ADT than those of the company base case which uses rPFS as the measure of progression.

5.2.2 Model structure

The following covers the modelling of AAP+ADT and ADT. The modelling of DOC+ADT essentially applies the hazard ratios of the company mHSPC ITC for DOC+ADT compared to AAP+ADT to the AAP+ADT probabilities, as described in greater detail at the end of this subsection.

The company develop a *de-novo* Markov model with a weekly cycle for the 1st year and a four weekly cycle thereafter. This has three main health states:

- Progression free survival (rPFS) when patients are in mHSPC;
- Post progression survival when patients are in mCRPC; and,
- Dead.

On the basis of differences in the cumulative log hazard plots for rPFS and overall survival (OS) in the LATITUDE trial data, the company apply the LATITUDE Kaplan Meier rPFS and OS curves for the first 5 months of the model. Subsequent to the first 5 months the transition probabilities between these health states are derived from a multi-state model (MSM) statistical analysis of the post 5 months LATITUDE trial IA1 data.

The model also requires that post progression, or mCRPC, survival be split into:

- Pre 1st line treatment for mCRPC;
- On 1st line treatment for mCRPC;
- Off 1st line treatment and prior to 2nd line treatment for mCRPC;
- On 2nd line treatment for mCRPC; and,
- On 3rd line treatment for mCRPC.

Within this, 1st line treatment for mCRPC is assumed to be largely composed of active treatment, though a small proportion who are "On treatment" only receive BSC. Larger proportions only receive BSC at 2nd line, while at 3rd line virtually all patients are assumed to only receive BSC.

For the MSM model the mCRPC survival is derived from the LATITUDE MSM probabilities. The arm specific probabilities of moving from mCRPC onto 1st line treatment for mCRPC are derived from the mean treatment free intervals in the LATITUDE trial. The other probabilities that split up mCRPC survival are based upon mean times estimated from COU-AA-302 trial data.

The company argue that treatments for mCRPC during the LATITUDE trial do not reflect UK practice. As a consequence, the LATITUDE data do not reflect the relevant mCRPC survival or the probabilities splitting up PPS survival. The company model has the option to model mCRPC survival and time on mCRPC 1st line treatment using the modelled survival and discontinuation curves of the discrete event simulation that the company presented for TA387. This is the MSM/TA387 model.[31]

The TA387 model yields a mCRPC OS curve and a discontinuation curves for 1st line abiraterone for mCRPC, and a similar pair of curves for 1st line placebo or BSC for mCRPC. The current model applies arm specific proportions of patients whose 1st line mCRPC treatment is abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223 and BSC. For instance, in the DOC+ADT arm no patients receive docetaxel for their mCRPC. For each 1st line active treatment for mCRPC the mCRPC OS hazard ratio for that treatment relative to abiraterone is applied to the abiraterone mCRPC OS curve to estimate that treatment's mCRPC OS curve. The arm specific 1st line mCRPC OS curve is then calculated as a weighted average of the treatment specific and BSC mCRPC OS curves.

For the base case of the MSM/TA387 model, based upon the mCRPC ITC of the company, it is assumed that all 1st line mCRPC active treatments have the same efficacy as abiraterone. This is varied in a sensitivity analysis that applies the central estimates of the mCRPC ITC of the company, [redacted].

The company finds that applying the OS curves derived from the TA387[31] model outputs causes the MSM/TA387 model not to fit the LATITUDE OS Kaplan Meier curves. Survival is overestimated due to the COU-AAP-302 mCRPC patients having a much better prognosis than the LATITUDE mHSPC patients who have progressed to mCRPC. As a consequence, the company estimates an ad hoc 2.62 hazard ratio, or "*conversion factor*", that when applied to the modelled mCRPC OS curves derived from the TA387 model minimises the difference between the MSM/TA387 model outputs and the unweighted LATITUDE OS Kaplan Meier curves.

In essence, the MSM/TA387 model coupled with the ad hoc 2.62 hazard ratio is a complicated, non-statistical way of fitting curves to the LATITUDE OS Kaplan Meier data. The MSM model and the MSM/TA387[31] model with the 2.62 hazard ratio adjustment estimate similar OS curves during the period of the LATITUDE trial. Survival estimates only really differ between them during the extrapolation period.

While the extrapolated survival curves of the MSM model and the MSM/TA387[31] model differ during extrapolation this is not the main difference between the output of the two models. The two models mainly differ in terms of the proportions of mCRPC survival spent

on 1st line mCRPC treatment, mainly costly active treatments, and spent on 3rd line mCRPC treatment, mainly the somewhat cheaper BSC.

The written submission lacks some detail, but it appears that the MSM model estimates 1st line mCRPC treatment discontinuation from the mean times spent on 1st line mCRPC treatment during the COU-AAP-302 trial.

In the MSM/TA387 model, given the 2.62 hazard ratio adjustment of the mCRPC OS curves, it is no longer sensible to apply the TA387[31] model discontinuation curves. The company revise these discontinuation curves so that the resulting proportions of mCRPC survival spent on 1st line mCRPC treatment are the same as those implied by the unadjusted TA387 model mCRPC discontinuation and OS curves.

For both the MSM model and the MSM/TA387[31] model the probabilities of ceasing 2nd line mCRPC treatment appear to be derived from mean times during the COU-AAP-302 trial. The times spent on 3rd line mCRPC treatment seem to be residuals determined by the modelled OS curves.

The above covers the modelling of the AAP+ADT arm and the ADT arm. The company also model a DOC+ADT arm. This uses the company mHSPC ITC estimates for the hazard ratios of overall survival and progression free survival, with the company choosing to apply these to the probabilities of the AAP+ADT arm. The hazard ratios are applied to the AAP+ADT Kaplan Meier, MSM and LATITUDE derived probabilities as follows:

- rPFS to dead probability: OS hazard ratio
- PPS to dead probability: OS hazard ratio
- rPFS to PPS probability: rPFS hazard ratio
- PPS to 1st line mCRPC treatment probability: rPFS hazard ratio

The mHSPC ITC hazard ratios are not applied to any of the model inputs that are derived from the TA387[31] mCRPC model.

5.2.3 Population

The modelled population reflects that of the LATITUDE trial: mHSPC patients.

5.2.4 Interventions and comparators

For the treatment of mHSPC the company compares three arms:

- AAP+ADT
- ADT
- DOC+ADT

But the comparison is of different treatment sequences. Patients who progress from mHSPC to mCRPC receive different treatments for their mCRPC depending upon which of the three mHSPC treatment arms they have come from.

In what follows AAP+ADT, ADT and DOC+ADT will refer to the three mHSPC treatment arms. However, docetaxel for mHSPC is only received for a maximum of 6 treatment cycles of 3 weeks each. For both costs and QALYs it is necessary to distinguish between mHSPC patients who are still receiving their course of docetaxel, DOC+ADT on docetaxel patients, and mHSPC patients who have completed their course of docetaxel and so are only receiving ADT, ADT (post DOC+ADT).

5.2.5 Perspective, time horizon and discounting

A 20 year time horizon, which is effectively a lifetime horizon, is applied. The perspective and discounting is as per the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness: mHSPC

For the first 5 months of the model, due to the LATITUDE log cumulative hazard plots varying as shown in Figures 26 and 27 of Document B of the submission, the model applies the Kaplan Meier OS and rPFS curves for AAP+ADT and ADT.

Thereafter the transition probability matrices estimated through a multi-state modelling analysis of the LATITUDE post 5 month data are applied.

The model requires that arm specific probabilities of moving from PPS pre-1st line mCRPC treatment to 1st line mCRPC treatment be derived. The company state that it was not possible to derive these within the MSM analysis as it failed to converge. Instead, the company derive these from the mean treatment free period in LATITUDE. The base case uses the mean

treatment free interval among patients who progressed during LATITUDE[a]. The company supply an additional scenario analysis at clarification that restricts this estimate to patients with data for both progression and receipt of 1st line treatment for mCRPC.

Table 28 Mean months mCRPC treatment free: LATITUDE

	AAP+ADT	ADT
rPFS patients	[redacted]	[redacted]
weekly probability	[redacted]	[redacted]
rPFS/TTST patients	[redacted]	[redacted]
weekly probability	[redacted]	[redacted]

The probabilities of moving from PPS pre-1st line mCRPC treatment to 1st line mCRPC treatment are subtracted from the MSM probabilities of remaining in PPS.

The DOC+ADT probabilities are estimated by applying the hazard ratios of the company mHSPC ITC as follows:

- OS hazard ratio of 1.09 applied to:
  - rPFS to dead probability:
  - PPS to dead probability
- rPFS hazard ratio of 1.32 applied to:
  - rPFS to PPS probability:
  - PPS to 1st line mCRPC treatment probability

This results in the following weekly transition probability matrices.

Table 29 Base case weekly TPMs: AAP+ADT

From \ To	rFPS	PPS Pre-Tx	PPS 1st line Tx	Dead
rPFS	[redacted]	[redacted]	[redacted]	[redacted]
PPS Pre-Tx		[redacted]	[redacted]	[redacted]
PPS 1st line Tx			[redacted]	[redacted]
Dead				[redacted]

[a] The company supplied a minor correction to this at clarification with an amended model. It appears not to have applied this correction to the final model submitted upon which the cost effectiveness estimates are based. Consequently the ERG retains the original estimates. This has minimal impact on results.

Table 30 Base case weekly TPMs: AAP+ADT

From \ To	rFPS	PPS Pre-Tx	PPS 1st line Tx	Dead
rPFS	[redacted]	[redacted]	[redacted]	[redacted]
PPS Pre-Tx		[redacted]	[redacted]	[redacted]
PPS 1st line Tx			[redacted]	[redacted]
Dead				[redacted]

Table 31 Base case weekly TPMs: DOC+ADT

From \ To	rFPS	PPS Pre-Tx	PPS 1st line Tx	Dead
rPFS	[redacted]	[redacted]	[redacted]	[redacted]
PPS Pre-Tx		[redacted]	[redacted]	[redacted]
PPS 1st line Tx			[redacted]	[redacted]
Dead				[redacted]

The probability of dying from PPS is similar for AAP+ADT and ADT. An anomaly arises in the application of the ITC OS HR of 1.09 for DOC+ADT, this resulting in a higher probability of dying from PPS than either AAP+ADT or ADT.

When the model changes to a 4-weekly cycle the probabilities off the principal diagonal are calculated as 1-(1-p)^4, with the principal diagonal being a residual so that the rows sum to 100%.

The MSM/TA387[31] model does not apply the transition probabilities for 1st line mCRPC treatment. When reviewing the above TPMs this is better seen as an absorbing health state which is then modelled separately through the TA387 model output 2.62 hazard rate adjusted OS and discontinuations curves.

Treatment effectiveness: mCRPC

For the MSM model the LATITUDE TPMs are applied, with the probabilities of discontinuing 1st line mCRPC treatment and moving onto 2nd line mCRPC treatment apparently[b] being derived from COU-AAP-302 mean treatment times.

[b] Based upon references given in the electronic model.

For the MSM/TA387 model the LATITUDE TPMs are mostly applied with the exception of those for 1st line mCRPC treatment which can be seen as being an absorbing state. These patients are then separately modelled using the TA387 model estimated OS curves and discontinuation curves. The TA387[31] model output OS and discontinuation curves are assumed to apply to 1st line mCRPC treatment with abiraterone and 1st line mCRPC treatment with placebo or BSC. The current model applies arm specific proportions of patients whose 1st line mCRPC treatment is abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223 and BSC. The OS curves for these 1st line mCRPC treatments is estimated using their mCRPC OS hazard ratio relative to 1st line abiraterone for mCRPC, applied to the 1st line abiraterone for mCRPC OS curve. The arm specific mCRPC OS curve is then estimated as the arm specific weighted average of the active and BSC 1st line mCRPC OS curves.

The company undertake a comparison of treatments' effectiveness for mCRPC as reviewed in the clinical effectiveness section above, the estimates of which are replicated below.

Table 32 Company hazard ratios for mCRPC

	Unadjusted	Adjusted
Overall Survival HR abiraterone versus:		
Radium-223	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
rPFS HR abiraterone versus:		
Radium-223	[redacted]	
Enzalutamide	[redacted]	

[redacted]. The company assume that the active treatments for 1st line mCRPC have identical OS curves. The company model contains the facility to apply the central estimates for the OS hazard ratios to the adjusted TA387 model estimated OS curve for abiraterone.[31]

The individual treatments' 1st line mCRPC OS curves are weighted according to the following proportions, derived from an expert panel. The model also permits the LATITUDE proportions observed at IA1 to be applied in a scenario analysis. For the LATITUDE scenario

the proportions for DOC+ADT are assumed to be those of ADT, only with the ADT docetaxel use being set to zero and these patients distributed equally between abiraterone and enzalutamide in the DOC+ADT arm.

Table 33 1st line mCRPC treatment proportions

	Base Case			LATITUDE		
	AAP+ADT	ADT	DOC+ADT	AAP+ADT	ADT	DOC+ADT
BSC	10%	5%	5%	35%	25%	25%
Enzalutamide	..	35%	39%	10%	13%	39%
AAP	..	35%	39%	3%	9%	34%
Docetaxel	60%	15%	..	51%	51%	..
Cabazitaxel	..	..	12%	1%	..	..
Radium-223	30%	10%	5%	1%	2%	2%

Applying the TA387 DES model OS curves as described above within the MSM/TA387[31] model results in OS curves that are not aligned with the LATITUDE KM OS curves. As a consequence, the company fit the MSM/TA387 model OS curves to the LATITUDE KM OS curves by estimating an ad hoc OS hazard ratio for LATITUDE mCRPC patients compared to the TA387 model output OS curves. This 2.62 hazard ratio or "*conversion factor*" is arrived at by minimising the sum of the differences between the MSM/TA387 model OS curves and the LATITUDE KM OS curves.

The LATITUDE KM OS curves, the MSM model OS curves, the unadjusted MSM/TA387 model OS curves (labelled "*No CF*") and the MSM/TA387 OS curves fitted to the LATITUDE KM OS curves using the 2.62 hazard ratio (labelled "*Base*") are as below.

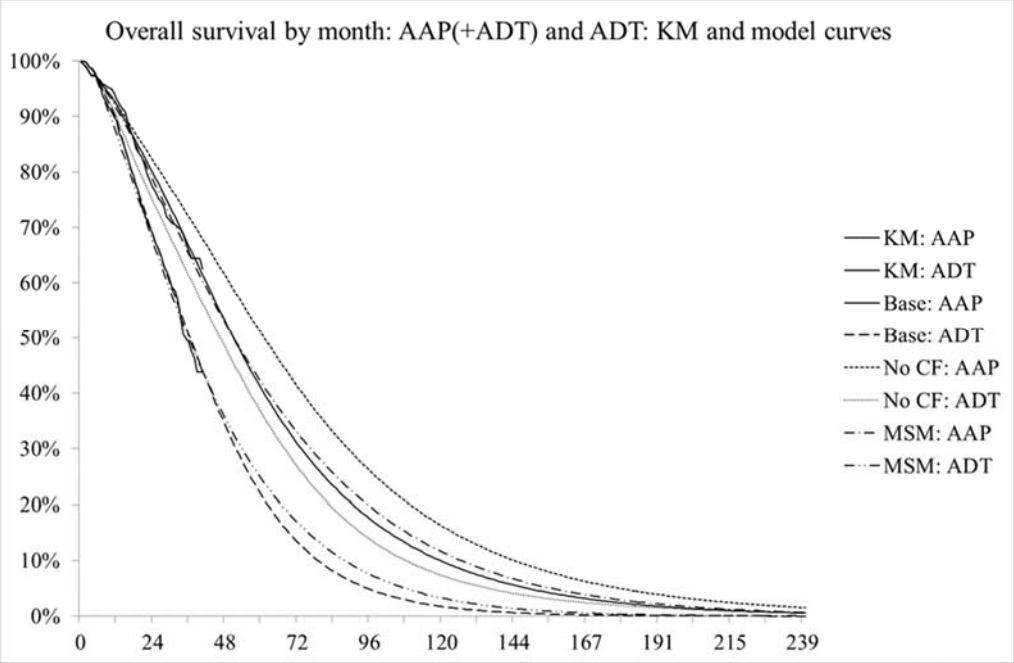


Figure 4 MSM model, MSM/TA387 model and LATITUDE KM OS curves

The above shows the poorness of fit of the original MSM/TA387[31] OS curves to the LATITUDE KM OS curves. Adjusting them by the ad hoc hazard ratio of 2.62 necessarily fits them to the LATITUDE KM OS curves. However, the separation between the AAP+ADT and the ADT 2.62 hazard ratio adjusted curves is also aligned with the separation between the LATITUDE KM OS curves, which is not a necessary result of the method used to fit the curves. This could be used to argue that LATITUDE patients who progress to mCRPC have a 2.62 hazard ratio of survival compared to the modelled curves of the TA387 model,[31] and so in turn to a greater or lesser extent to the mCRPC patients of the COU-AAP-302 trial.

The above also illustrates that the MSM model and the MSM/TA387[31] model estimate near identical OS curves during the period of LATITUDE. These only really diverge during extrapolation. The MSM model OS curves lie above those of the MSM/TA387 model OS curves, but with this applies less to AAP+ADT than to ADT. Consequently, the MSM model estimates a smaller survival gain from AAP+ADT over ADT than does the MSM/TA387 model.

Adjusting the TA387 modelled mCRPC OS curves by the 2.62 hazard ratio requires that the TA387 modelled mCRPC discontinuation curves also be adjusted. The company assume that

the adjusted mCRPC discontinuation curves are the same proportions of the adjusted mCRPC OS curves as in the originally modelled unadjusted TA387 mCRPC curves.

Extrapolation

The TPMs and curves as described above are applied to the end of the 20 year time horizon, effectively a lifetime horizon.

As far as the ERG can ascertain, the sum of

- the 1st line mCRPC incident patients
- minus the sum of 1st line mCRPC patients who have discontinued
- minus the sum of 1st line mCRPC patients who have died

leaves a residual that provides an estimate of those who have received 1st line treatment but are no longer receiving it. This in turn provides an estimate of the incidence of those coming off 1st line mCRPC treatment. A portion of these incident patients are assumed to receive 2nd mCRPC line treatment which appears to be based upon mean treatment times subsequent to 1st line treatment in the COU-AAP-302 trial. The proportion of patients receiving 3rd line mCRPC treatment appears to be the residual implied by the mCRPC OS curve.

The treatment proportions for 2nd line and 3rd line mCRPC have no effect upon clinical outcomes but do determine the QALYs and costs that are applied at these stages of the model.

Table 34 2nd line mCRPC treatment proportions

	Base Case			LATITUDE		
	AAP+ADT	ADT	DOC+ADT	AAP+ADT	ADT	DOC+ADT
BSC	65%	45%	60%	84%	75%	75%
Enzalutamide	..	10%	5%	4%	8%	10%
AAP	..	10%	5%	1%	4%	7%
Docetaxel	..	10%	..	3%	5%	..
Cabazitaxel	15%	5%	5%	4%	5%	5%
Radium-223	20%	20%	25%	3%	2%	2%

Table 35 3rd line mCRPC treatment proportions

	Base Case			LATITUDE		
	AAP+ADT	ADT	DOC+ADT	AAP+ADT	ADT	DOC+ADT
BSC	90%	90%	95%	96%	91%	91%
Enzalutamide	..	..	..	1%	2%	3%
AAP	..	..	..	1%	2%	3%
Docetaxel	..	..	..	1%	1%	..
Cabazitaxel	2%	1%	1%	1%	2%	2%
Radium-223	8%	9%	4%	1%	1%	1%

5.2.7 Health related quality of life

Reports of HRQOL and utility data were sought by the company by searching MEDLINE AND EMBASE (via Embase.com), MEDLINE In-Process (vis Pubmed), NHS Economics Evaluation Database (NHS EED) and HTA Database (via Cochrane Library) in September 2015 and updated in July 2017. The searches were restricted to studies published between 2005-2017and restricted to English language publications

The search strategies are documented in full in Appendix H and are reproducible however the company conducted the MEDLINE and EMBASE searches using the EMBASE.com platform which is not accessible to the ERG.

The MEDLINE and EMBASE searches combined three search facets using the Boolean operator AND: prostate cancer; abiraterone or comparator; and HROL terms. The search strategies were considered fit for purpose, including both relevant

mHSPC quality of life values: AAP+ADT and ADT

EQ-5D-5L quality of life data was collected during LATITUDE at baseline, monthly from cycles 2-13 and every 2 months thereafter until radiographic or clinical progression of disease, at the end of study treatment, and every four months until 60 months, death, loss to follow up, withdrawal or death.

The company examined the LATITUDE EQ-5D-5L data, cross walked to EQ-5D-3L, to estimate quality of life values relationship with individual variables. These were considered for inclusion in a multivariate repeated measures mixed effect model if they had a p-value of 10% or less. The list of predictors used to derive the most appropriate utility regression equation was guided by clinical opinion, identifying the factors most likely to influence patients' HRQL, and on information from prior submissions in the mCRPC setting. This may be the reason for the exclusion of the subsequent treatment variable and the off treatment

variable from the multivariate analysis despite their p values being less than 10%. Correlation between the variables was then tested, resulting in the cycle number variable being excluded from the regression as this was found to be highly correlated with other time-dependent variables. The variables for AEs and SREs were separated out by treatment line due to possible differences between the two treatments. The univariate regression and the base case multivariate regression are as below.

Table 36 LATITUDE Regressions: univariate and base case multivariate

	Univariate (s.e.)		Multivariate (s.e.)	
Age	[redacted]	[redacted]		
Baseline EQ5D	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent Tx	[redacted]	[redacted]	[redacted]	[redacted]
Intercept			[redacted]	[redacted]
Off treatment	[redacted]	[redacted]	[redacted]	[redacted]
rPFS	[redacted]	[redacted]	[redacted]	[redacted]
AAP+ADT Tx	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]
SAE | AA			[redacted]	[redacted]
SAE | PBO			[redacted]	[redacted]
SRE	[redacted]	[redacted]	[redacted]	[redacted]
SRE | AA			[redacted]	[redacted]
SRE | PBO			[redacted]	[redacted]
Cycle No.	[redacted]	[redacted]	[redacted]	[redacted]

To estimate quality of life values based on the above requires that the arm specific proportions of time spent having had an SAE and having had an SRE are applied: [redacted] and [redacted] for AAP+ADT and [redacted] and [redacted] ADT respectively. Taken together these result in quality of life decrements for SAEs and SREs of [redacted] for AAP+ADT and [redacted] for ADT.

The company base case does not apply the LATITUDE quality of life decrements for SAEs and SREs. The company derive a range of estimates of quality of life decrements associated with 14 SAEs and for grouped SREs, and couple these with various durations to arrive at QALY decrements. Then they apply these to rates derived from LATITUDE for AAP+ADT and for ADT and from the literature for DOC+ADT. This results in an estimated quality of life decrement for SAEs and SREs of [redacted] for mHSPC in all three arms. This decrement is an order of magnitude less than the decrements of the LATITUDE regression. It substitutes

for them, thereby raising the quality of life values of the model above those observed during LATITUDE.

The company assume that the quality of life for DOC+ADT is as per that of AAP+ADT, but with the additional decrements outlined below.

mHSPC quality of life decrements: DOC+ADT

Due to there being no quality of life values directly attributable to DOC+ADT the company commission a quality of life study from MAPI values[c]. This concludes that, among those remaining in rPFS, on average the quality of life among those receiving docetaxel for their mHSPC and among those who have received docetaxel for their mHSPC but are now only receiving ADT is unambiguously worse than that of patients who have only ever received ADT. The worse quality of life post docetaxel use is due to depression.

Health state vignettes are developed with the aid of clinical opinion, and valued using TTO and VAS by 200 members of the general public, 88 male and 112 female, recruited through "*a panel of the general public that had expressed an interest in participating in research, members of the public responding to an advert, and snowballing/word-of-mouth*." This results in the following estimates.

Table 37 Mean values of QoL study

	VAS	(s.e.)	TTO	(s.e.)
ADT	[redacted]	[redacted]	[redacted]	[redacted]
DOC+ADT	[redacted]	[redacted]	[redacted]	[redacted]
ADT (post DOC+ADT)	[redacted]	[redacted]	[redacted]	[redacted]

The VAS and the TTO values are noticeably different, but the ratios between them are more aligned. A repeated measures GEE analysis found the cubes of the TTO estimates for the three main health states to be statistically significantly different[d].

[c] This also informs some of the adverse event quality of life values.

[d] This did not use the raw TTO values but rather used the cubes of the TTO values on grounds of skew in the data.

The company base case uses the TTO values to derive a QoL decrement for those receiving docetaxel treatment for mHSPC, DOC+ADT on treatment, of [redacted] compared to ADT and a QoL decrement for those who have finished their course of docetaxel treatment for mHSPC, ADT (post DOC+ADT), of [redacted] compared to ADT.

mCRPC quality of life values

The mCRPC quality of life values similarly ignore the LATITUDE regression decrements for SAEs and SREs and use the somewhat smaller decrements derived from the literature. These are coupled with the LATITUDE quality of life regression decrement for progression to yield the quality of life estimate for those who have progressed but are yet to receive 1st line mCRPC treatment. Those receiving mCRPC treatments have additional quality of life adjustments for treatment specific SAEs and SREs rates.

The quality of life increment of 0.02 from TA387[31] is applied to those who receive abiraterone for their mCRPC in the ADT arm and DOC+ADT arm.

The TTO quality of life decrements for those who receive docetaxel for their mCRPC are not applied in the AAP+ADT arm or the ADT arm.

The quality of life values for 2nd line mCRPC and 3rd line mCRPC are assumed to be proportionate to the values that would apply were the treatment mix being received for 1st line mCRPC. These proportions are based upon the 0.830, 0.625 and 0.500 values used in TA387 resulting in ratios of 75% and 60%.

Quality of life values: summary

The quality of life values that apply within the model are as below.

Table 38 Modelled quality of life values

	ADT+ADT	ADT	DOC+ADT
mHSPC	[redacted]	[redacted]	[redacted]
mHSPC ADT (post DOC+ADT)			[redacted]
mCRPC Pre 1st line mCRPC Tx	[redacted]	[redacted]	[redacted]
1st line mCRPC Tx	[redacted]	[redacted]	[redacted]
1st line mCRPC Off Tx	[redacted]	[redacted]	[redacted]
2nd line mCRPC Tx	[redacted]	[redacted]	[redacted]
3rd line mCRPC Tx	[redacted]	[redacted]	[redacted]

5.2.8 Resources and costs

Drug and administration costs: mHSPC

The direct drug costs are largely estimated from BNF coupled with SmPC dosing.[22] The costs for abiraterone include the commercial access arrangement, but the costs for enzalutamide, cabazitaxel and radium-223 do not include their respective patient access schemes. Dosing reflects pack size and duration, and the resulting wastage among patients who come off treatment.

The cost per docetaxel dose uses a methods of moments to calculate the distribution of LATITUDE patient BSAs and thereby the number of 20mg and 80mg docetaxel vials that would be required for the LATITUDE patient group[e]. Based upon eMIT vial costs of £3.85 and £14.74 for 80mg this results in an average cost per dose of £28.04. Using the LATITUDE patient group BSA distribution results in the same £28.04 average cost.

A compliance ratio for abiraterone for mHSPC of [redacted] is calculated from LATITUDE data, and applied to the direct drug costs.

Cycle completion rates for the six cycles of docetaxel of 96%, 93%, 91%, 89%, 85% and 84% are drawn from James et al[57] and Sweeney et al[21] and applied to the £28 docetaxel drug cost per cycle. These completion rates are not applied to the £260 chemotherapy administration cost per cycle.

[e] The cost per cabazitaxel dose for mCRPC uses the same method of moments, estimating that 0.7% of patients have a BSA of at least 4.8m^2 and so require two 60mg vials per dose. With a list price of £3,696 this results in an average cost per dose of £3,722. Using the LATITUDE patient group BSA distribution suggests marginally more, 1.1%, of patients requiring two 60mg vials and an average cost per dose of £3,736.

ADT use is assumed to be equally balanced between goserelin, leuprorelin and triptorelin, with 30% of these patients also receiving bicalutamide. The average cost per injection is assumed to be £42, with a quarter of patients incurring this cost.

Planned medical resource use (MRU): mHSPC

The submission provides limited detail of the planned MRU for treatments, though notes that it is based upon a questionnaire completed by 5 clinicians, who also subsequently attended an advisory board. The electronic model contains the following planned MRU per 4 week period for mHSPC.

Table 39 Planned mHSPC MRU: clinical advisory board

		AAP+ADT		DOC+ADT		
	Cost	<3 mth	3 mth+	≤18 Wks	18+ Wks	ADT
Oncologist visit	£101	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FBC	£3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CT scan	£123	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone scan	£292			[redacted]	[redacted]	
PSA	£7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testosterone	£1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver function test	£1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kidney function test	£1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 weekly cost		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual cost		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.15=26 wkly, 0.22=18 wkly, 0.25=16 wkly, 0.33=12 wkly 0.44= 9 wkly, 0.67=6 wkly, 1.33=3 wkly						

The above outlines how the planned MRU for AAP+ADT lessens at 3 months, in line with the SmPC. Similarly, for DOC+ADT the planned MRU lessens after 18 weeks and completion of the docetaxel course so as to be similar to that for ADT. This is with the exception of CT scan and bone scans which are both more frequent for DOC+ADT than in the other arms and increase in frequency for DOC+ADT after 18 weeks.

Unplanned MRU, SAE and SRE costs: mHSPC

For mHSPC the company derive unplanned annual MRU frequencies from the LATITUDE trial as below. DOC+ADT is assumed to incur the same unplanned MRU as AAP+ADT.

Table 40 Unplanned medical resource use: mHSPC

	Unit cost	AAP+ADT	ADT
Radiotherapy procedure	£101	[redacted]	[redacted]
Radiotherapy preperation	£288	[redacted]	[redacted]
MRI	£180	[redacted]	[redacted]
CT scan	£120	[redacted]	[redacted]
X-ray	£171	[redacted]	[redacted]
Hospitalisation	£307	[redacted]	[redacted]
Oncologist	£173	[redacted]	[redacted]
Urologist	£103	[redacted]	[redacted]
Surgery	£12,778	[redacted]	[redacted]
Emergency room	£148	[redacted]	[redacted]
General practitioner	£38	[redacted]	[redacted]
Annual cost		£1,192	£1,513

This is augmented with the adverse event frequencies taken from the LATITUDE trial for AAP+ADT and ADT, and from Gravis et al[58] for DOC+ADT which result in additional annual costs of around £630, £580 and £1,105 respectively. The higher cost for DOC+ADT is due to 32% having neutropenia which may be reasonable to apply to those receiving docetaxel but may be less reasonable to those who have completed their course of docetaxel: ADT (post DOC+ADT) patients.

mCRPC drug and administration costs

The 1st line mCRPC compliance ratios for abiraterone and enzalutamide are assumed to be 100%[f]. This seems appropriate due to the curves that they are applied to being labelled discontinuation curves. However, for docetaxel, cabazitaxel and radium-223 the company uses treatment completion rates to estimate compliance rates of 73%, 64% and 79%. Given the discontinuation curves these are applied to, they underestimate the direct drug costs of docetaxel, cabazitaxel and radium-223 for 1st line mCRPC.

As far as the ERG can ascertain, the 1st line mCRPC treatment costs are calculated as the prevalent 1st line mCRPC on treatment population multiplied by a time invariant arm specific

[f] As reviewed later, an adjustment is applied to the costs of abiraterone for 1st line mCRPC with the intention of allowing for the [redacted], but this has little to no effect and can be ignored.

weekly treatment cost[g]. These are then qualified by whether the model cycle is during the 1st year, so 1 week long, or subsequent to this, so 4 weeks long. The treatment costs relate to those who are on treatment and incurring costs. This will not address the time dependent profiles[h] of:

- Abiraterone costs, [redacted]
- Docetaxel costs, due to a maximum of 10 cycles of 3 weeks
- R-223 costs, due to a maximum of 6 treatments separated by 4 weeks
- Cabazitaxel costs, due to a maximum of 10 cycles of 3 weeks

Planned medical resource use: mCRPC

The planned MRU for mCRPC is outlined below. The unit costs that are applied are the same as for mHSPC, these being omitted below for reasons of space.

Table 41 Planned mCRPC MRU: clinical advisory board

	AAP	DOC	ADT	ENZA	R-223	CABA
Oncologist visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FBC	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
CT scan	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Bone scan	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
PSA	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Testosterone	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Liver function test	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Kidney function test	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
4 weekly cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Applied cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.15=26 wkly, 0.22=18 wkly, 0.25=16 wkly, 0.33=12 wkly 0.44= 9 wkly, 0.67=6 wkly, 1.33=3 wkly						

For reasons that are not given the company have not used the values of the clinical advisory board but have rather assumed that the planned MRU for mCRPC is equal between abiraterone and enzalutamide, and between docetaxel, R-223 and cabazitaxel. Applying the values of the clinical advisory board has minimal impact upon results.

[g] The drug cost is actually split into AAP drug costs and non-AAP drug costs with the former being qualified by the incorrect adjustment factor for the AAP cycle cap, but this can be ignored for present purposes.
[h] If as seems reasonable the same docetaxel quality of life decrements should be applied for mCRPC as for mHSPC, the time dependent profile of this will also have to be taken into account.

The values for abiraterone, ADT and docetaxel for mCRPC differ from those for mHSPC. However, while the frequencies of bone scans and CT scans increases for abiraterone, the frequencies of these for docetaxel increase by a similar amount.

The values for abiraterone are not differentiated for being prior to and subsequent to 3 months. The values for docetaxel are not differentiated for being up to and subsequent to 30 weeks, up to 10 cycles being recommended for mCRPC compared to up to 6 cycles for mHSPC.

Unplanned MRU, SAE and SRE costs and QALYs: mCRPC

For mCRPC a common annual unplanned MRU cost of £1,125 is taken from TA387, and is coupled with treatment specific SAE and SRE rates to suggest the following annual cost and quality of life effects for the mCRPC treatments.

Table 42 Unplanned MRU, SAE and SRE costs and QALYs: mCRPC

	AAP	ENZA	DOC	CABA	R-223	BSC
QoL	-0.003	-0.001	-0.004	-0.006	-0.001	0.000
Cost	£1,404	£1,286	£1,750	£2,573	£1,461	£1,125

The values applied in the AAP+ADT, ADT and DOC+ADT arms are the weighted average of these amounts.

5.2.9 Cost effectiveness results

The cost estimates of the revised company base case are as below.

Table 43 Company base case cost breakdown

	AAP+ADT	ADT	DOC+ADT
mHSPC			
Drug	[redacted]	[redacted]	[redacted]
Admin	£341	£244	£1,760
mCRPC Drug and Admin			
mCRPC: 1st line	£9,109	£16,525	£18,304
mCRPC: 2nd line	£245	£364	£309
mCRPC: 3rd line	£1,322	£1,396	£697
Other			
MRU	£20,104	£15,058	£19,533
AEs	£2,446	£1,440	£2,090
Total	[redacted]	[redacted]	[redacted]

There are large additional drug costs in the AAP+ADT arm for mHSPC, but there are also quite large cost offsets for 1st line mCRPC. The 1st line mCRPC drug and administration costs provide an offset of £7,416 for the comparison with ADT and £9,195 for the comparison with DOC+ADT. This highlights the importance of the choice of which active treatments are received for 1st line mCRPC. The choice of the lower cost DOC+ADT as the main 1st line mCRPC treatment in the ADT+AAP arm is the principal reason for the size of these cost offsets, though it has no effect upon patient outcomes in the company base case[i].

The company base case results are as follows. Note that the net amounts and ICERs are for AAP+ADT versus the comparator.

Table 44 Company base case: deterministic

	LYs	QALYs		Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	4.993	3.420		[redacted]				
ADT	3.430	2.325		[redacted]	1.563	1.095	£19,066	£17,418
DOCE	4.322	2.824		[redacted]	0.672	0.596	£10,618	£17,828

ADT is estimated to result in an undiscounted overall survival of 3.43 year, with AAP+ADT extending this by 1.56 years to 4.99 years. A patient gain of 1.09 QALYs is anticipated but

[ii] There is an insignificant effect upon quality of life due to adverse events.

costs for AAP+ADT are £19,066 higher. The cost effectiveness of AAP+ADT against ADT is estimated to be £17,418 per QALY.

DOC+ADT is estimated to result in an undiscounted overall survival of 4.32 year, with AAP+ADT extending this by 0.67 years. A patient gain of 0.60 QALYs is anticipated but costs for AAP+ADT are £10,618 higher. The cost effectiveness of AAP+ADT against AAP is estimated to be £17,828 per QALY.

The probabilistic results are in line with the deterministic results with central estimates of £17,349 per QALY for the comparison with ADT and £18,168 per QALY for the comparison with DOC+ADT[j].

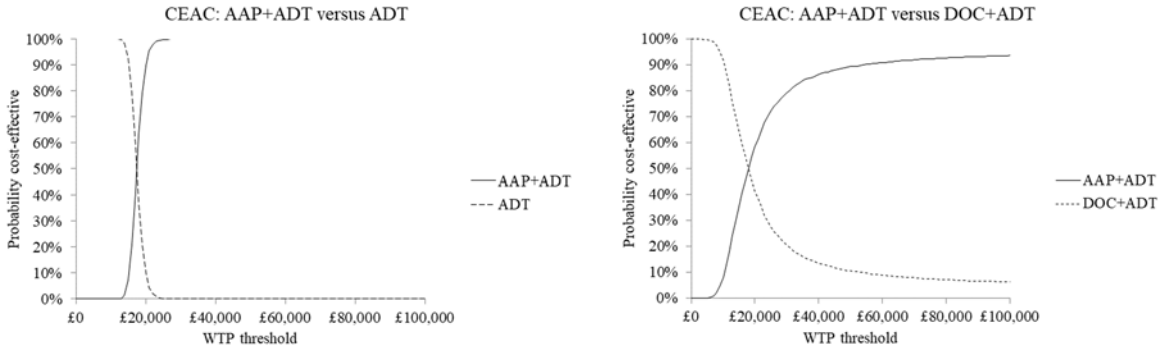


Figure 5 Company base case CEACs

5.2.10 Sensitivity analyses

Company sensitivity analyses

The company present a range of univariate sensitivity analyses, with the tornado diagrams presented as Figures 39 and 40 on page 156 of Document B of the submission and as replicated below. For data with 95% confidence intervals these were used, other parameters being varied by ±10%.

[j] The values relate to the CEACs below, which have been rerun by the ERG. The values are virtually the same as reported in Table 34 of Document B of the company submission.

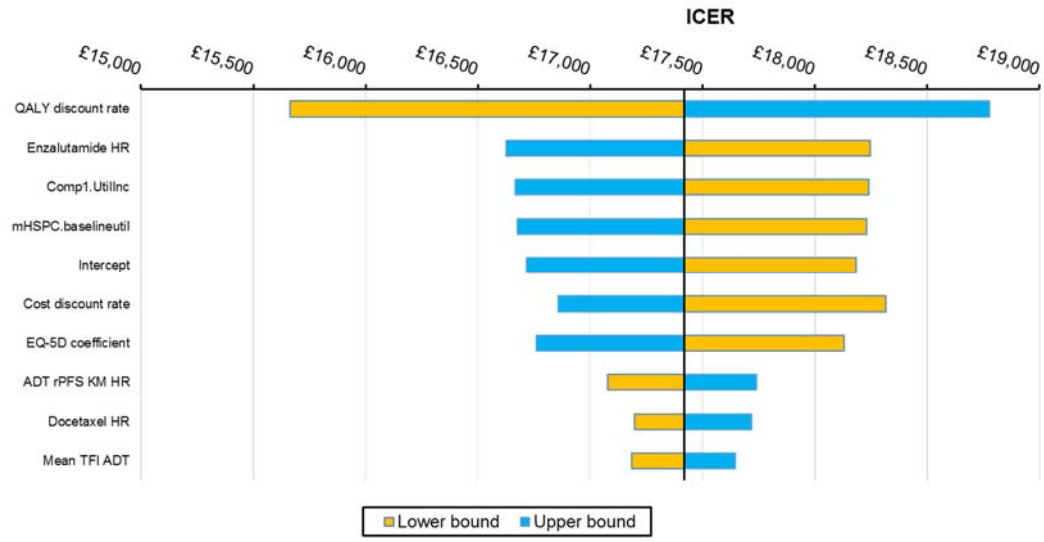


Figure 6 Company sensitivity analyses: AAP+ADT vs ADT

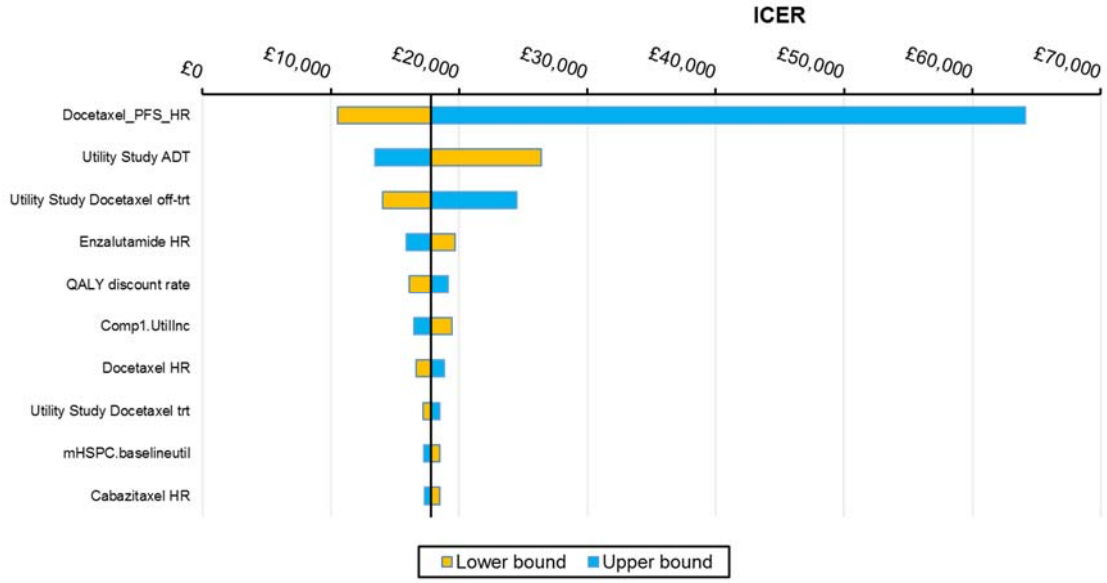


Figure 7 Company sensitivity analyses: AAP+ADT vs DOC+ADT

Company scenario analyses

The company presents a range of scenario analyses as below.

Table 45 Company scenario analyses

Model assumption	Scenario	ICER v ADT	ICER v DOC+ADT
Base Case		£17,418	£17,828
Definition of progression	TTST used as an alternative definition of progression	£14,079	£11,287
Survival and subsequent therapy source	Survival estimates and subsequent therapy market shares estimated from LATITUDE data alone	£21,504	£22,218
ITC	ITC including STAMPEDE	£17,418	£17,813
Time horizon	15 years 10 years 5 years	£17,508 £18,100 £25,856	£18,048 £19,435 £33,085
AA utility increment	Applied until death No increment applied	£16,775 £18,697	£16,656 £20,394
DOC+ADT QoL	On-treatment decrement applied only	£17,418	£20,027
AE disutilities	Using literature values alone Set to zero	£17,414 £17,361	£17,818 £17,578
mCRPC utilities	Assumed constant through mCRPC	£17,508	£17,975
AA increment (mCRPC)	AA increment from TA387 removed during mCRPC	£17,333	£17,667
Subsequent treatment ITC	Different HR are applied for each subsequent Tx based on subsequent therapy ITC	£17,129	£17,095
Vial wastage	Set to zero	£15,997	£15,077
Docetaxel cost source	MIMS price is assumed	£20,273	£16,305
AE/SRE HRQL source	Values sourced from regression	£17,510	£21,389[k]

Results show some sensitivity to:

- the time to subsequent therapy being used as the definition of progression,
- the TA387 curves being rejected in favour of just the LATITUDE MSM TPMs with this being coupled with the LATITUDE mCRPC treatment proportions,
- a time horizon of only 5 years
- applying the abiraterone quality of life increment until death
- the ADT (post DOC+ADT) TTO quality of life decrement
- vial wastage
- applying the LATITUDE QoL regression coefficients instead of a subset

Kaplan-Meier to MSM transition point

At clarification the company presented additional analyses that varied the data time point from which the MSM was performed, and so also varied the cut-off up to which the Kaplan

[kk] There is a typo in Document B of the submission, this being reported as £31,389.

Meier data was applied in the model. The ERG have updated these for the MSM/TA387 model and extended them to the MSM model as below.

Table 46 Scenario analyses around MSM start point: AAP+ADT cost effectiveness

	MSM/TA387 model		MSM model	
KM cut-off	vs ADT	vs DOC + ADT	vs ADT	vs DOC + ADT
4 months	£16,936	£17,180	£19,884	£26,001
5 months (BC)	£17,418	£17,828	£20,438	£26,909
6 months	£17,638	£18,358	£20,636	£27,619
7 months	£17,825	£19,326	£21,001	£28,545

5.2.11 Model validation and face validity check

DOC+ADT vs ADT estimates

The NICE summary of DOC+ADT compared to ADT for mHSPC states that "*In men with hormone-sensitive metastatic prostate cancer at 4 years, estimates based on a meta-analysis of the 3 RCTs (STOpCaP, n=2992)… a 9% absolute improvement in overall survival with docetaxel compared with ADT alone (49% compared with 40%, p<0.0001)… a 16% absolute improvement in time to disease progression with docetaxel compared with ADT alone (treatment failure 64% compared with 80%, p<0.0001)* ".

The company base case predicts survival at 4 years of 47% for DOC+ADT compared to 34% for ADT, so a similar absolute survival for DOC+ADT but somewhat lower for ADT and hence a larger net gain of 13%.

Taking rPFS as the measure of progression the company base case predicts progression at 4 years of 75% for DOC+ADT and 87% for ADT suggesting that the model overestimates progression for both arms and particularly for DOC+ADT.

Linking the OS and rPFS together may suggest that the model overestimates the time that DOC+ADT patients spend in post progression survival. Given the importance of post progression mCRPC costs in the DOC+ADT arm for the company base case, any overestimation of the time spent in post progression in the DOC+ADT arm may of concern.

Additional ERG structural analysis

The company scenario analysis that uses the MSM model rather than the MSM/TA387 model also revises the mCRPC treatment proportions to be those of the LATITUDE trial. The company argument is that the LATITUDE data were generated by these mCRPC treatment

proportions. The results of this scenario analysis can be compared with the results of a parallel scenario analysis, but which retains the mCRPC treatment proportions of the company base case.

Table 47 Company scenario analysis: MSM model

	LYs	QALYs	Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	5.129	3.397	[redacted]				
ADT	3.597	2.302	[redacted]	1.532	1.096	£23,564	£21,504
DOCE	4.365	2.753	[redacted]	0.764	0.644	£14,312	£22,218

Table 48 ERG scenario analysis: MSM model

	LYs	QALYs	Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	5.129	3.397	[redacted]				
ADT	3.597	2.303	[redacted]	1.532	1.094	£22,356	£20,438
DOCE	4.365	2.753	[redacted]	0.764	0.644	£17,329	£26,909

The retention of the treatment proportions of the company base case has no discernible impact upon the clinical outputs of the MSM model. The net survival and net QALYs are almost unchanged. Consequently, in the opinion of the ERG when choosing which source to use for the mCRPC treatment proportions for the MSM modelling this should be driven by the need to accurately reflect the cost composition of UK mCRPC treatment patterns. By the company argument this suggests that the proportions of the company base case should be retained.

The outputs of the MSM model can also be compared with those of the MSM/TA387 model of the company base case.

Table 49 Company base case: MSM/TA387 model

	LYs	QALYs	Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	4.993	3.420	[redacted]				
ADT	3.430	2.325	[redacted]	1.563	1.095	£19,066	£17,418
DOCE	4.322	2.824	[redacted]	0.672	0.596	£10,618	£17,828

The MSM/TA387 model estimates that survival among UK mHSPC patients will be worse than that suggested by the MSM model by around 50 days for AAP+ADT patients, 60 days

for ADT patients and 16 days for DOC+ADT patients. The company MSM/TA387 model consequently suggests a larger survival gain from AAP+ADT compared to ADT but a smaller survival gain from AAP+ADT compared to DOC+ADT than the MSM model.

The net QALYs are virtually the same between the two models for the comparison of AAP+ADT with ADT. However, the net costs improve by 15% and the cost effectiveness estimate correspondingly improves by 15% when using the MSM/TA387 model.

The net QALYs for the comparison of AAP+ADT with DOC+ADT are 7.5% worse with the MSM/TA387 model than with the MSM model. This is dwarfed by the improvement in the net costs of around 40% and the cost effectiveness estimate correspondingly improves by around 35%.

As in the consideration of whether to use the LATITUDE mCRPC treatment proportions or the base case mCRPC proportions within the MSM modelling, the decision whether to use the MSM/TA387 model or the MSM model mainly affects costs. These can be further explored as below.

Table 50 MSM/TA387 and MSM model costs

	MSM/TA387 model			MSM model		
	AAP+ADT	ADT	DOC+ADT	AAP+ADT	ADT	DOC+ADT
mHSPC						
Drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin	£341	£244	£1,760	£348	£253	£1,761
mCRPC Drug and Admin						
mCRPC: 1st line	£9,109	£16,525	£18,304	£3,399	£6,513	£6,527
mCRPC: 2nd line	£245	£364	£309	£2,003	£2,673	£2,160
mCRPC: 3rd line	£1,322	£1,396	£697	£2,429	£2,709	£1,199
Other						
MRU	£20,104	£15,058	£19,533	£19,555	£14,695	£18,924
AEs	£2,446	£1,440	£2,090	£2,405	£1,440	£2,044
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The two models mainly differ in the mCRPC 1st line and 2nd line treatment costs. Both models in the above apply the same company base case mCRPC treatment proportions. Virtually all patients are assumed to receive an active 1st line mCRPC treatment, the majority

are assumed to receive an active 2nd line mCRPC treatment while the vast majority are assumed to only receive BSC at 3rd line.

The MSM/TA387 model estimates very much higher 1st line mCRPC treatment costs than the MSM model. However, the increase is less for AAP+ADT than for ADT, and is considerably less for AAP+ADT compared to DOC+ADT. The MSM/TA387 model estimates that 2nd line mCRPC treatment costs are almost negligible. These costs can be further related to the modelled undiscounted weeks spent in each health state.

Table 51 MSM/TA387 and MSM model health state durations: weeks

	MSM/TA387 model			MSM Model		
	AAP+ADT	ADT	DOC+ADT	AAP+ADT	ADT	DOC+ADT
PFS	189	106	152	189	106	152
mCRPC						
pre 1st line Tx	15	11	12	15	11	12
1st line On Tx	35	41	39	13	16	14
1st line Off Tx	1	1	1	7	8	7
2nd line	1	1	1	8	9	8
3rd line	19	19	19	35	37	34
OS Total	260	178	225	267	187	227

Within the MSM/TA387[31] model patients spend the majority of their post progression mCRPC survival in or around 1st line treatment, with around 35 to 40 weeks being spend on 1st line treatment. When these patients move on to 2nd line mCRPC treatment they are modelled as spending only around 1 week receiving it before moving into 3rd line mCRPC for around 19 weeks. The MSM/TA387 model estimates of 2nd line mCRPC duration do not seem credible.

The MSM model suggests a more evenly balanced period spent on 1st line and 2nd line mCRPC treatment, around 13 to 19 weeks for 1st line and 8 to 9 weeks for 2nd line. It also estimates a longer period at the end of survival spent at 3rd line mCRPC of around 35 weeks.

An alternative way of viewing the above is that the MSM/TA387 model estimates that patients spend around 35-40 weeks on 1st line mCRPC treatment and around 20 weeks at the end of their survival on BSC while the MSM model estimates something close to the reverse.

Fitting parameterised curves to the LATITUDE OS KM data

As noted by the company, all other companies submitting in the area have adopted a partitioned survival analysis. The ERG have not had time to explore this, and to do so would stray too far into advancing an ERG model. As a consequence, the ERG have only explored the fitting of parameterised curves to the LATITUDE OS Kaplan Meier data supplied by the company at clarification.

Up to 5 months survival in the AAP+ADT arm is that bit worse than that in the ADT arm, but is thereafter is superior to it. For an analysis assuming proportionate hazards, as per the company submission Figure 26 log-cumulative hazard plot, there is an argument that this should be restricted to the Kaplan Meier OS data subsequent to 5 months. The ERG explores both (a) using all the Kaplan Meier OS data and (b) restricting it to 5 months plus.
This suggests the following information criteria, with the Weibulls providing the best fit[l].

Table 52 ERG exploratory OS proportionate hazards analyses: information criteria

	Obs	ll(null)	ll(model)	df	AIC	BIC
All KM OS data						
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5mth+ KM OS data						
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The resulting Weibulls are as below.

[l] Analyses available to the company on request.

Fitting Weibulls with proportionate hazards between the arms, i.e., a common shape parameter, to all the Kaplan Meier OS data compared to just the post 5 months Kaplan Meier OS data has a reasonable effect on the extrapolated survival gains, and in particular the net gain from AAP+ADT over ADT.

Table 53 ERG's exploratory OS proportionate hazards analyses: survival estimates

	AAP+ADT	ADT	Net
Kaplan Meier "month" = 1/12 year			
All data	[redacted]	[redacted]	[redacted]
5mth +	[redacted]	[redacted]	[redacted]
Kaplan Meier "month" = 4 weeks			
All data	[redacted]	[redacted]	[redacted]
5mth +	[redacted]	[redacted]	[redacted]

The treatment of the Kaplan Meier data in the electronic model suggests that within the Kaplan Meier data a month relates to a calendar month[m]. This is not obviously the case, but if applied to the Weibulls estimated from the Kaplan Meier data from month 5 onwards then a partitioned survival analysis might estimate similar survival gains for AAP+ADT over ADT as both the MSM/TA387 model of the company base case and the MSM model. However, if within the Kaplan Meier data a month relates to a 4 week period the estimated survival gains

[m] If the Kaplan Meier months relate to 4 week periods this should not particularly affect the MSM/TA387 or MSM model outputs as the raw Kaplan Meier data is only applied for the first 5 months of the models, provided that the weekly MSM TPMs have correctly treated the Kaplan Meier months as 4 week periods.

for AAP+ADT over ADT fall by around 8% and are much worse than both the MSM/TA387 model and the MSM model.
The above shows how the restriction of the Weibulls to the Kaplan Meier data from month 5 onwards increases the anticipated survival gains by a reasonable margin.

The above does not address the question of whether a partitioned survival analysis would estimate a similar rPFS gain for AAP+ADT over ADT compared to both the MSM/TA387 model of the company base case and the MSM model. To do so might be for the ERG to stray too close to building an ERG model. Nevertheless, it would be relatively simple for the company to present this analysis as a confirmatory cross check of their models.

The above also does not address how a partitioned survival analysis should determine the proportions of post progression survival that are spent on 1st line, 2nd line and 3rd line mCRPC treatment. These are the main differences between the MSM/TA387 model and the MSM model.

1st line mCRPC abiraterone [redacted] implementation

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

[redacted]

5.3 *ERG cross check and critique*

5.3.1 Base case results

The ERG have rebuilt the model cohort flows, QALY calculations, mHSPC costs and pre 1st line mCRPC costs using the company base case assumptions.

[redacted] The ERG have not rebuilt the 1st line, 2nd line or 3rd line mCRPC costs. In the opinion of the ERG the company model has major structural errors in the calculation of the 1st line mCRPC costs. As a consequence, there seems little point trying to rebuild them.

The ERG rebuild and the company MSM/TA387[31] model that excludes 1st line, 2nd line and 3rd line mCRPC costs result in the following undiscounted life year estimates and discounted QALY and cost estimates.

Table 55 ERG model rebuild compared to company MSM/TA387 model

	ERG Rebuild			Company MSM/TA387 model		
	AAP+ADT	**ADT**	**DOC+ADT**	**AAP+ADT**	**ADT**	**DOC+ADT**
Total						
LY	5.062	3.549	4.405	4.993	3.430	4.322
QALYs	3.455	2.379	2.863	3.420	2.325	2.824
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net						
LY		1.513	0.657		1.563	0.672
QALYs		1.077	0.592		1.095	0.596
Costs		£27,185	£19,195		£26,903	£19,136

The total undiscounted life years of the ERG rebuild are slightly higher than those of the company MSM/TA387 model, but the models' estimates are within 2-3% of one another. Total QALY estimates are similarly close between the ERG rebuild and the company MSM/TA387 model. The total cost estimates are little different between the models. The estimates of net amounts differ less between the models than the estimates of the total amounts.

The correspondence between the ERG rebuild and the company MSM/TA387 model is good. Nevertheless, these values cannot be taken forward to cost effectiveness estimates because they do not include 1st line, 2nd line or 3rd line mCRPC costs. These are major drivers of the cost effectiveness estimates.

5.3.2 Data inputs: correspondence between written submission and sources cited

Mapping the EQ-5D-5L to the EQ-5D-3L

The company state that the DSU recommends the van Hout mapping algorithm.[56] The DSU report on mapping the EQ-5D-5L to the EQ-5D-3L[59] states that "*The DSU and van Hout approaches… do not perform substantially differently from each other ... The DSU approach slightly outperforms van Hout in terms of predicting the category of response. The van Hout method is marginally better for some measures of summary fit to utility scores. However, we outline how these summary measures mask differences between the approaches in different parts of the health distribution. There are concerns about the validity of the pairwise deletion method employed by van Hout et al and how this distorts fit measures*." This could be read as the DSU preferring the DSU mapping method over the van Hout method. The ERG cannot

comment upon the impact that using the DSU method would have upon results. The company do not state whether this method was explored.

1st line mHSPC SAEs and SREs: DOC+ADT

The 32% for grade 3/4 hypertension with DOC+ADT corresponds with that reported in Gravis et al 2013[58] it also being necessary to note that the reported rate for ADT was 0%. The ERG has not been able to source SRE rates for DOC+ADT or for ADT from Gravis et al 2013[58] As a consequence it may not be reasonable to assume a relative risk of 91% for DOC+ADT compared to ADT, when the relative risk from LATITUDE for AAP+ADT compared to ADT is 79%.

Chemotherapy administration cost

The ERG have not been able to source the £260 chemotherapy administration cost that is applied for docetaxel administrations. The 2015-16 reference costs for outpatient administration suggest first administration costs of £265 for more complex parenteral chemotherapy and £304 for complex chemotherapy including prolonged infusion, and £212 for subsequent cycles. Applying these would have little impact upon the cost effectiveness estimates.

ADT administration cost

The ERG have been unable to source the average cost of £10.85 for ADT administrations. This has been calculated as £42*(15.5/60).

5.3.3 Data inputs: correspondence between written submission and electronic model

The ERG have not identified any important discrepancies between the written submission and the electronic model.

5.3.4 ERG commentary on model structure, assumptions and data inputs

Modelling of mCRPC

Most of the 1st line mCRPC treatments are time limited. It appears that both the MSM model and the MSM/TA387 model assume that they are not. The costs of mCRPC treatments are applied indefinitely while on 1st line mCRPC treatment. A similar issue applies to any time dependent quality of life values.

Given the centrality of the mCRPC costs to the cost effectiveness estimates, if these are incorrect it is doubtful whether any of the modelling results of the company or the ERG are reliable.

In the opinion of the ERG the time profile of 1st line mCRPC treatments' costs and quality of life values should be modelled. A possible method might be to calculate discontinuation curve adjusted present values for the mCRPC active treatments and BSC. Arm specific weighted average present values could then be calculated and applied to each cycles' incident 1st line mCRPC patients on treatment. These present values might need to be cycle specific to avoid projecting costs and benefits beyond the time horizon. The ERG have not attempted to implement this because:

- The extent of model revision would result in it being in large part an ERG model, and
- Committee has previously rejected similarly extensive model revisions by the ERG.

Choice of MSM model, MSM/TA387 model or partitioned survival analysis model

The company argue that the MSM/TA387[31] model is appropriate because:

- The LATITUDE OS data are of limited maturity.
- More patients in the ADT arm than the AAP+ADT arm of LATITUDE received subsequent mCRPC treatment.
- Some mCRPC treatments in LATITUDE are not available in the UK, and the proportions of subsequent treatments are not aligned with market shares and modelling mCRPC survival as in the MSM/TA387 model permits this to be addressed.
- A Markov model is appropriate due to the discrete event simulation of TA387 being poorly received by the Committee.

The MSM model and the MSM/TA387 model estimate very similar net survival estimates and net QALY estimates for AAP+ADT compared to ADT.

The MSM model and the MSM/TA387[31] model estimate some differences in net survival and net QALYs for AAP+ADT compared to ADT. But these are dwarfed by the differences in the net cost estimates. These in turn are driven by the proportions of mCRPC time modelled as being spent on 1st line, 2nd line and 3rd line mCRPC treatments. The choice between the MSM

model and the MSM/TA387 model largely boils down to a choice between these modelled durations. In the opinion of the ERG the MSM/TA387 model estimates for 2nd line mCRPC treatment durations lack credibility.

Applying the unadjusted TA387 OS curves results in the MSM/TA387 model fitting the LATITUDE OS Kaplan Meier curves not very well at all. The company adjust the TA387 modelled OS curves using an *ad hoc* hazard ratio of 2.62 to fit the MSM/TA387 model OS curves to the LATITUDE OS Kaplan Meier curves. This calls into question the relevance of the TA387 model outputs to mHSPC patients who progress to mCRPC.

The use of the TA387[31] model outputs as axiomatic inputs to the MSM/TA387 model may raise procedural issues. As the company note, it chose a Markov model due to the discrete event simulation of TA387 being poorly received by the Committee. The ERG also cannot be expected to have, and has not, cross checked, rebuilt, stress tested or indeed done anything very much with the TA387 model. That TA387 approved abiraterone for use for mCRPC does not imply that the Committee viewed the TA387 model outputs as the most likely central estimates that would apply in practice.

The application of the *ad hoc* hazard ratio of 2.62 to the TA387[31] modelled OS curves is essentially a laborious and non-statistical means of fitting curves to the LATITUDE OS Kaplan Meier data. If this is the intention it would be simpler to fit parameterised curves to the LATITUDE OS Kaplan Meier data. This would benefit from well-established formal statistical methods and would permit time varying probabilities to be explored. An exploratory ERG's analysis of the LATITUDE OS Kaplan Meier data suggest Weibulls are a better fit than exponentials.

Kaplan Meier cut-off

The LATITUDE Kaplan Meier curves are applied for the first 5 months of the model. The probabilities of the MSM analysis are estimated from the LATITUDE post 5 months data, and are applied in the model from 5 months.

This is a choice based upon the company examination of the log cumulative hazard plots for OS and rPFS. Viewed in isolation the log cumulative hazard plot for OS might suggest a later cut-off. Later cut-offs worsen the cost effectiveness estimates.

mCRPC treatment sequencing

There are some uncertainties around treatment sequencing, whether patients are currently only permitted one "*novel agent*" for treatment of metastatic prostate cancer and whether approval of a novel agent for mHSPC by NICE might in time increase the number of novel agents mHSPC patients will be able to receive for their metastatic prostate cancer.

The ERG accept the company argument that patients who are receiving a course of docetaxel treatment have a lower quality of life than if they were to receive a novel agent. If patients who have received abiraterone for their mHSPC can exercise choice over their treatment for mCRPC it seems likely that many if not most will prefer enzalutamide over docetaxel.

The effect of 1st, 2nd and 3rd line treatments for mCRPC on the MSM/TA387 model are not obvious from the headline results. To better understand the working of the model these can be simplified through the following 6 scenario analyses:

1. 1st, 2nd and 3rd line all receive BSC.
2. 1st line all receive enzalutamide, 2nd and 3rd line all receive BSC.
3. 1st line all receive enzalutamide, 2nd line all receive cabazitaxel, 3rd line all receive R-223.
4. 1st line AAP+ADT patients receive docetaxel while ADT and DOC+ADT patients receive enzalutamide, 2nd and 3rd line all receive BSC.
5. 1st line AAP+ADT patients receive docetaxel while ADT and DOC+ADT patients receive enzalutamide, 2nd line all receive cabazitaxel, 3rd line all receive R-223.
6. 1st line all receive enzalutamide, 2nd line AAP+ADT and ADT patients receive docetaxel while DOC+ADT patients receive cabazitaxel, 3rd line AAP+ADT and ADT patients receive cabazitaxel while DOC+ADT patients receive R-223.

These scenario analyses result in the following for the MSM/TA387 model.

Table 56 mCRPC treatment sequencing scenario analyses

	AAP+ADT vs ADT			AAP+ADT vs DOC+ADT		
	Δ QALYs	**Δ Costs**	**ICER**	**Δ QALYs**	**Δ Costs**	**ICER**
Base	1.095	£19,066	£17,418	0.596	£10,618	£17,828
SA01	1.126	£26,750	£23,752	0.619	£19,060	£30,788
SA02	1.106	£22,233	£20,095	0.608	£16,713	£27,488
SA03	1.106	£20,934	£18,920	0.608	£15,594	£25,646
SA04	1.104	£3,076	£2,785	0.606	-£2,444	Dominant
SA05	1.105	£1,776	£1,608	0.606	-£3,564	Dominant
SA06	1.107	£21,195	£19,155	0.607	£14,953	£24,625

Note that the above does not take into account the competitor PASs, and in particular the enzalutamide PAS. The 4th and 5th scenario analyses should consequently not be taken too literally, but rather as an indication of how the mCRPC treatment sequencing affects the model outputs. SA06 is also sensitive to competitor PASs due to only the 3rd line treatment for AAP+ADT and ADT being subject to a PAS while both 2nd and 3rd line treatment for DOC+ADT are subject to a PAS. The equivalent of the above table inclusive of the competitor PASs is presented in the cPAS appendix.

The net QALYs are only really affected by differentiation of the 1st line mCRPC treatment; SA02 and SA03 have the same net QALYs and those of SA04 and SA05 are little different. This is driven by changing the proportions who receive BSC rather than an active treatment due to all active 1st line mCRPC treatments being assumed to have the same efficacy.

The net QALYs increase slightly in all the scenario analyses compared to the base case. This appears to be due to the company base case assuming that in the ADT+AAP arm 90% of mCRPC patients receive an active 1st line mCRPC treatment while in the ADT and DOC+ADT arms this is 95%.

If the treatment sequences for mCRPC are similar between the arms the net costs increase and the cost effectiveness of AAP+ADT worsens markedly. This would correspond to the situation where patient choice leads to patients preferring the newer agents rather than docetaxel for their mCRPC regardless of their previous treatment for mHSPC.

The 6th scenario analysis suggests that differentiation of 2nd and 3rd line treatments for mCRPC is of secondary importance compared to differentiation of 1st line treatments for mCRPC.

MSM TPMs and application of DOC+ADT hazard ratios

The company choose to apply the DOC+ADT versus AAP+ADT hazard ratios to the AAP+ADT Kaplan Meier curves and MSM TPMs. It could have chosen to apply the DOC+ADT versus ADT hazard ratios to the ADT Kaplan Meier curves and MSM TPMs.

It appears that the MSM TPMs for AAP+ADT are estimated separately from the MSM TPMs for ADT. This is akin to parameterised curves not imposing proportionate hazards between the arms, but curves being estimated separately for each arm. In these situations applying the hazard ratios of an ITC to the curves of one of the arms of the trial will not necessarily result in the same or even similar results as applying the implied hazard ratios to the curves of the other arm of the trial.

The ERG have already highlighted that applying the DOC+ADT versus AAP+ADT hazard ratios to the AAP+ADT MSM TPMs results in the anomaly of DOC+ADT patients having a higher probability of dying once they have progressed to mCRPC than AAP+ADT patients and ADT patients.

The company could equally well have chosen to apply the hazard ratios for DOC+ADT versus ADT to the ADT Kaplan Meier curves and MSM TPMs. A crude application of the central estimates of the hazard ratios of Table 18 of Document B of the submission suggests hazard ratios of 0.67 (0.62/0.92) for OS and 0.62 (0.47/0.76) for rPFS for DOC+ADT compared to ADT. Applying these to the ADT MSM TPM results in the following TPM for DOC+ADT.

Table 57 Scenario analysis TPMs: DOC+ADT

From \ To	rFPS	PPS Pre-Tx	PPS 1st line Tx	Dead
rPFS	[redacted]	[redacted]	[redacted]	[redacted]
PPS Pre-Tx		[redacted]	[redacted]	[redacted]
PPS 1st line Tx			[redacted]	[redacted]
Dead				[redacted]

Most of the values in the above are in line with intuition when compared with the TPMs of AAP+ADT and ADT. However, the probability of dying among those who have progressed is anomalous and is now lower than that of both AAP+ADT and ADT. It can be argued that this anomaly is worse than that of the DOC+ADT TPM of the company base case.

Application of the above TPM considerably worsens the deterministic MSM/TA387 model cost effectiveness estimate for AAP+ADT compared to DOC+ADT from £17,828 per QALY to £25,530 per QALY. The ERG implementation of sampling of this within the probabilistic modelling may be formally incorrect and may not properly take into account confidence intervals and correlations. Nonetheless, this results in a smaller change in the central probabilistic estimate, it only worsening from £18,168 per QALY to £20,867 per QALY. The non-linearity of the model may relate to the DOC+ADT versus ADT OS hazard ratio being somewhat further from unity than the DOC+ADT versus AAP+ADT hazard ratio.

The above does not argue that the company choice is incorrect. It only highlights that it is a choice which has not been justified, another choice could equally well have been made and that the most reasonable estimate may lie somewhere between the two.

MSM/TA387 model: Differentiation of 1st line mCRPC treatment effects

As already highlighted, the company comparison of 1st line mCRPC treatments' effectiveness estimates an OS hazard ratio central estimate which [redacted]

The company MSM/TA387 model structure is largely justified by the company on the basis of the need to properly model the effects of extending rPFS upon OS; i.e., the LATITUDE data for rPFS are reliable but thereafter the modelling needs to depart from the LATITUDE data. [redacted].

The only means of approximating this within the MSM/TA387 model is to differentiate 1st line mCRPC treatments by the company central estimates of the OS hazard ratios. The ERG will apply this as a sensitivity analysis.

The NICEimpact Cancer publication[60] provides prescription data for enzalutamide and abiraterone for mCRPC which suggest a strongly rising market share for enzalutamide and a falling market share for abiraterone, with a prescribing ratio of around 2:1 in April 2017. It also notes that "*Enzalutamide is similar to abiraterone, but it is less likely to cause liver toxicity and may be more convenient to take for some people*". In the light of this the ERG sensitivity analyses that differentiate 1st line mCRPC treatment effectiveness will apply the treatment proportions of the ERG base case and a second set of proportions that sets the proportion of abiraterone to zero and adds this to the proportion for enzalutamide in the ADT and DOC+ADT arms.

MSM model: What proportions of mCRPC treatments to apply?
The company scenario analysis which uses the MSM model also applies the LATITUDE mCRPC treatment proportions. The implicit company argument appears to be that it is these treatment proportions that gave rise to the LATITUDE clinical data, so these should be applied in the mainly LATITUDE based MSM model.

The company argument might be reasonable if the MSM model survival estimates and QALY estimates are sensitive to the mCRPC treatment proportions. They are not. In the light of this the ERG consider it more important to accurately estimate the costs of mCRPC treatment. According to the company, this is best achieved using the estimates of the company's clinical Advisory Board.

The ERG are unclear whether the proportions receiving BSC for 1st line mCRPC should be differentiated between the arms. For the ERG revised base case the ERG make minor amendments to the company clinical advisory board estimates as below.

Table 58 ERG revised 1st line mCRPC treatment proportions

	AAP+ADT	ADT	DOC+ADT
1st line mCRPC			
BSC	5%	5%	5%
Enzalutamide	0%	35%	39%
AAP	0%	35%	39%
Docetaxel	65%	15%	0%
Cabazitaxel	0%	0%	12%
Radium 223	30%	10%	5%
2nd line mCRPC			
BSC	60%	45%	60%
Enzalutamide	0%	10%	5%
AAP	0%	10%	5%
Docetaxel	0%	10%	0%
Cabazitaxel	15%	5%	5%
Radium 223	25%	20%	25%
3rd line mCRPC			
BSC	95%	90%	95%
Enzalutamide	0%	0%	0%
AAP	0%	0%	0%
Docetaxel	0%	0%	0%
Cabazitaxel	2%	1%	1%
Radium 223	3%	9%	4%

The ERG provide a scenario analysis that applies the company Advisory Board estimates.

LATITUDE QoL Regression

The univariate model estimates *Off Treatment* and *Subsequent Treatment* to be significant at not just the 10% level but at the 5% level. Despite this they are excluded from the multivariate analysis. The univariate coefficients for both of these are somewhat larger than those of the other variables, with the exception of the *Baseline EQ5D* and *SREs*. The ERG asked the company to supply the internal reports that underlay the estimates reported in the submission, but none were forthcoming.

In the light of the above, the ERG cannot comment further upon why *Off Treatment* and *Subsequent Treatment* were excluded from the multivariate analysis, how justified it was to

exclude them and what the impact of including them would have been. But the following can be noted.

- The *Off Treatment* health state is intrinsic to the model structure. When calculating the quality of life value for those on AAP+ADT the increment for receiving AAP+ADT of [redacted] is qualified by the [redacted] of time prior to cessation of therapy that patients actually receive AAP+ADT. Inclusion of the *Off Treatment* variable in the regression equation might reduce the quality of life during this period in the AAP+ADT arm.
- The amount of time spent *Off Treatment* prior to treatment for mCRPC in the MSM/TA387 model[n] is 3.4 months for AAP+ADT, 2.5 months for ADT and 2.8 months for DOC+ADT. Inclusion of the *Off Treatment* variable in the regression equation might reduce the quality of life during this period in the AAP+ADT arm more than that in the other arms.
- The distinction between those with rPFS who are receiving subsequent treatment and who are not is also inherent to the model. The quality of life differences between these is modelled as being minimal and only due to the adverse events associated with the various treatments. Whether the inclusion of the *Subsequent Treatment* variable within the analysis would increase this difference is unclear.

LATITUDE QoL Regression: Differentiating SAE and SRE effects by arm

The ERG requested additional analyses that variously pooled the coefficients for SAEs and for SREs between the arms, and asked what statistical justification there is for separating them by arm. It supplies the following models for the rPFS QoL analysis.

[n] Taken to be the sum of the elements of Column J of the markov worksheets, conditioned by 0.23 months to cycle 52 and then 0.92 months.

Table 59 LATITUDE QoL regressions: pooling of coefficients

	Base case (s.e.)	Pooled SAE (s.e.)	Pooled SRE (s.e.)	Both pooled (s.e.)
Baseline EQ5D	[redacted]	[redacted]	[redacted]	[redacted]
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
rPFS	[redacted]	[redacted]	[redacted]	[redacted]
AAP+ADT Tx	[redacted]	[redacted]	[redacted]	[redacted]
SAE		[redacted]		[redacted]
SAE | AA	[redacted]		[redacted]	
SAE | PBO	[redacted]		[redacted]	
SRE			[redacted]	[redacted]
SRE | AA	[redacted]	[redacted]		
SRE | PBO	[redacted]	[redacted]		
-2 Res LL	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]
AICC	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]

All coefficients are significant at the 1% level.

At clarification the ERG asked to what extent there was statistical evidence that the SAE and SRE coefficients differed by arm. The company note that:

- *"LATITUDE evidence suggests that the impact of having experienced an AE or SRE was different in the AAP + ADT arm than in the ADT alone arm. The utility regression analysis highlighted some difference, with the coefficient for AE being -* [redacted] *for AAP + ADT and* [redacted] *for ADT alone, and the coefficient for SRE being -* [redacted] *for AAP + ADT and* [redacted] *for ADT alone."*
- *"Each of the variables included in the utility regression model 1.0, which estimates treatment-specific AE and SRE coefficients, were found to be statistically significant … The p-values for the AE and SRE coefficients separated by treatment arm are all well below 0.01."*

The above arguments examine the arm specific coefficients in isolation and do not address whether the coefficients are statistically different between the arms. Pooling the SAE coefficients quite noticeably improves the information criteria, though further pooling the SRE coefficients provides little additional gain. The company maintain that the cost effectiveness estimates are not sensitive to which model is chosen, largely because the pooling of SAE and SRE coefficients is balanced by an increase in the AAP+ADT treatment effect coefficient.

The ERG will apply the coefficients of the model that pools the SAE coefficients due to the improvements in the information criteria, slightly improving the cost effectiveness estimates for AAP+ADT. However, as the company notes the choice of model from those available has relatively little impact upon the cost effectiveness estimates due to the AAP+ADT treatment effect coefficient increasing.

Selective application of the LATITUDE QoL Regression

As already noted the company chooses not to apply the QoL decrements for SAEs and SREs that are implied by the LATITUDE QoL regression. It estimates decrements from the literature that are an order of magnitude smaller than those implied by the LATITUDE QoL regression. This causes the quality of life estimates used in the model to be higher than those observed during LATITUDE. This biases the model in favour of AAP+ADT.

The ERG can think of no reason for adopting this approach for the comparison of AAP+ADT with ADT. There might be an argument for qualifying the LATITUDE QoL regression decrements for SAEs and SREs for AAP+ADT before applying them to DOC+ADT if the literature estimates suggested wildly differing values. However, the company estimates based upon the literature are minimally different, a decrement of [redacted] for AAP+ADT compared to [redacted] for DOC+ADT.

The ERG will apply the LATITUDE regression in full in its revised base case, this also applying the minor qualification to the DOC+ADT decrement implied by the literature based estimates of the company for AAP+ADT and DOC+ADT.

DOC+ADT and ADT (post DOC+ADT) QoL compared to ADT QoL: mHSPC

The company commission a QoL study from MAPI values. This develops three main health states based upon literature review and the input of 4 patients, 3 expert clinicians and 2 nurses. An additional 6 health states are developed by adding adverse events to one of the main health states.

The study notes that

“[redacted]

[redacted] [ERG emphasis]".

The three main health states are ADT, DOC+ADT while on docetaxel treatment and ADT after having completed a course of docetaxel. The full health descriptions are presented in Appendix 1, but for reasons of space and clarity only the elements that differed are presented below.

Table 60 Quality of life study health state descriptors

ADT	DOC+ADT	ADT (post DOC+ADT)
[redacted]	[redacted]	[redacted]

These health states were further reviewed by 5 clinicians and 1 nurse who had not been previously involved in the study, a key question being whether patients were more depressed following a course of docetaxel. The 6 experts were equally split, with 3 reporting that some patients were more depressed following docetaxel treatment. It is unclear whether they thought that these patients were more depressed due to the docetaxel treatment or simply due to having had a longer duration of disease.

In the opinion of the ERG the heath state descriptors for DOC+ADT and ADT (post DOC+ADT) are unambiguously worse than the health state descriptor for ADT. It is inevitable that when valued by members of the public they will result in quality of life decrements for DOC+ADT and ADT (post DOC+ADT) compared to ADT

The first criticism of the QoL study is that it did not investigate any AAP+ADT health state. This would provide an estimate of the QoL detriment for ADT compared to AAP+ADT, and so some cross check about the alignment and reliability of the study estimates against estimates based upon trial data and real patients' experiences.

The health state descriptors may be biased against the DOC+ADT and ADT (post DOC+ADT) health states.

- In the opinion of the ERG "[redacted]" seems likely to be viewed as having a better prognosis than "[redacted]"[o]. To the ERG the former suggests the possibility of treatment while the latter suggests something immutable and unchanging. There is no justification for the difference in wording between ADT and DOC+ADT. It also seems questionable whether this wording should be differentiated between AAP+ADT and ADT (post DOC+ADT) given that the quality of life decrements are applied for the duration of mHSPC.
- For the ADT (post DOC+ADT) health state it is not obvious why "[redacted]" needs to be included in the health state description. To the ERG it seems questionable whether members of the general public can sensibly infer what effect past treatment as specified in the health state descriptor will have on their quality of life, but its inclusion seems likely to push responses by members of the public in only one direction. The anticipated effects of this would seem to be covered by the subsequent depression related wording, which does form what can reasonably be described as part of someone's health state.
- For the DOC+ADT health state "[redacted]" seems to overstate the

[o] [redacted]

restriction on daily activities given that docetaxel administration is only once every three weeks. The patient who reported on this also only restricted his social activities during the week he received treatment.

- There seems to be considerable uncertainty about whether there is a difference in depression for ADT (post DOC+ADT) compared to DOC+ADT, and indeed compared to ADT. This uncertainty is not reflected in the wording of the health state for ADT (post DOC+ADT) for which depression is unambiguously "[redacted]" rather than "[redacted]" for ADT and DOC+ADT.
- It seems peculiar to assume that depression among patients worsens when they complete their course of docetaxel.
- It would have been simple to include an indication of median future survival within the health state descriptors. The better prognosis for ADT (post DOC+ADT) patients than for ADT patients at the same time point is not reflected in the health state descriptors. The better prognosis for ADT (post DOC+ADT) patients than for ADT patients at the same time point may result in them being less depressed.

Given the uncertainty around the likelihood of increased depression for the ADT (post DOC+ADT) compared to ADT, it might be better to explore this as an adverse event rather than as an inseparable aspect of ADT (post DOC+ADT) health state.

In the light of the above and the FACT-P values reported in section 5.1.4 above, the ERG revised base case will set the quality of life decrement for ADT (post DOC+ADT) compared to ADT to zero. The ERG will apply the [redacted] TTO decrement within sensitivity analyses. In the light of the FACT-P results of section 5.1.4 above, the ERG will also apply half the LATITUDE quality of life regression increment for AAP+ADT to ADT (post DOC+ADT) within a sensitivity analysis.

DOC+ADT and ADT (post DOC+ADT) QoL compared to ADT QoL: mCRPC

The company does not apply the quality of life decrements for DOC+ADT and ADT (post DOC+ADT) QoL compared to ADT for those treated with docetaxel for mCRPC in either the AAP+ADT arm or the ADT arm. This biases the model in favour of AAP+ADT when compared to DOC+ADT, to a lesser extent in favour of AAP+ADT when compared to ADT.

Given the ERG's concerns around the modelling of time dependent mCRPC costs the ERG have not attempted to address this in their revised base case. The same issue applies to time dependent mCRPC quality of life values.

AAP+ADT abiraterone treatment compliance estimate: mHSPC

The company calculate that patients in the AAP+ADT arm receive treatment with AAP+ADT for [redacted] of the time they spend in rPFS. While the percentage affects both costs and QALYs in the AAP+ADT arm, it reduces costs more than QALYs. Not applying the percentage reduction worsens the costs effectiveness estimate for AAP+ADT compared to ADT[p] from £17,418 to £20,038 per QALY, and for AAP+ADT compared to DOC+ADT from £17,828 to £22,593 per QALY. The [redacted] estimate is essentially based upon the differences in the areas underneath the rPFS and TTD curves as outlined below.

[redacted]

The areas under the curves are around [redacted] months for the rPFS KM curve and [redacted] months for TTD KM curve, which results in a ratio of [redacted] time on treatment compared to time in rPFS.

[p] This has also set the corresponding proportion for ADT to 100%.

The above figure raises concerns about the [redacted] compliance ratio.

- Some of the separation between the curves appears to be protocol driven, due to the rPFS curve being flat for 4 months and followed by a step at the assessment point.
- Over the 40 months the sum of events and censoring events was the same for both curves at [redacted]. But the balance between events and censoring events was considerably lower in the rPFS curve at [redacted] compared to [redacted] for the TTD curve. The definition of censoring events for the rPFS curve was broader than for the TTD curve. If the ERG understand the company clarification response correctly, for the TTD curve only remaining on treatment at IA1 counted as censoring with all other events being TTD events. Consequently, lost to follow up is treated as censoring for the rPFS curve, which is unaffected by it, whereas it is treated as an event in the TTD curve, causing it to fall. Like may not be being compared with like.
- The [redacted] ratio does not take into account the numbers at risk. At baseline the ratio is near 100% and almost all patients remain at risk. By 40 months there are virtually none at risk and the ratio between the curves has dropped to around [redacted]. The 100% and [redacted] are given equal weight.

If the company have confidence in the curves there is a clear downward trend in the ratio as time passes. The company should extrapolate from this steeply downward sloping curve. It has not done so. This suggests that the company do not find the end of curve ratios credible.

There does not seem to be an agreed method for handling this, what censoring should be informative and what uninformative in the TTD curve and how any estimate should be qualified by the numbers at risk. But there may be no need to address these issues. The CSR contains data on treatment compliance in the safety population as outlined below, with this being described as "*Percent of doses (tablets) taken out of the protocol-specified dose*".

Table 61 CSR compliance data for AAP/placebo

Compliance range		AAP+ADT		ADT	
	75%	[redacted]	[redacted]	[redacted]	[redacted]
>75%	80%	[redacted]	[redacted]	[redacted]	[redacted]
>80%	85%	[redacted]	[redacted]	[redacted]	[redacted]
>85%	90%	[redacted]	[redacted]	[redacted]	[redacted]
>90%	95%	[redacted]	[redacted]	[redacted]	[redacted]
>95%	100%	[redacted]	[redacted]	[redacted]	[redacted]

The ERG may have misinterpreted this data, which could explain the more convoluted approach of the company.

Given the clear rightward skew in the compliance data, it seems reasonable to assume a similar skew within each of the ranges. There is the problem of the 1st compliance range of up to 75%, and the ERG have little option other than to treat this as 75%. Taking the upper limit of the other ranges results in mean compliances of [redacted] for AAP+ADT and [redacted] for ADT, while the midpoints result in mean compliances of [redacted] for AAP+ADT and [redacted] for ADT.

The rightward skew may argue for the upper limit estimates to be used. But given the difficulty around the 1st compliance range the ERG revised base case will apply the mid-point estimates.

DOC+ADT docetaxel treatment compliance estimate: mHSPC

As previously mentioned the docetaxel compliance estimates are only applied to the relatively minor £28 direct drug costs per docetaxel administration and not to the other cost elements such as chemotherapy administration costs. The mHSPC docetaxel compliance estimates are not applied in the same manner as the mHSPC abiraterone compliance estimates.

Compliance estimates: mCRPC

For mCRPC abiraterone and enzalutamide are assumed to be taken for 100% of the mCRPC discontinuation curve. These mCRPC treatments are mainly received in the ADT and DOC+ADT arms.

The other treatments have compliance percentages applied to them that do not take into account the effects of the MSM/TA387 model discontinuation curves; i.e., the compliance percentages of the trials will include some discontinuations. These mCRPC treatments are mainly received in the AAP+ADT arm.

Given the ERG's concerns around the mCRPC cost estimates the ERG have not attempted to address this issue.

Bone scans and CT scans

The company base case assumes that there will be no bone scans for AAP+ADT or for ADT, but that for DOC+ADT there will be and that the frequency of these will increase when patients have completed their course of docetaxel and are on ADT (post DOC+ADT)[q].

The ERG cannot find any reference to monitoring with bone scans or CT scans in either the docetaxel SmPC or the abiraterone SmPC, or any link from an increased risk of bone disease to this. Within the SmPCs it seems that LHRH agonists can reduce bone mineral density. The abiraterone SmPC states that "*Decreased bone density may occur in men with metastatic advanced prostate cancer. The use of ZYTIGA in combination with a glucocorticoid could increase this effect*". The ERG have not been able to find anything similar in the prostate cancer section of the docetaxel SmPC.

Given the above the ERG will equalise the number of bone scans in the DOC+ADT arm with those in the AAP+ADT arm. This has a reasonable impact upon the cost effectiveness of AAP+ADT compared to DOC+ADT, worsening it from £17,828 per QALY to £21,695 per QALY.

A scenario analysis will revert to the estimates of the company. Nevertheless, this does not particularly address:

- the frequency of bone scans for DOC+ADT for patients receiving docetaxel
- the frequency of bone scans for ADT (post DOC+ADT) patients in the longer term.

The second bullet is the more important.

[q] This differentiation of resource use between ADT (post DOC+ADT) and ADT also introduces some modelling complications if the costing of DOC+ADT takes into account compliance in the same manner as the costing of AAP+ADT.

Scenario analyses

The company do not provide any scenario analyses limiting the duration of treatment effect as outlined in the NICE methods guide section 5.1.16.

Calculation of mean time between rPFS and subsequent therapy: Minor issue

In response to the ERG clarification question B18 the company have confirmed that calculation of the mean time between rPFS and subsequent treatment is based upon all patients with rPFS data including those censored for time to subsequent therapy (TTST). At clarification the company has confirmed that there was a minor error in this calculation. Restricting the data to those with both an rPFS and a TTST event has a reasonable impact upon the estimates.

Table 62 Mean time between rPFS and subsequent therapy: months

	AAP+ADT	ADT	net
Patients with rPFS data			
Original submission	[redacted]	[redacted]	[redacted]
Correction at clarification	[redacted]	[redacted]	[redacted]
Patients with rPFS and TTST data	[redacted]	[redacted]	[redacted]

For the sake of argument suppose that all patients were recruited at the same time point with all patients in the ADT arm progressing at 6 and all patients in the AAP+ADT arm progressing at 7 months. Suppose further that the time between rPFS and subsequent therapy was 2 months in both arms and that IA1 corresponded to 8 months. The company method would estimate a mean time to treatment of 2 months in the ADT arm and 1 month in the AAP+ADT arm. While an extreme and unrealistic example, it does illustrate that for immature data the company method may be biased and underestimate the mean time from rPFS to subsequent treatment more for the arm that postpones rPFS for longer; i.e. in favour of AAP+ADT.

Similarly, given immature data, ignoring those censored for TTST may ignore those who never receive any subsequent treatment. This might bias the estimates in the opposite direction.

The estimates from the alternative method are quite different, though the net effect between the arms is less so. Applying them within the company model has little impact.

1st line mCRPC modelling during the 1st year of the MSM/TA387 model: Minor issue

The model needs to simulate newly incident mCRPC patients in every cycle of the model. This requires it to append the TA387 mCRPC discontinuation and OS curves to the newly incident mCRPC patients in each cycle. Error appears to have crept into the look-up of the cycle specific probabilities of discontinuation and death for mCRPC patients who are incident during the 1st year.

For instance, the week 1 incident mCRPC patients in the AAP+ADT arm have the correct weekly mortality probabilities applied up to week 52 of the model. At this point the model switches to a 4-weekly cycle and 4-weekly probabilities are applied. But rather than apply the 4-weekly probability from week 52 to week 56 of 4.6%, the model applies the 4-weekly probability from week 208 to week 212 of 7.2%. All the subsequent 4-weekly probabilities are similarly taken from 52*4=208 weeks too far down the relevant survival curves.

Application of full LATITUDE QoL regression for mCRPC: Minor Issue

If it is felt that the LATITUDE QoL regression should be applied in full when estimating the QoL values for the mHSPC health states, in the opinion of the ERG it should also be applied when deriving the QoL values for the mCRPC health states. The company scenario analysis around this only alters the QoL values for the mHSPC health states. However, applying parallel changes to the mCRPC health states has relatively little effect on the cost effectiveness estimates as it seems to affect all arms to much the same extent.

Abiraterone last administration cost: Minor issue

It is unclear why the company start dosing and costings not from baseline but from after 1 week. This may also be related to the fact that the company only apply 74% of the pack price of abiraterone for the last costed administration. This could in turn account for some of the differences in cost between the company model and the ERG rebuild.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

A key question for the Committee for this appraisal is whether they prefer the MSM/TA387 model, the MSM model or is somewhere between the two. The ERG supply a full set of analyses for the MSM/TA387 model and a full set of analyses for the MSM model in what

follows. This mainly alters the balance between time spent on 1st line mCRPC treatment mCRPC and time spent on 3rd line mCRPC treatment.
The results of this section include the effects of the abiraterone commercial access arrangement but do not include the effects of the patient access schemes of enzalutamide, cabazitaxel or radium-223. These are supplied in the cPAS Appendix.

The ERG have revised the company model base case to:

- Apply the full set of LATITUDE quality of life regression coefficients, these also being rolled through to the quality of life values that are implied for mCRPC patients.
- Apply the LATITUDE quality of life regression that does not differentiate the SAE coefficient between the arms.
- Set the quality of life decrement for ADT (post DOC+ADT) relative to ADT to zero.
- Apply the compliance percentage for abiraterone derived from the CSR mid-point values.
- Apply compliance percentages in the DOC+ADT arm in the same manner as in the AAP+ADT arm.
- Apply the ERG preferred mCRPC treatment percentages that do not differentiate the proportions receiving BSC between the arms.
- Equalise the frequency of monitoring with bone and CT scans for those receiving a course of docetaxel in the DOC+ADT arm with those of the AAP+ADT arm.
- Equalise the frequency of monitoring with bone scans for those who have completed a course of docetaxel in the DOC+ADT arm, ADT (post DOC+ADT) patients, with those of the AAP+ADT arm.
- Apply corrections for minor issues.

Given the complexity of the company modelling the ERG provide a range of sensitivity and scenario analyses.

- SA01: Kaplan Meier to MSM TPM cut-offs of 4 months and of 7 months.
- SA02: Apply a common probability of PPS patients receiving 1st line mCRPC treatment for DOC+ADT and AAP+ADT, rather than conditioning the AAP+ADT probability of mCRPC treatment by the DOC+ADT hazard ratio for rPFS.
- SA03: Differentiate 1st line mCRPC treatment effectiveness in line with the central estimates of the company ITC.

- SA04: Differentiate 1st line mCRPC treatment effectiveness in line with the central estimates of the company ITC, also setting 1st line mCRPC abiraterone use to zero with these patients instead being treated with enzalutamide.
- SA05: Apply a quality of life increment for ADT (post DOC+ADT) compared to ADT of half that of AAP+ADT treatment effect of the LATITUDE quality of life regression.
- SA06: Apply a quality of life decrement for ADT (post DOC+ADT) compared to ADT of [redacted] as per the company base case.
- SA07: Drop the LATITUDE quality of life regression coefficients for SAEs and SREs and instead apply the smaller decrements that the company derives from the literature.
- SA08: Apply the LATITUDE quality of life regression that does differentiate the SAE coefficient between the arms.
- SA09: Apply the company base case mCRPC treatment percentages.
- SA10: Apply the compliance percentage for abiraterone derived by the company from the LATITUDE rPFS and TTD Kaplan Meier curves.
- SA11: Differentiate the frequency of monitoring with bone scans for those receiving a course of docetaxel and for those who have received a course of docetaxel in the past from that of the AAP+ADT arm as per the company base case.

The ERG revised base case which applies the MSM/TA387 model results in the following estimates.

Table 63 ERG revised base case: MSM/TA387 model: deterministic

	LYs	QALYs	Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	5.030	3.289	[redacted]				
ADT	3.505	2.213	[redacted]	1.525	1.076	£19,362	£17,992
DOCE	4.360	2.845	[redacted]	0.671	0.444	£13,965	£31,439

The MSM/TA387 model probabilistic estimates are aligned with the deterministic estimates. The CEACs are presented below.

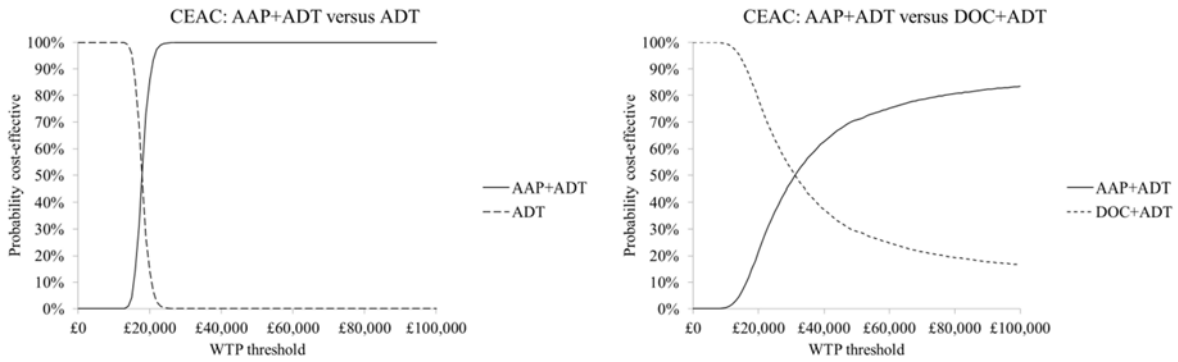


Figure 10 ERG revised base case: MSM/TA387 model: CEACs

The ERG revised base case which applies the MSM model results in the following estimates.

Table 64 ERG revised base case: MSM model: deterministic

	LYs	QALYs	Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	5.129	3.249	[redacted]				
ADT	3.597	2.158	[redacted]	1.532	1.091	£22,751	£20,855
DOCE	4.365	2.761	[redacted]	0.764	0.488	£20,353	£41,697

The MSM model probabilistic estimates are aligned with the deterministic estimates. The CEACs are presented below.

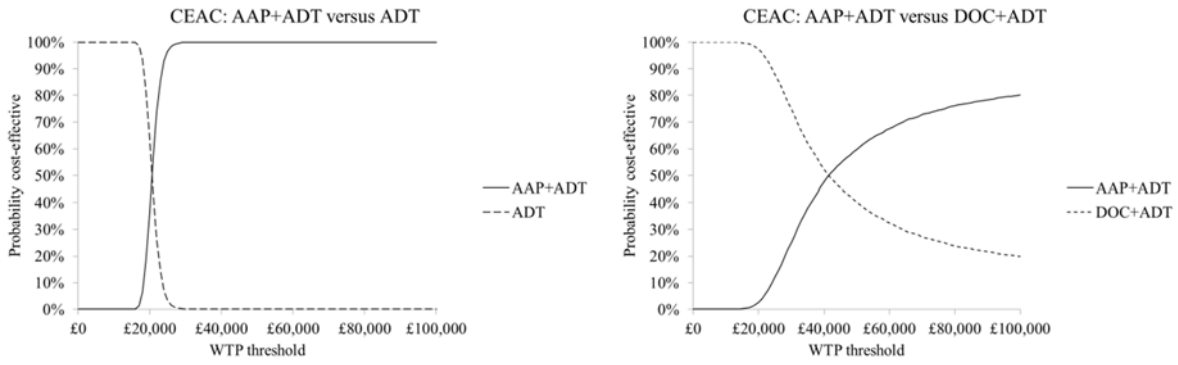


Figure 11 ERG revised base case: MSM model: CEACs

The ERG sensitivity analyses which apply the MSM/TA387 model result in the following estimates.

Table 65 ERG scenario analyses: MSM/TA387 model

	AAP+ADT vs ADT			AAP+ADT vs DOC+ADT		
	Δ QALYs	Δ Costs	ICER	Δ QALYs	Δ Costs	ICER
Base case	1.076	[redacted]	£17,992	0.444	[redacted]	£31,439
01a: KM 4mth	1.106	[redacted]	£17,479	0.460	[redacted]	£30,270
01b: KM 7mth	1.036	[redacted]	£18,453	0.419	[redacted]	£34,479
02: Same prob PPS Tx	..	[redacted]	..	0.441	[redacted]	£33,897
03: Diff effect mCRPC Tx	1.059	[redacted]	£17,687	0.425	[redacted]	£31,001
04: 03 + ENZA Tx prop.	1.049	[redacted]	£12,118	0.414	[redacted]	£16,714
05: DOC QoL increment	..	[redacted]	..	0.396	[redacted]	£35,255
06: DOC QoL decrement	..	[redacted]	..	0.516	[redacted]	£27,077
07: Company SAE/SRE QoL	1.112	[redacted]	£17,417	0.563	[redacted]	£24,805
08: Original LATITUDE QoL	1.086	[redacted]	£17,828	0.436	[redacted]	£32,046
09: Company mCRPC prop.	1.069	[redacted]	£18,336	0.437	[redacted]	£32,499
10: Company AAP % use	1.069	[redacted]	£16,837	0.437	[redacted]	£28,840
11: Company DOC scans	1.076	[redacted]	£18,181	0.444	[redacted]	£26,285

The ERG sensitivity analyses which apply the MSM model result in the following estimates.

Table 66 ERG scenario analyses: MSM model

	AAP+ADT vs ADT			AAP+ADT vs DOC+ADT		
	Δ QALYs	Δ Costs	ICER	Δ QALYs	Δ Costs	ICER
Base case	1.091	[redacted]	£20,855	0.488	[redacted]	£41,697
01a: KM 4mth	1.127	[redacted]	£20,295	0.503	[redacted]	£40,258
01b: KM 7mth	1.036	[redacted]	£21,407	0.462	[redacted]	£44,826
02: Same prob PPS Tx	..	[redacted]	..	0.483	[redacted]	£43,544
03: Diff effect mCRPC Tx	1.091	[redacted]	£20,858	0.488	[redacted]	£41,704
04: 03 + ENZA Tx prop.	1.093	[redacted]	£18,733	0.490	[redacted]	£37,562
05: DOC QoL increment	..	[redacted]	..	0.440	[redacted]	£46,253
06: DOC QoL decrement	..	[redacted]	..	0.560	[redacted]	£36,366
07: Company SAE/SRE QoL	1.127	[redacted]	£20,182	0.610	[redacted]	£33,386
08: Original LATITUDE QoL	1.101	[redacted]	£20,666	0.480	[redacted]	£42,425
09: Company mCRPC prop.	1.091	[redacted]	£21,690	0.488	[redacted]	£43,562
10: Company AAP % use	1.084	[redacted]	£19,735	0.481	[redacted]	£39,491
11: Company DOC scans	1.091	[redacted]	£20,903	0.488	[redacted]	£36,676

The two models are sensitive to the same elements:

- Applying the LATITUDE Kaplan Meier data for a longer period worsens the cost effectiveness estimates.
- Assuming that DOC+ADT patients who progress have the same probability of receiving treatment for mCRPC as those in the AAP+ADT arm worsens the cost effectiveness estimate.
- Differentiating 1st line mCRPC treatments' effectiveness has little effect. But assuming patients prefer enzalutamide rather than abiraterone for 1st line mCRPC treatment improves the cost effectiveness estimates. Both costs and QALYs are affected due to enzalutamide not being associated with a quality of life treatment effect increment compared to ADT, whereas abiraterone is.
- Quality of life increments and decrements for ADT (post DOC+ADT) have the predictable effects.
- Not applying the LATITUDE QoL regression in full but deriving SAE and SRE decrements from values in the literature improves the cost effectiveness estimates by quite a lot.
- Applying the company mHSPC abiraterone compliance percentage improves the cost effectiveness estimates.
- Applying the company bone scan frequencies for DOC+ADT improves the cost effectiveness estimates by quite a lot.

5.5 Conclusions of the cost effectiveness section

In the opinion of the ERG the 1st line mCRPC costs and benefits estimates of both the MSM/TA387 model and the MSM model are not reliable. This calls into question the reliability of the cost effectiveness estimates.

The company have a strong preference for the MSM/TA387 model over the MSM model. But given the ad hoc 2.62 OS hazard ratio, the implementation of the MSM/TA387 model is in large part an elaborate non-statistical method of fitting curves to the LATITUDE Kaplan Meier OS curves. This seems to negate the main company argument for developing the MSM/TA387 model: that neither the LATITUDE post rPFS survival data nor the LATITUDE Kaplan Meier OS curves are relevant to the UK. If curves are to be fitted to the LATITUDE Kaplan Meier OS curves it may be better to use the usual well-established

statistical methods, which would also allow time varying probabilities such as those of the Weibulls.

The company choose to apply the hazard ratio estimates of the mHSPC ITC to the AAP+ADT probabilities to estimate the DOC+ADT probabilities. It could equally well have chosen to apply them to the ADT probabilities to estimate the DOC+ADT probabilities. This worsens the cost effectiveness estimates. Both methods result in an anomalous estimate for DOC+ADT for the probability of mCRPC patients receiving 1st line mCRPC treatment.

The Committee may be more equipoise between the MSM model and the MSM/TA387 model than the company. The most important difference between them is the amount of time they model patients spending on 1st line, 2nd line and 3rd line mCRPC treatment. These durations are not affected by the ERG's concerns around the estimates of 1st line mCRPC costs and benefits. Alternatively, the Committee may prefer a partitioned survival analysis, or a presentation of fitted curves by way of model validation.

Given the company preferred modelling approach and the company ITC results [redacted]. This does not much affect results.

There is uncertainty about what 1st line mCRPC treatments proportions should be applied subsequent to AAP+ADT, ADT and DOC+ADT treatment for mHSPC. This is likely to become more important if the models' estimates of 1st line mCRPC treatments' costs and benefits are corrected.

The ERG view the company cost effectiveness estimates as perhaps biased in favour of AAP+ADT because:

- It is questionable whether there is a quality of life decrement for those who have completed a course of docetaxel compared to those who have only ever received ADT. There are reasons to suppose there may be an increment.
- If there is a quality of life decrement for those who have completed a course of docetaxel the company commissioned TTO study that estimates this may be biased.

- The company estimates of the quality of life decrements for docetaxel are only applied in the DOC+ADT arm, and not to docetaxel treatment for mCRPC in the AAP+ADT arm or the ADT arm.
- The company only partially apply the results of the LATITUDE QoL regression, which pushes up quality of life values to above those observed during the LATITUDE trial.
- The treatment compliance estimate for abiraterone for mHSPC seems low compared to CSR data on compliance.
- The treatment compliance estimate for docetaxel for mHSPC is not applied to the same range of costs as the compliance estimate for abiraterone.
- The treatment compliance estimates for mCRPC do not take into account that they reflect discontinuations during the relevant trials. Unadjusted compliance rates are applied to the MSM/TA387 model mCRPC treatment discontinuation curves. This mainly affects mCRPC treatments in the AAP+ADT arm.
- The ERG cannot find evidence that DOC+ADT is associated with more bone scans than both AAP+ADT and ADT, or that ADT (post DOC+ADT) is associated with more bone and CT scans than both AAP+ADT and ADT. It is mainly the latter that affects results.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG have made a number of revisions and corrections to the MSM/TA387 model and the MSM model. Most notably:

- Applying the full LATITUDE quality of life regression so that the quality of life values reflect those observed during the trial.
- Not applying the company quality of life decrement for those who have completed a course of docetaxel for mHSPC. The ERG consider the evidence presented by the company for this as rather thin. There is trial data which suggest there may actually be an increment.
- Applying an estimate of the proportion of abiraterone mHSPC patients that incurs abiraterone treatment costs based upon compliance data in the clinical study report. The company estimate derived from the LATITUDE rPFS and TTD curves seems too low, particularly towards the end of these curves.
- Equalising the frequency of bone scans for those who have completed a course of docetaxel for mHSPC with those receiving abiraterone for mHSPC in the AAP+ADT arm.

Each of these changes has a reasonable impact upon the cost effectiveness estimates. The full details of this and other sensitivity analyses are presented in section 5.4 above.

When using the MSM/TA387 model these changes taken together worsen the cost effectiveness estimates from £17,418 per QALY to £17,992 per QALY for the comparison of AAP+ADT with ADT and from £17,828 per QALY to £31,439 per QALY for the comparison of AAP+ADT with DOC+ADT.

When using the MSM model these changes taken together worsen the cost effectiveness estimates from £20,438 per QALY to £20,855 per QALY for the comparison of AAP+ADT with ADT and from £26,909 per QALY to £41,697 per QALY for the comparison of AAP+ADT with DOC+ADT.

The probabilistic estimates are aligned with these deterministic estimates.

7 Overall conclusions

The company's submission considered abiraterone acetate (Zytiga, Janssen-Cilag Ltd.) with prednisone/prednisolone (AAP) plus androgen deprivation therapy (ADT) for the treatment of adults with newly diagnosed, high risk mHSPC.

7.1 Clinical effectiveness evidence

The NICE final scope specified AAP+ADT compared with ADT alone or docetaxel+ADT in adults with newly diagnosed high risk metastatic hormone-naïve prostate cancer (mHNPC). The population addressed in the company submission is adults with newly diagnosed, high risk mHSPC. The company state that the terms mHNPC and newly diagnosed mHSPC are effectively the same because newly diagnosed patients are, by default, hormone naïve. The company submission also did not consider orchidectomy and bicalutamide monotherapy, as part of ADT alone treatment, as their clinical experts advised that these are seldom used in the UK.

The submission focuses on the results of the LATITUDE trial, which provide evidence of the benefits of AAP over ADT for the treatment of men with mHSPC. The benefit found in LATITUDE is evident for the primary outcomes of overall survival and progression measured by rPFS and extends to the secondary outcomes for safety and quality of life. The results of LATITUDE are similar to those from the STAMPEDE study. However, the STAMPEDE patient group was broader and while the company have conducted similar analyses on a post hoc subgroup meant to be similar to the LATITUDE population, they rightly have not combined them in any further analyses.

Less reliable are the company results of AAP compared with other treatments, predominately docetaxel. With no head-to-head studies available, these were compared using indirect methods. The company chose NMA at this stage, which the ERG agree, was sensible. When conducting the NMA the company used the recommended WinBUGS program from the NICE DSU TSD 2.[49] They were restricted to only fixed effects models because of the lack of studies and links between treatment groups. Further concerns are the many aspects of heterogeneity between the

studies, all recognised by the company. So while the ERG confirm the results provided showing AAP to be at least equivalent to docetaxel, there is a concern that estimates from these results will not be robust. There were no checks of statistical heterogeneity or consistency commented on. As such any economic modelling on these estimates will require caution and various scenarios to reflect these concerns.

The company also attempted to assess the efficacy of AAP+ADT for patient with disease progression (mCRPC) compared with other treatments. They focus on docetaxel, radium-223 and enzalutamide. The more robust method of NMA was not chosen and instead the company used Bucher pairwise comparisons. While NMA are more useful when making choices between multiple alternatives, the ERG confirm that NMA models did not converge probably due to the limited number of studies and data so that Bucher pairwise estimates were a reasonable alternative. For this patient group, the estimates show AAP to be comparable with other treatments. However, since checks of statistical heterogeneity or fit were not provided and as before the conceptual heterogeneity (e.g., differences in study populations, study setting, follow-up procedures, outcome measures) was extensive, caution for further economic modelling is warranted.

7.2 Cost-effectiveness evidence

It appears that the 1st line mCRPC costs and benefits estimates of both the MSM/TA387 model and the MSM model are not reliable. All cost effectiveness estimates may consequently not be reliable.

The company have a strong preference for the MSM/TA387 model over the MSM model. Due to the ad hoc 2.62 hazard ratio this is in large part an elaborate non-statistical method of fitting curves to the LATITUDE Kaplan Meier OS curves. If curves are to be fitted to the LATITUDE Kaplan Meier OS curves it may be better to use the usual well-established statistical methods, which would also allow time varying probabilities to be explored.

The Committee for this appraisal may be more equipoise between the MSM model and the MSM/TA387 model than the company. The most important difference between them is the amount of time they model patients spending on 1st line, 2nd line

and 3rd line mCRPC treatment. Alternatively, the Committee may prefer a partitioned survival analysis, or a presentation of statistically fitted curves by way of model validation.

There is uncertainty about what 1st line mCRPC treatments proportions should be applied subsequent to AAP+ADT, ADT and DOC+ADT treatment for mHSPC. This is likely to become more important if the models' estimates of 1st line mCRPC treatments' costs and benefits are corrected.

The company cost effectiveness estimates may be biased in favour of AAP+ADT because:

- It is questionable whether there is a quality of life decrement for those who have completed a course of docetaxel compared to those who have only ever received ADT. There are reasons and trial data to suppose there may be an increment.
- If there is a quality of life decrement for those who have completed a course of docetaxel the company commissioned TTO study that estimates this may be biased.
- The company estimates of the quality of life decrements for docetaxel are only applied in the DOC+ADT arm, and not to docetaxel treatment for mCRPC in the AAP+ADT arm or the ADT arm.
- The company only partially apply the results of the LATITUDE QoL regression, which pushes up quality of life values to above those observed during the LATITUDE trial.
- The treatment compliance estimate for abiraterone for mHSPC seems low compared to the CSR data on compliance.
- The treatment compliance estimate for docetaxel for mHSPC is not applied to the same range of costs as the compliance estimate for abiraterone.
- The treatment compliance estimates for mCRPC do not take into account that they reflect discontinuations during the relevant trials. This mainly affects mCRPC treatments in the AAP+ADT arm.
- The ERG cannot find evidence that mHSPC patients who have completed their course of docetaxel and are only receiving ADT in the DOC+ADT arm have more routine bone scans than mHSPC patients in the AAP+ADT arm.

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9 Appendices

Appendix 1 TTO study three main health states

ADT	DOC+ADT	ADT (post DOC+ADT)
[redacted]		

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Abiraterone for treating newly diagnosed metastatic hormone-naive prostate cancer [ID945]

You are asked to check the ERG report from the Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 20 April** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Clinical effectiveness – Bayesian ITC in mHSPC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 4 of the ERG report it incorrectly states: *"These probabilities represent a level of certainty that AAP+ADT patients may be more likely to survive or have progression free survival using AAP+ADT compared with DOC+ADT."*	The proposed amendment is to change the wording to: *"These probabilities represent a level of certainty that AAP+ADT patients may be more likely to survive longer or have longer progression free survival using AAP+ADT compared with DOC+ADT."*	Words are missing when describing the definition of Bayesian pairwise probabilities in the clinical summary, meaning the current text does not interpret results correctly.	We appreciate that the wording proposed by the company is more precise. However, this does not affect the overall results and conclusions. No revision required.
On page 6 of the ERG report it incorrectly states: *"The NMA results showed no evidence of a difference in OS and rPFS between AAP+ADT and DOC+ADT, despite the many sub-group analyses using many combinations of patient groups in an attempt to mirror the LATITUDE population."* It is incorrect to state there is no evidence of a difference in OS and rPFS between AAP+ADT and DOC+ADT, when Bayesian ITC results have been presented. Additionally, on page 65 the Bayesian ITC results for OS and rPFS have been inaccurately interpreted: *"The results suggest non-significant effects for OS (HR 0.92, 95% CrL 0.69-*	The proposed amendment is to change the wording to: *"The Bayesian ITC showed that, when compared to DOC+ADT, AAP+ADT was highly likely to be superior in terms of rPFS, and at least as effective, but likely superior, in terms of OS. Consistent results were attained through sub-group analyses using many combinations of patient groups in attempt to mirror the LATITUDE population."* The proposed amendment is to change the wording to: *"The results presented in Table 21 demonstrate that, when compared to docetaxel+ADT, AAP+ADT has a 71.8% probability of being the better life*	There is no concept of statistical significance in Bayesian statistics. Point estimates present the median value of the 50,000 run-in iterations performed and are accompanied by credible intervals (CrIs; indicating a 95% probability of where the true value lies within the CrIs) and a Bayesian pairwise probability (indicating the probability of the treatment of interest being more effective than the other comparators assessed in the network). In contrast to a Frequentist ITC, which reports confidence intervals (CIs) and interprets the CIs crossing one as an indication of a lack of statistical significance, credible intervals crossing one in a Bayesian ITC has no relation to statistical significance.	The ERG accepts the proposed amendments. For clarity we have also added the following sentence in the paragraph proposed by the company on page 6: "*However, there is uncertainty about the size of effect as reflected in the credible intervals."*

1.23) and rPFS (HR 0.76, 95% CrL 0.53-1.10) presented in Table 21 but with Bayesian probabilities of 71.8% and 92.9%, respectively, suggesting AAP+ADT is a better life prolonging treatment option."	*prolonging treatment option (HR 0.92, 95% CrL 0.69-1.23) and a 92.9% probability of being better at delaying disease progression (HR 0.76, 95% CrL 0.53-1.10)."*		
On page 4 of the ERG report, the Bayesian ITC results for AST and ALT have been inaccurately interpreted: [redacted] Similar statements are made on page 65.	The proposed amendment is to change the wording to: [redacted]	As above	This sentence should be read in the context of the entire paragraph on page 4 where risk associated to anaemia, constipation, fatigue, peripheral oedema, AST, ALT and hot flushes are described. No revision required.
On page 81 of the ERG report, the Bayesian probability of [redacted]% has been incorrectly converted to a p-value of [redacted].	Janssen request incorrect interpretation of this Bayesian probability and a p-value is removed from the report.	As above	Proposed amendments accepted.
On page 5 of the ERG report, the Bayesian ITC results for FACT-P and BPI have been incorrectly interpreted: *"At 3 months, AAP+ADT had a significant positive and beneficial increase on FACT-P over DOC+ADT, with difference of change = 4.20 (95% CrL 1.18-7.19) and a 99.7% probability of AAP being better than DOC. AAP estimates improved further over time as*	The proposed amendment is to change the wording to: *"At 3 months, there was 99.7% probability that AAP+ADT was associated with better quality of life than DOC+ADT (95% CrL 1.18-7.19). AAP estimates improved further over time as did the DOC estimates (not to the same extent and never to the level of AAP), and the probability of AAP+ADT being*	As above	Some findings have been incorrectly interpreted due to typographical errors in Table 21 of the company submission. Paragraph on page 5 has been revised.

did the DOC estimates (not to the same extent and never to the level of AAP), but differences between AAP and DOC were not significant by 6 months or even at 1 year. BPI results showed larger decreases in pain estimates for indirect comparisons between AAP and DOC, but the results were not significant." Similar statements are made on page 66.	*superior remained high at 6, 9 and 12 months (94.5%, 97.0% and 92.3%, respectively). BPI results showed an 88-100% probability of AAP+ADT being better at reducing pain than DOC+ADT over the 12-month period."*		
On page 73 + 147 of the ERG report it states: *"Less reliable are the company results of AAP compared to other treatments, predominately docetaxel.."*	The proposed amendment is to change the wording to: *"Less certain are the company results of AAP+ADT versus docetaxel+ADT in patients with newly diagnosed high-risk mHSPC"*	Janssen believe that the current text is both inaccurate and misleading for two key reasons. Firstly, in mHSPC, AAP is indicated with ADT and therefore should be recognised as 'AAP+ADT' when discussed in relation to this setting. Secondly, there are only two treatments available in mHSPC: ADT alone and docetaxel+ADT. The clinical benefit of AAP+ADT vs. ADT alone is clear (as agreed by the ERG) and Janssen acknowledge the comparative evidence of AAP+ADT vs. docetaxel+ADT is associated with a degree of uncertainty; there are no other treatments.	We agree that the wording could have been more precise. However, this does not impact on the overall results and conclusions. No revision required.

Issue 2 Clinical effectiveness – Bucher's ITC in mCRPC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 5 of the ERG report it states: *[Whole paragraph] "In the absence of any head-to head studies, further indirect comparisons were conducted for a group of men with disease progression (for the mCRPC group with respect to the effectiveness of AAP with other treatments including DOC). […] In general, the estimates show that AAP is comparable with other treatments."* Similar discussion is made on page 67. On page 6 of the ERG report it states: *[Whole paragraph] "For the relapsing/progression patients, the mCRPC group, the ITC used were Bucher pairwise estimates comparing other treatments with AAP. […] The conclusion that AAP is comparable to other treatments with regard to OS and rPFS is probably reasonable. […] However, no checks were provided for statistical heterogeneity or consistency."* Similar discussion is made on page 74.	Janssen request that the ERG move text currently on pages 5 and 6 to Section 1.4. as they are both a summary of methodology used in the cost-effectiveness evidence submitted by the manufacturer. Janssen request that the ERG move text currently on pages 67 and 74 to Section 5.2.6 as they are both discussion of methodology used in assessing treatment effectiveness in mCRPC.	This appraisal is assessing the clinical effectiveness of AAP+ADT in mHSPC and clinical discussion should focus on the pivotal data presented by Janssen for this specific indication. The Bucher's ITC assessing treatments in mCRPC was conducted to inform the mCRPC health states of the economic model only. It is therefore inappropriate and misleading to discuss the two ITCs (Bayesian in mHSPC and Bucher's in mCRPC) in parallel, as the latter is not directly informing the clinical effectiveness of AAP+ADT in mHSPC. Janssen emphasise that discussion of this analysis is only relevant for critique of the methods used in cost-effectiveness analysis and should be reserved for the appropriate sections of the ERG report, not discussed in the forefront of clinical evidence.	We agree that the Bucher's ITCs assessing treatments in mCRPC were conducted to inform the health states of the economic model. However, they provide evidence on the effects of AAP+ADT versus other treatments for people who progressed to mCRPC. For this reason we decided to present and critique them in the clinical effectiveness section of the ERG report. We have also stated in our report (page 67) that the company did not present these ITCs in the clinical effectiveness section of the submission. Not a factual error. No revision required.

On page 6-7 of the ERG report it incorrectly states: *"All of these mean that clinically, the ERG agree with the company's conclusions that AAP is at least as effective as other treatments for both newly diagnosed patients and those who have relapsed or progressed."*	Janssen request that this inaccurate interpretation of ITC results in both mHSPC and mCRPC be removed from the report. The proposed amendment is to change the wording to: *"All of these mean that clinically, the ERG agree with the company's conclusions that, in patients with newly diagnosed high-risk mHSPC, AAP+ADT is clinically superior to ADT alone and is at least as effective as docetaxel+ADT, and in patients with mCRPC, AAP is as effective as other novel therapies available."*	Current text in the ERG report is factually inaccurate and misleading as it combines conclusive statements on the clinical effectiveness of AAP+ADT in mHSPC and AAP in mCRPC. Janssen conclude that the use of AAP+ADT in patients with newly diagnosed high-risk mHSPC is statistically and clinically superior to ADT alone, in terms of both rPFS and OS. Janssen also conclude that, in this same setting, AAP+ADT is highly likely to be superior (92.9%) to DOC+ADT in terms of rPFS, and at least as effective, but likely superior (71.8%) in terms of OS. When subsequently assessing the effectiveness of treatments in mCRPC for economic modelling, Janssen propose that, given the highly heterogeneous Bucher's ITC, it is reasonable to conclude AAP has comparable effectiveness to other novel agents in 1L mCRPC.	We appreciate that the wording suggested by the company is more precise. However, this does not affect the overall results and conclusions. No revision required.
On page 125 of the ERG report it states: *"The company MSM/TA387 model structure is largely justified by the company on the basis of the need to properly model the effects of extending rPFS upon OS; i.e., the LATITUDE data for rPFS are reliable but thereafter the modelling needs to depart from the LATITUDE data. This argument would*	The proposed amendment is to change the wording to: *"The company MSM/TA387 model structure is largely justified by the company on the basis of the need to properly model the effects of extending rPFS upon OS; i.e., the LATITUDE data for*	The results of the Bucher's ITC for mCRPC therapies were not used in the company's base case due to limitations in this analysis. These included, notable clinical heterogeneity between the trials, differences in the criteria for patients enrolled in each study, heterogeneity between patient's time from diagnosis, and differences between the treatments received in each of the comparator	The paragraph on page 125 has been amended. We do not consider the statements on pages 67 and 72 misleading.

seem to imply that the statistically significant rPFS hazard ratio for enzalutamide treatment of mCRPC compared to abiraterone should also be reflected in the company base case." Similarly, inaccurate statements are made on pages 67 and 72. This text is currently misleading and provides an inaccurate interpretation of the Bucher's ITC which is misaligned with previous conclusions made by the ERG in which they a	*rPFS are reliable but thereafter the modelling needs to depart from the LATITUDE data."*	arms. Results of the Bucher's ITC were only presented to show the level of uncertainty in this analysis and hence justify simplifying assumption of equal efficacy between the active mCRPC therapies. The statistically significant HR produced for enzalutamide vs. abiraterone for rPFS is almost entirely driven by the difference in the comparator arms between the COU-AA-302 and PREVAIL study. Patients in the control arm of the COU-AA-302 study received placebo plus prednisolone and experienced median rPFS of 8.2 months, while patients in PREVAIL received placebo alone and experienced median rPFS of 3.9 months. Inspection of the rPFS KM data for enzalutamide and abiraterone demonstrates that there are minimal differences between the rPFS results between the two groups. In addition, the Bucher's ITC does not demonstrate any statistically differences in OS between abiraterone and enzalutamide. This is supported by the fact that the COU-AA-302 and PREVAIL trials appear to show comparable OS between the treatments (median OS of 35.3 months for abiraterone and 32.4 months for enzalutamide).	

Issue 3 The MSM/TA387 model scenario

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 12 of the ERG report it states: *"The company prefer the MSM/TA387 model over the MSM model. Due to the ad hoc 2.62 hazard ratio this is in large part an elaborate non-statistical method of fitting curves to the LATITUDE Kaplan Meier OS curves. The fitting of the MSM/TA387 model OS curves to the LATITUDE Kaplan Meier OS curves also seems to largely negate the reason for adopting the MSM/TA387 modelling approach."* Similar statements are made on pages: 8, 12, 83, 88, 121, 144 and 149. Janssen highlight that it is inaccurate of the ERG to state that the 2.62 value is 'ad hoc', and that the calibration factor is applied as a 'hazard ratio'.	The proposed amendment is to change the wording to: "*The company prefer the MSM/TA387 model over the MSM model. This method utilises a calibration factor of 2.62 to adjust the mCRPC survival curves to minimise the population differences between TA387 and LATITUDE patients who became mCRPC using the LATITUDE Kaplan Meier OS curves."*	The ERG is correct that the MSM/TA387 model uses a value of 2.62 to adjust the survival estimates from TA387 for mCRPC, however, this is not accurately described as a 'hazard ratio' and is also not 'ad hoc'. This value of 2.62 is a calculated calibration factor which is estimated using survival data from LATITUDE. The calibration is then applied to the survival by raising each estimate of OS to the power of the calibration factor. As discussed extensively within health economic literature calibration is a useful tool for estimating uncertain parameters (in this case, the difference in prognosis between patients with mCRPC who have progressed on front line treatment for newly diagnosed high-risk mHSPC, and those who were enrolled in trials for mCRPC yet include patients coming from different populations).[1] Calibration has been used in prior NICE submissions in similar circumstances where data are not available (e.g. TA322).	Not a factual error. No revision required. "*Ad hoc*" can be defined as follows: "*for a particular purpose or need, esp. for an immediate need*". It is common practice to apply a hazard ratio, HR, to a survival curve, S(t), as S(t)^HR. So, it seems reasonable to describe the calibration factor as a hazard ratio, and in this particular case as an *ad hoc* hazard ratio, rather than to use the vague description of "*calibration factor*".

Issue 4 STAMPEDE

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 2 & 28 of the ERG report it incorrectly states: *"The manufacturer-sponsored STAMPEDE trial.."*	The proposed amendment is to change the wording to: *"The investigator-sponsored STAMPEDE trial.."*	STAMPEDE is an investigator-sponsored study, not a manufacturer-sponsored trial.	Proposed amendment accepted. Phrases have been revised on pages 2 and 38 (not 28).
On page 11 of the ERG report it incorrectly states: *"the company submission is weakened by being reliant upon data from only one RCT."*	The proposed amendment is to change the wording to: *"the majority of the company submission is based on the pivotal RCT, LATITUDE, and is strengthened by supportive evidence from STAMPEDE."* As such, Janssen highlight that this is a strength and not a weakness to the submission therefore suggest this text is moved to Section 1.6.1.	Although majority of data is provided from the LATITUDE study, STAMPEDE provides strong supportive evidence for the clinical effectiveness of AAP+ADT in mHSPC throughout. STAMPEDE represents the largest evidence base investigating AAP+ADT in early prostate cancer, providing data specific to UK clinical practice therefore Janssen would challenge statements suggesting the clinical evidence base was a weakness of the submission.	In the company submission, the main source of evidence is the LATITUDE trial. Not a factual error. No revision required.
On page 46 (Table 12) of the ERG report: The confidence intervals for both time to PSA progression and time to next SRE outcomes are marked as AIC.	This data can be unmarked	Minor inaccuracy	CIs have been unmarked.

Issue 5 mCRPC treatment costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 10 of the ERG report it states: *"It appears that the 1st line mCRPC costs and benefits estimates of both the MSM model and the MSM/TA387 model are not reliable. All cost effectiveness estimates may consequently not be reliable."* Similar statements are also made on pages: 12, 120, 144 and 149 On page 86 of the ERG report it states: *"As far as the ERG can ascertain, the 1st line mCRPC treatment costs are calculated as the prevalent 1st line mCRPC on treatment population multiplied by a time invariant arm specific weekly treatment cost. These are then qualified by whether the model cycle is during the 1st year, so 1 week long, or subsequent to this, so 4 weeks long. The treatment costs relate to those who are on treatment and incurring costs. This will not address the time dependent profiles of:* • *Abiraterone costs, due to* [redacted] • *Docetaxel costs, due to a maximum of 10 cycles of 3 weeks* • *R-223 costs, due to a maximum of 6 treatments separated by 4*	The proposed amendment is to change the wording to: *"As far as the ERG can ascertain, the 1st line mCRPC treatment costs are calculated as the prevalent 1st line mCRPC on treatment population multiplied by an arm specific weekly treatment cost. These are then qualified by whether the model cycle is during the 1st year, so 1 week long, or subsequent to this, so 4 weeks long."* Janssen request the addition of CIC marking as indicated in the description of the problem. In addition, Janssen would ask the ERG to consider the proposed amendment as evidence to alleviate concerns around fixed duration treatment given the ERG were unable to address the concern.	Throughout the ERG report concerns are raised regarding the estimation of treatment costs throughout the mCRPC phase of the model. Although Janssen acknowledge that there are potentially some limitations in the way that these costs are estimated, some of the claims from the ERG are misleading. Whilst the ERG are right to acknowledge that there are limitations in the way fixed duration treatment costs (docetaxel, radium-223 and cabazitaxel) are calculated during the mCRPC phase of the model, they have not recommended any alternative, nor attempted any rectification. As such, the way the report is currently written only over-states the limitations and does not provide the Committee with the information needed for decision making. Janssen acknowledge that these limitations are in part due to the cohort structure of the model, which limits the ability of the model to track individual patients over time and calculate treatment costs with complete precision. However, an alternative method for estimating these costs, which attempts to	Not a factual error. No textual revision required. However, the ERG agrees with the Janssen request about the confidentiality of nature of the abiraterone. Janssen is incorrect to state that the ERG has not proposed any correcting amendment. The first sub-section of section 5.3.4 discusses in reasonable detail applying a present value of time varying mCRPC costs and quality of life values, taking into account the time horizon. It also outlines why the ERG has not undertaken this.

weeks • *Cabazitaxel costs, due to a maximum of 10 cycles of 3 weeks."* And: *"The ERG is particularly concerned about the handling of the costs and benefits of 1st line treatment for mCRPC among patients who have progressed from their mHSPC. These are central to the cost effectiveness estimates because for AAP+ADT they provide net cost offsets to the mHSPC abiraterone drug costs.* *The ERG have not attempted to address its concerns about the handling of 1st line mCRPC costs and benefits. To do so requires extensive remodelling to the extent that the major part of the model would be an ERG model rather than a company model. Moreover, it is not responsibility of the ERG to conduct such extensive remodelling."* The way the report is currently written over-states the limitations and as no attempt at rectification was attempted does not provide the Committee with the information needed for decision making, and is misleading.		address the concerns raised by the ERG, has been applied to the ERGs version of the model. This method calculates the cost of therapies which are given continuously (abiraterone, enzalutamide, BSC) in the same manner, utilising the calibrated discontinuation curve from TA387 to estimate time on treatment; however it estimates the costs of the fixed duration therapies in a different manner. Due to the difficulties in tracking patients over time, the costs of these therapies are applied as a one-off cost at the point at which patients are assumed to start receiving treatment. When this alternative method is applied in the ERGs base case model, the results remain fairly consistent with the previous method utilised (presented in Issue 13 below). This highlights that the results of the model are reliable.	

Issue 6 Compliance and discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 9 of the ERG report it states: *"Drug costs for mHSPC have treatment compliance percentages applied to them. The company estimate an 88% percentage for abiraterone based upon the areas under the LATITUDE AAP+ADT arm rPFS and TTD curves."* Similar statements are made on pages: 11, 13, 101, 135, 136, 146, 147 and 150. The ERG report claims that an estimate of 88% was applied to adjust the cost of abiraterone based on treatment compliance however this is incorrect as the 88% does not represent compliance.	The value of 88% value was applied to patients in the pre-progression health state to estimate the proportion of patients who were still on treatment, based on the time to treatment discontinuation (TTD) curve. This value enables the adjustment of costs based on treatment discontinuation prior to rPFS, and not compliance. Compliance is a separate issue. The proposed amendment is to change the wording to: *"In the absence of an "on-treatment" health state, the drug costs for abiraterone in mHSPC are estimated by multiplying the number of patients in the pre-progression health state by the ratio of the mean time on treatment and the mean pre-progression period. This ratio was estimated using the TTD and rPFS KM data which produced a value of 0.88."* The correction for this issue in the model is described in Issue 12 below.	As per the LATITUDE protocol, patients treated with AAP+ADT or ADT alone could discontinue treatment for reasons other than progression and thus still experience a pre-progression period off-treatment. Since docetaxel treatment is fixed duration, this logic is also applicable for patients treated with docetaxel+ADT. The inspection of the TTD and rPFS KM curves demonstrated that the majority of patients discontinued therapy prior to disease progression, meaning that an estimate of the time on treatment was required to calculate the cost of abiraterone. However, the average time patients spent on or off treatment during the mHSPC phase of the model could not be estimated using MSM, as including an off-treatment health state in the analysis resulted in the MSM failing to converge. The TTD KM data was thus used to estimate the mean time patients spent on treatment and dividing it by the mean time prior to disease progression, which is estimated in the same way using KM data for rPFS. This ratio (0.875 for AAP + ADT) was then multiplied by the number of	Not a factual error. No revision required. The ERG agrees that this issue is central to the assessment. The ERG has been careful in the wording around the treatment of the data the ERG takes from the CSR as per Table 61 of the ERG report. These data may need further consideration and explanation during the AC. This also cannot be considered in isolation from the ERG discussion of the rFPS and TTD curves of pages 133-134 of the ERG report, Figure 9 of the ERG report and the company uncritical acceptance of the end of curves TTD/rPFS ratio which to the ERG seems rather lower than might be anticipated in practice. Expert opinion during the AC may be able to comment upon what proportion of mHSPC patients who remain progression free and in mHSPC at 40 months would be expected to have discontinued their AAP+ADT treatment at 40 months.

		patients in the pre-progression health state in each cycle. This value does not represent compliance. It should be noted that the compliance estimates applied by the ERG in the model represent a separate issue altogether. It is based on compliance being assessed in LATITUDE only while patients were still on treatment, confirming it is capturing something separate from discontinuation. In conclusion, the TTD to rPFS ratio of 0.88 still needs to be applied in the model either instead of, or in addition to, the compliance values applied by the ERG. If this is not applied then the ERG base case analysis assumes that all patients receive treatment till radiographic disease progression, which is not accurate based on the data reported from LATITUDE and does not result in an accurate estimate of the abiraterone treatment costs.	

Issue 7 Text relating to the CAA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 25 of the ERG report it states: [redacted]	The proposed amendment is to change the wording to: [redacted]	Janssen request the text be updated to align with revised submission.	Proposed amendment accepted.
On page 50 of the ERG report it states: [redacted]	The proposed amendment is to change the wording to: [redacted]	Janssen request the text be updated to align with revised submission.	Proposed amendment accepted.

Issue 8 Interpretation of Morgans et al.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 81/82 of the ERG report it states: *"The company have not explored the possibility of mapping from FACT-P to quality of life using the LATITUDE data as a possible means of exploring estimates based upon RCT data for AAP+ADT, DOC+ADT and ADT (post DOC+ADT) relative to ADT"*	Janssen request that the ERG removes this statement, and other similar statements, as they do not present a balanced case of the submission process.	This section of the report currently implies that evidence was deliberately omitted in relation to the quality of life for docetaxel. The ERG refers to the Morgan et al (2018) paper as their main source of evidence to justify that mapping analysis should had been conducted. It should be noted that the paper by Morgan et al was published on 9th March 2018, therefore was not identified through literature review, nor had it been available at the time of the submission on 5th February 2018. As the ERG rightly acknowledge, the Morgans et al paper does not provide information in the same format as the model health states (although some of the wording around this is unclear in parts and would benefit clarification) and thus is not easy to compare to what is required in the model because: - FACT-P is not utility data - The Morgans et al paper does not provide information on the modelled health states – instead it provides trends over time regardless of health state In this context, Janssen should not be criticised for not conducting additional analysis to map	Not a factual error. No revision required. The main results of Morgan et al (2018) are reported in the abstract that the company summarises in Appendix H. However poor, it may have been preferable for the company to explore actual trial FACT-P patient data and what it might be taken to imply when viewed through summary statistics rather than completely ignore the trial FACT-P data when considering the likely quality of life in the DOC+ADT arm. As noted in the ERG report, the effect of relapses on the net improvement of FACT-P for AAP+ADT vs ADT and upon the net improvement of FACT-P for DOC+ADT vs ADT might be expected to favour AAP+ADT vs ADT.

		utilities from the FACT-P. Furthermore, in this section of the report the ERG also suggest that mapping from FACT-P, based upon summary statistics, might have been possible in order to compare to DOC+ADT. This suggestion is inappropriate and should be removed because, without access to patient level data, this sort of mapping is not possible. Indeed, this is the reason that the TTO study has been relied upon.	

Issue 9 Utility increment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 81-82 of the ERG report it states: *"The model requires estimates for quality of life increments or decrements relative to ADT for patients in rPFS. For rPFS specific estimates of FACT-P changes there may be some confounding between both AAP+ADT and ADT and DOC+ADT and ADT in the RCT data due to more progression with ADT than with either AAP+ADT or DOC+ADT.* *However, given the greater rPFS superiority for AAP+ADT over ADT compared to DOC+ADT over ADT, any such confounding might be expected to benefit AAP+ADT more than DOC+ADT. Yet, it cannot be unambiguously stated that the literature concludes that FACT-P changes for those remaining in rPFS are better among AAP+ADT patients than among ADT (post DOC+ADT) patients, or that they are better among ADT (post DOC+ADT) patients than among ADT patients."* Janssen believe these statements are unwarranted and misleading.	Janssen request that the ERG removes this statement, and other similar statements, as they are not aligned with the cost-effectiveness evaluation expected to be presented as part of a NICE submission and in their current form are misleading.	It is currently unclear what the ERG mean when saying *'it cannot be unambiguously stated'* of "*there may be some confounding".* However, Janssen believe these statements cast unwarranted uncertainty over QALY estimates presented in the submission. Janssen do not believe discussion of confounding is accurate in this context because the calculation of a QALY is dependent on the increased HRQL over time. As such, it is unclear how accounting for both increased quality of life and increased quantity of life associated with AAP+ADT over comparator treatments would cause confounding.	Not a factual error. No revision required. The ERG is simply trying to state that the model requires QoL values for rPFS when the trial FACT-P data will be among reporting patients some of whom will be in rPFS and some not. At a given time point more patients in the AAP+ADT arm than in the ADT arm will be in rPFS, though whether this rolls through to reporting patients is less clear. Consequently, the FACT-P values in the AAP+ADT arm are likely to be dragged down less by those in rPFS than in the ADT arm. The net effect may be to exaggerate the net FACT-P between rPFS patients in the AAP+ADT arm compared to the ADT arm. A similar but lesser effect is likely to apply in the Morgan et al data. Hence, the likely overall bias when comparing the net effect of AAP+ADT vs ADT and DOC+ADT vs ADT probably being in favour of AAP+ADT.

Adverse event costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 103 of the ERG report it states: *"The higher cost for DOC+ADT is due to 32% having neutropenia which may be reasonable to apply to those receiving docetaxel but may be less reasonable to those who have completed their course of docetaxel: ADT (post DOC+ADT) patients."* This statement is incorrect.	The proposed amendment is to change the wording to: *"The higher cost for DOC+ADT is due to 32% having neutropenia which may be reasonable to apply to those receiving docetaxel but may be less reasonable to those who have completed their course of docetaxel, i.e. ADT (post DOC+ADT) patients, which is why the model applies the AE rates related to ADT during the off-treatment period following completion of treatment with docetaxel."*	The wording is mis-leading to the reader and therefore would benefit from additional clarity. The ERG are correct that it would be less reasonable to apply these higher AE rates related to docetaxel to patients once they have competed their course of docetaxel therapy. The company base case model therefore only applies these higher AE rates for the first 18 weeks while patients receive treatment with docetaxel, and applies the AE rates of patients treated with ADT for the off-treatment period. Therefore, the ERGs statement may be interpreted in a mis-leading manner as it may imply to the reader that this is not the case.	The company is correct and the ERG accepts the proposed amendment. Paragraph on page 102 (not 103) has been revised.

Issue 10 Administration costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 119 of the ERG report it states: *"The ERG have not been able to source the £260 chemotherapy administration cost that is applied for docetaxel administrations."* On page 119 of the ERG report it also states: *"The ERG have been unable to source the average cost of £10.85 for ADT administrations. This has been calculated as £42*(15.5/60)."*	Janssen propose that these statements can be amended as further clarity has now been provided in response. The proposed amendment is to change the wording to: *"The ERG were able to source the £260 chemotherapy administration cost that is applied for docetaxel administrations following clarification from the company."* *"The ERG were able to source the average cost of £10.85 for ADT administrations following clarification from the company. This has been calculated as £42*(15.5/60) in line with the TA404 submission."*	The administration cost for chemotherapy is taken from the 2016-17 NHS reference costs. The cost can be found under chemotherapy regimens: description: DCRDN, code: Daycase and Reg Day/Night case, Detail: SB12Z. Deliver Simple Parenteral Chemotherapy at First Attendance. This cost was in line with the cost applied for chemotherapy in TA387; abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. The company submission reports that the administration cost of ADT therapy was sourced from based values reported in the UK National Schedule of Reference Costs. However, this statement was in fact an error. The administration cost for ADT was calculated in line with TA404; Degarelix for treating advanced hormone-dependent prostate cancer. The hourly cost of nurse time (£42) taken from PSSRU 2017 was used, assuming an average appointment length of 15.5 minutes in line with TA404.	The additional information provided by the company is welcomed. However, this is not a factual error. No revision required.

Issue 11 mCRPC scheduled MRU costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 104 the ERG report states: *"For reasons that are not given the company have not used the values of the clinical advisory board but have rather assumed that the planned MRU for mCRPC is equal between abiraterone and enzalutamide, and between docetaxel, R-223 and cabazitaxel. Applying the values of the clinical advisory board has minimal impact upon results."*	No amendment is required, however, for clarity this omission was an error within the original model rather than a deliberate omission. We agree with the ERG that the values from the advisory board should be used and would recommend using these in the base case.	Information provided for clarity.	Not a factual error. No revision required.

Issue 12 Suggested alterations to the ERG's model / correction of inaccuracies within ERG scenarios

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Following the review of the ERGs version of the model, Janssen believe that some minor alterations and corrections would increase the validity and robustness of the results. Therefore, Janssen have built in the functionality to allow the ERG to:
• See the results</td>
<td>A) Correctly applying the appropriate ADT AE disutility to patients who have completed their course of docetaxel therapy

In the amended ERG model there is the option to apply the ADT AE disutility value when the docetaxel off-treatment disutility of -0.03 is excluded. This is done by changing cell B95 on the ERG sheet to "TRUE". The formula contained in cell C32 on the "Utilities" sheet has been amended in order to apply this correction.

B) Applying treatment</td>
<td>Janssen believe that the suggested amendments will make the ICERs estimated by the ERG more robust as they not only address issues raised about the model by the ERG and also corrects errors in the ERG model identified by</td>
<td>A) Not an ERG factual error.
No revision required.

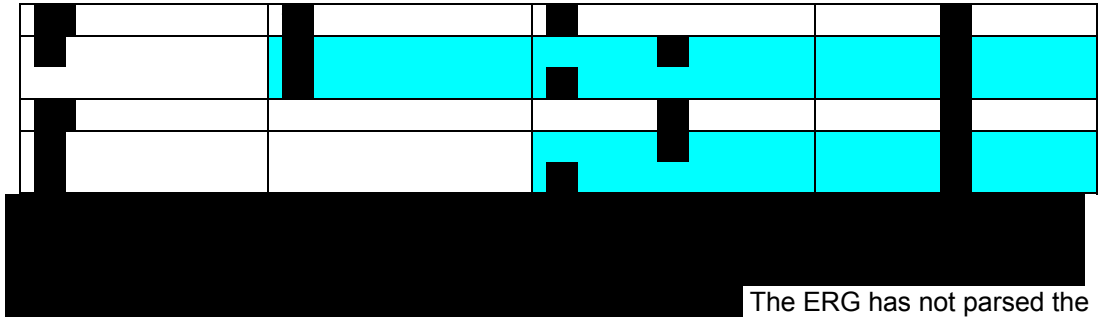
The company suggests that the ERG implementation of removal of the [redacted] decrement for ADT (post DOC+ADT) is incorrect. This is not the case. The ERG implementation correctly removes the [redacted] decrement[1]. The error the company alludes to has nothing to do with the ERG implementation of removal of the [redacted] decrement for ADT (post DOC+ADT).

The error is in the company implementation of the application of the full LATITUDE QoL regression. When this option is selected in the originally submitted company electronic model it worsens the cost effectiveness of AAP+ADT from £28,616/QALY to £34,322/QALY. When this option is selected in the company model submitted alongside the 6 Feb 2018 Document B submission it worsens the cost effectiveness of AAP+ADT from £17,828/QALY to £21,389/QALY.

The company model, with no ERG revisions, when the option of applying the full LATITUDE QoL regression is selected assumes that DOC+ADT "patients experience no AEs or that the AEs that they experience have no impact on a patients HRQL". As a consequence the mHSPC quality of life values that are applied are as below.
<table>
<tr><td></td><td>AAP+ADT</td><td>ADT</td><td>DOC+ADT</td></tr>
<tr><td>On treatment</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
</tr>
</table>

[1] The ERG amends the formula for the decrement in cell ?? of the Utilities worksheet from = p_Utility_TTO_docetaxeloff - p_Utility_TTO_ADT to = IF (ERG_TTO_ADT_post_Doc = "Company" ,p_Utility_TTO_docetaxeloff -p_Utility_TTO_ADT ,IF (ERG_TTO_ADT_post_Doc ="None",0, IF(ERG_TTO_ADT_post_Doc="Increment", Comp1.UtilInc/2,"Error"))) with "None" setting the decrement to zero and "increment" setting it equal to half the AAP+ADT increment.

with ERG original approach • See the results for each of the suggested alterations either independently or as a group • Trace where the alterations have been implemented Switches for each change are located on the ERG sheet in the model on B95:103. A description of each proposed amendment is	*discontinuation* In the amended ERG model there is the option to apply abiraterone treatment discontinuation. This is done by changing cell B97 on the ERG sheet to "TRUE". The formula contained in cell H3 on the "Restricted mean" sheet has been amended in order to apply this correction. This cell has been renamed "RR.TTDPFS.AAP" and cell "I3" in the same sheet has been renamed "RR.compliance.AAP" to allow for the application of both treatment discontinuation and treatment compliance. The formulae contained in columns BD, BE, BF, BG and BI on the AAP + ADT patient flow sheet have been amended to allow for application of both treatment discontinuation and treatment compliance. *C) Applying the fix to the 1L mCRPC Abiraterone CAA* In the amended ERG	Janssen. To aid in this process Janssen have supplied a version of the ERG's model that applies these changes in a manner that maximises usability and transparency.	ADT (Post DOC+ADT) [redacted] The values for DOC+ADT apply the [redacted] decrement for DOC+ADT patients receiving a course of docetaxel and the [redacted] decrement for ADT (post DOC+ADT), as is most easily seen by the values being [redacted] apart. However, the decrements are applied to a QoL of [redacted] which has no allowance for SAEs or SREs. Given the model submitted alongside the 6 Feb 2018 Document B submission, the [redacted] and [redacted] decrements should be applied to a quality of life value that includes an additional [redacted] decrement for SAEs and SREs. This applies the company assumption that the efficacy of DOC+ADT is more similar to AAP+ADT than to ADT in the longer term, so it is more reasonable to apply the AAP+ADT decrement. At error check the company appears to wish to change this assumption and apply the ADT [redacted] SAE and SRE decrement. There is a more general error in that the company model does not apply the DOC+ADT on treatment decrement for SAEs and SREs. The error causes the company model that partially applies the LATITUDE QoL regression and draws SAE and SRE decrements from the literature to be slightly biased in favour of DOC+ADT. It causes the company model that applies the full LATITUDE QoL regression to be more seriously biased in favour of DOC+ADT. It is rather ungracious of BresMed or the company to try to palm its error off onto the ERG. The ERG's fault is to not have identified the BresMed/company error. **B)** Not a factual error. No revision required. See the ERG's response to Issue 6 above. C) Not a factual error. No revision required. The revised company approach appears to be a modified version of the previous approach. This can be critiqued on the same grounds as the previous approach by examining the estimated reduction in mCRPC abiraterone drug costs when the CAA is applied and when it

outlined below: *A) Correctly applying the appropriate ADT AE disutility to patients who have completed their course of docetaxel therapy* There is an error in how the ERG have removed the docetaxel off-treatment disutility of [redacted] as the AE utility decrement associated with patients treated with ADT alone needs to be applied instead for consistency as an AE utility decrement is applied for every other health state in the model. The ERG's base case currently either assumes	model there is the option to apply the correction for the 1L mCRPC abiraterone CAA. This is done by changing cell B101 on the ERG sheet. To apply this correction, a new formula has been added on the "Controls" sheet in cell C88 to calculate [redacted]. New formulae have been added to columns B:D on the treatment discontinuation tunnel state sheets e.g. "Calc_mCRPC_disc_L1_AAP + ADT" which calculate [redacted], taking into account the change in cycle length at 52 weeks. The formulae contained in column E has been amended to estimate the correct proportion of patients who have discontinued [redacted]. Finally, the formulae in column AG on the AAP + ADT patient flow sheet, and column AF on the ADT alone and docetaxel + ADT patient		is not. For the company model submitted at error check this results in the following estimates.  The ERG has not parsed the company implementation of this, but the effects are very much more in line with what would be expected given the mCRPC TA387 adjusted discontinuation curves. The company revision has similar effects upon the abiraterone costs in the MSM model. **D)** Not a factual error. No revision required. The ERG is content to accept the company assurance that the effect of this is minimal. Given time constraints the ERG has not examined this further. **E)** Not a factual error. No revision required. The mCRPC cost offsets seem important to the ERG. The company accepts there are errors in its model and has supplied a quite heavily modified model to try to account for these. The ERG has not had time to parse this. **F)** Not a factual error. No revision required. The justification for the ERG adopting the market shares for UK clinical practice is discussed in detail in section 5.2.11 on pages 109-110 of the ERG report, with particular reference to Tables 47 and 48 of the ERG report.

that these patients experience no AEs or that the AEs that they experience have no impact on a patients HRQL. *B) Applying treatment discontinuation* As stated in Issue 5 above, the ERG have replaced the value applied in the model to adjust the abiraterone treatment costs based on time on treatment with compliance values taken from the LATITUDE CSR. Treatment discontinuation and treatment compliance are two separate issues, and therefore the "0.875" value	flow sheets have been amended to ensure that mortality is no longer double-counted [redacted]. *D) Correctly applying planned MRU values for mCRPC (enzalutamide and radium-223)* The ERG model already contained the functionality to correct the mCRPC planned MRU for enzalutamide and radium-223 by changing cell B43 in the ERG sheet to "Clinboard". However, this correction has not been applied in the ERG base case as it appears that the ERG were unclear whether this was in fact an error. Now that it has been confirmed as a calculation error this should now be applied in the ERG base case to allow for an accurate calculation of costs. *E) Apply alternative mCRPC cost calculations*		**In brief** These are not ERG's factual errors. No revision required. The company does not identify any ERG errors in this section. The company identifies a company error that the ERG did not pick up. This is addressed under Issue 14 below. The company revised implementation of the abiraterone CAA for abiraterone treatment of mCRPC in the ADT and the DOC+ADT arms has not been parsed by the ERG but does appear to result in approximately the reduction that would be anticipated. The implementation of it is still rather peculiar for reasons the ERG can expand upon if required. It is unclear why the company has revised the odd approach of the original company model for the abiraterone CAA for abiraterone treatment of mCRPC in the ADT and the DOC+ADT when in the AAP+ADT arm it tries to adopt a more sensible approach to the time varying treatment costs of docetaxel and radium-223. This different approach to estimating mCRPC costs in the AP+ADT arm compared to that in the ADT and DOC+ADT arm may raise further concerns. It should also be noted that the company makes no attempt to correct other biases identified by the ERG. It is of particular concern that the company has tried to modified mCRPC costs in the AAP+ADT arm to account of their time varying profile but has made no attempt to modify the model to apply the time varying QoL decrement for treatment of mCRPC with docetaxel, or indeed to apply it at all

applied in the company's version of the model should to be applied instead or, in addition to the compliance values utilised by the ERG. C) *Applying the fix to the 1L mCRPC Abiraterone CAA* Janssen recognise there is an error in the way that the abiraterone 1L mCRPC CAA is applied. This has been corrected, and the impact of fixing this error on the results is in line with the expectations of the ERG. D) *Correctly applying planned MRU values*	In the amended ERG model there is the option to apply an alternative method for applying the treatment costs of fixed duration therapies in mCRPC which attempts to address the ERGs concerns regarding the methods applied. This is done by changing cell B99 on the ERG sheet to "TRUE". To apply this correction, new formulae have been added on the mCRPC costs sheet. Cells E51:E55 contain the maximum number of cycles that patients can receive, which are then used to calculate the average number of cycles received patients for each treatment in cells F51:55. New formulae have also been added in cells G22:J44 which estimate the costs of treatments which are given continuously separately to those given for fixed number of cycles, to allow for them to be applied in different ways in the model.		

for mCRPC (enzalutamide and radium-223) The ERG highlighted a small error in the planned MRU costs which are being applied for enzalutamide and radium-223 in mCRPC, which was discussed in Issue 11 above. Although the impact on the results is minimal, the correction applied by the ERG should be incorporated into the ERGs base case analysis to provide a more accurate estimate of the results. *E) Apply alternative mCRPC*	The formulae in cells C22:D24 on the Drug costs sheet have been amended to change from weekly costs to per cycle costs so that the costs can be applied as a lump-sum rather than per cycle. New formulae have been added in columns V:X on the patient flow sheets to estimate the incident number patients in the 1L, 2L and 3L mCRPC health states to allow for the application of these lump sum costs. Finally, the formulae contained in the 1L, 2L and 3L mCRPC treatment costs columns in the three patient flow sheets have been amended (columns BJ:BL on the AAP + ADT patient flow sheet, and BH:BJ on the ADT alone and docetaxel + ADT patient flow sheets). These formulae now allow for the costs of therapies given continuously and those given in a fixed number of cycles to be estimated on the patient flow sheet. *F) Apply AAP + ADT and*		

cost calculations The ERG raised concerns with the way that treatment costs are calculated during the mCRPC phase of the model, particularly as it relates to fixed duration therapies. As highlighted in Issue 5, we do not believe that there are serious limitations in the methods used to estimate these costs. However, in an attempt to address the ERGs concerns, an alternative method for calculating the costs for fixed duration therapies is applied in the model. *F) Apply AAP*	*ADT alone subsequent therapy market shares from LATITUDE in MSM model* In the amended ERG model there is the option to apply LATITUDE subsequent therapy market share values for AAP + ADT and ADT alone when the MSM model is selected to ensure the costs and efficacy are aligned. This is done by changing cell B103 on the ERG sheet to "TRUE". The formulae in cells E64:F69, E77:F82, and E90:F95 on the mCRPC costs sheet have been altered to allow for these market shares to be applied. These market shares are only applied if the MSM model is applied and cell B103 on the ERG sheet is set to "TRUE".		

+ ADT and ADT alone subsequent therapy market shares from LATITUDE in MSM model The ERG have presented ERG base case results for both the MSM/TA387 and the MSM model. However, in the MSM model base case the ERG have applied the subsequent treatment market shares for UK clinical practice. However, if survival is being estimated from LATITUDE data alone then the market share data should align with those observed in the			

clinical trial to ensure that costs and efficacy are aligned.			

Issue 13 Results from the amended version of the ERG's model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Based on the alterations/corrections to the ERG model (as summarised in Issue 12 above) there is a need to generate updated cost-effectiveness results.	See revised tables of results below. Results were run for both the MSM/TA387 and MSM models. Each of the amendments outlined in Issue 12 were firstly applied individually. Then a scenario is presented were the errors identified in the ERG model are corrected. Finally, a scenario were all of the amendments outlined in Issue 12 were applied.	To provide the ERG and NICE with what we believe are more correct cost-effectiveness results.	Not an ERG factual error. No revision required. However, the ERG did not identify the Bresmed/company modelling error as outlined under Issue 13(A) above. If required, the ERG can supply a revised set of deterministic analyses shortly prior to the AC that correct the company error in the context of the model that the company submitted alongside the Document B dated 6 Feb 2018. The usefulness of this may be questionable without the other company proposed model revisions being parsed and the other biases identified by the ERG being addressed.

Equivalent of Table 65 in ERG report (Company further model revisions at error check: MSM/TA387 model)

	AAP+ADT vs ADT			AAP+ADT vs DOC+ADT		
	Δ QALYs	Δ Costs	ICER	Δ QALYs	Δ Costs	ICER
Base case	1.076	[redacted]	£17,992	0.444	[redacted]	£31,439
A) Apply AE disutility for docetaxel + ADT post-docetaxel therapy	1.076	[redacted]	£17,992	0.548	[redacted]	£25,489
B) Apply treatment discontinuation	1.061	[redacted]	£15,531	0.429	[redacted]	£25,836
C) Apply the fix to the 1L mCRPC Abiraterone CAA	1.076	[redacted]	£18,858	0.444	[redacted]	£33,589
D) Correctly apply planned MRU values for mCRPC	1.076	[redacted]	£17,947	0.444	[redacted]	£31,229
E) Apply alternative mCRPC cost calculations	1.076	[redacted]	£15,455	0.444	[redacted]	£26,515
Correction of ERG model errors (A, B)	1.061	[redacted]	£15,531	0.532	[redacted]	£20,804
All changes (A-E)	1.061	[redacted]	£13,790	0.532	[redacted]	£18,315

Equivalent of Table 66 in ERG report (Company further model revisions at error check: MSM model)

	AAP+ADT vs ADT			AAP+ADT vs DOC+ADT		
	Δ QALYs	Δ Costs	ICER	Δ QALYs	Δ Costs	ICER
Base case	1.091	[redacted]	£20,855	0.488	[redacted]	£41,697
A) Apply AE disutility for docetaxel + ADT post-docetaxel therapy	1.091	[redacted]	£20,855	0.592	[redacted]	£34,391
B) Apply treatment discontinuation	1.075	[redacted]	£18,469	0.473	[redacted]	£36,951
C) Apply the fix to the 1L mCRPC Abiraterone CAA	1.091	[redacted]	£21,180	0.488	[redacted]	£42,380
D) Correctly apply planned MRU values for mCRPC	1.091	[redacted]	£20,861	0.488	[redacted]	£41,636
E) Apply alternative mCRPC cost calculations	1.091	[redacted]	£22,320	0.488	[redacted]	£42,607
F) Apply AAP + ADT and ADT alone subsequent therapy market shares from LATITUDE in MSM model	1.093	[redacted]	£22,837	0.489	[redacted]	£32,458
Correction of ERG model errors (A, B)	1.075	[redacted]	£18,469	0.576	[redacted]	£30,302
All changes (A-F)	1.077	[redacted]	£20,999	0.577	[redacted]	£24,021

Issue 14 Other factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 1 of the ERG report it incorrectly states: *"Several novel agents are now available, such as abiraterone acetate, and the order in which a patient may receive them is determined by clinical symptoms and manifestations, prior treatment, NICE recommendation and NHS policy."*	The proposed amendment is to change the wording to: [New paragraph] *"Several novel agents are now available in mCRPC setting, such as abiraterone acetate, and the order in which a patient may receive them is determined by clinical symptoms and manifestations, prior treatment, NICE recommendation and NHS policy."*	Current text implies that there are several novel agents available in mHSPC which is not correct.	This sentence should not be read in isolation but as part of the second paragraph on page 1 where we clearly refer to mHSPC. No revision required.
On page 8 of the ERG report it states: *"The company argue that the LATITUDE OS data are not relevant to the UK due to different treatments for mCRPC and that it is important to model the effects of these."*	The proposed amendment is to change the wording to: *"The company believe the LATITUDE data are generalisable to the UK however outline the challenge of accounting for subsequent therapies that were received in the trial but which are not permitted in sequence in the NHS. As such, the company suggest results of these sequences may not be representative of current UK clinical practice."*	Current text is factually inaccurate as Janssen never made such claim. Janssen believe the LATITUDE data are generalisable to the UK whilst acknowledge that, since LATITUDE was an international trial, some patients had access to novel therapies in mCRPC that are not available in sequence in the NHS. As such, results attained through these sequences may not be fully representative of current UK clinical practice.	We appreciate that the wording suggested by the company is more precise; however it does not change the overall meaning of the sentence. No revision required.
On page 70 of the ERG report it states: *"Since the company felt they had to compare DOC with AAP, the resulting estimates are of*	The proposed amendment is to change the wording to: *"Since docetaxel+ADT is considered a standard of care in mHSPC and was named in the NICE scope, the resulting*	Janssen does not believe the current text acknowledges the importance of aligning to the NICE Scope and recognising that docetaxel+ADT is also standard of care now in this setting.	We appreciate that the wording suggested by the company is more precise; however it does not change the overall meaning of the sentence. No revision required.

interest.."	*estimates are of interest."*		
On page 109 of the ERG report it states: *"The company base case predicts survival at 4 years of 47% for DOC+ADT compared to 34% for ADT, so a similar absolute survival for DOC+ADT but somewhat lower for ADT and hence a larger net gain of 13%."* This statement is made in comparison to the STOpCaP NMA resulting in an inaccurate assessment of face validity.	Janssen request that the ERG removes this statement, and those related to it, as they do not present a balanced case to accurately assess face validity.	The assessment of face validity conducted by the ERG is inaccurate because the patient populations that are utilised in the NMA of the STOpCaP publication were broader than the licensed indication for AAP+ADT in newly diagnosed high-risk mHSPC. Whilst Janssen have quoted this publication in the submission, it was only used as supporting evidence to further substantiate the positive trend in clinical conclusions.	The ERG accepts that the ERG text should be qualified by: The company outlines that this comparison is based upon the STOpCaP NMA and in a broader population that the licensed indication for AAP+ADT in newly diagnosed high-risk mHSPC.
The ERG uses terms for AAP and DOC interchangeably when referring to their use in mHSPC and mCRPC, which is often misleading. For example, on page 4 on the ERG report it states: *"the comparison of effectiveness of AAP with DOC for the mHSPC patient group was made…"*	The proposed amendment is to change the wording to: *"the comparison of effectiveness of AAP+ADT with DOC+ADT for the mHSPC patient group was made…"*	The report would benefit from clarifying the terminology when used in relation different settings. Since ADT is a mandatory addition in mHSPC, the terms AAP+ADT and docetaxel + ADT should be used when discussing the mHSPC setting, whilst this is not the case in mCRPC.	Minor inaccuracies. No revision required.

References

1. Vanni T, Karnon J, Madan J, et al. Calibrating models in economic evaluation: a seven-step approach. *PharmacoEconomics* 2011; 29: 35-49. 2010/12/15. DOI: 10.2165/11584600-000000000-00000.

Aberdeen HTA Group

Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer

Erratum to the ERG report

Completed 30 April 2018

This report was commissioned by the NIHR HTA Programme as project number 16/108/08.

Contains CIC/AIC

This document is intended to replace pages 2, 5, 6, 25, 38, 46, 50, 65, 81, 102, 109 and 124 of the original ERG assessment report for *Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer,* which contained a few inaccuracies. The amended pages follow in order of page number below.

newly diagnosed high risk mHSPC in combination with ADT and that the terms mHNPC and newly diagnosed mHSPC are effectively the same because newly diagnosed patients are, by default, hormone naïve. The company did not consider orchidectomy and bicalutamide monotherapy as clinical experts advised that these are seldom used in the UK. The comparators presented in the company submission are ADT alone (including LHRH agonist therapy) and docetaxel (DOC) plus ADT. The company state that clinical experts provided validation that there is no difference in the type of ADT, thus justifying their approach. The company submission includes all the outcomes listed in the NICE scope and reports additional outcomes from the LATITUDE trial: progression free survival following subsequent therapy, time to symptomatic local progression, prostate cancer-specific survival, time to chronic opiate use, castration status.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence submitted by the company consist of one RCT, the LATITUDE trial (1199 participants), with supporting evidence of one further RCT, the STAMPEDE trial (1917 participants). LATITUDE is a manufacturer-sponsored, multinational, randomised, double-blind, placebo-controlled Phase III trial that investigated abiraterone acetate with prednisone/prednisolone (AAP) plus ADT (597 participants) versus ADT plus placebo (602 participants). The company consider the ADT plus placebo arm equivalent to ADT alone. The company also maintain that LATITUDE is the only RCT providing data specific to the target population of people with newly diagnosed, high-risk mHSPC. The investigator-sponsored STAMPEDE trial represents the largest evidence base of AAP plus ADT in early prostate cancer data relevant to UK practice but include a broader patient population than LATITUDE, and does not report data separately for high risk disease/high volume patients.

The co-primary outcomes assessed in the LATITIDE trial were overall survival (OS) and radiographic progression free survival (rPFS). OS was also the primary outcome in STAMPEDE whilst failure free survival (FFS) was the intermediate primary outcome. In the LATITUDE trial, treatment with AAP plus ADT was associated with a 38% reduction in the risk of death compared with ADT alone (HR=0.62 [95%CI: 0.51–0.76]; p<0.001). The overall survival rate at three years was 66% in the AAP +

The Functional Assessment Cancer Therapy-Prostate (FACT-P) and Brief Pain Inventory (BPI) quality of life measures, looked at differences of change from baseline for both AAP+ADT and DOC+ADT treatment groups over four time points 3, 6, 9 and 12 months in LATITUDE (ITT) and CHAARTED (high volume disease - HVD). Sub-group analyses were conducted by the company whereby high risk disease (HRD) and HVD patients in LATITUDE were selected post-hoc. At 3 months, there was a 99.7% probability that AAP+ADT was associated with better quality of life than DOC+ADT (95% CrL 1.18-7.19). AAP estimates improved further over time as did the DOC estimates (not to the same extent and never to the level of AAP), and the probability of AAP+ADT being superior remained high at 6, 9 and 12 months (94.5%, 97.0% and 92.3%, respectively). BPI results showed an 88-100% probability of AAP+ADT being better at reducing pain than DOC+ADT over the 12-month period. Pain in the DOC group increased with time whereas with AAP they remained steady if not further reduced. The sensitivity analyses were comparable for FACT-P and BPI.

In the absence of any head-to head studies, further indirect comparisons were conducted for a group of men with disease progression (for the mCRPC group with respect to the effectiveness of AAP with other treatments including DOC). These were not presented in the clinical effectiveness section of the submission but only in the cost-effectiveness section. The company used the COU_AA_302 study, which directly compared abiratone plus prednisolone with placebo plus with prednisolone, and other studies which compared different treatments with placebo or best standard care. In particular, the company focused on DOC (the TAX327 study comparing DOC to a different placebo, mitoxantrone), radium-223 (the ALSYMPCA study with prednisolone as placebo) and enzalutamide (the PREVAIL study with prednisolone as placebo). In general, the estimates show that AAP is comparable with other treatments.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

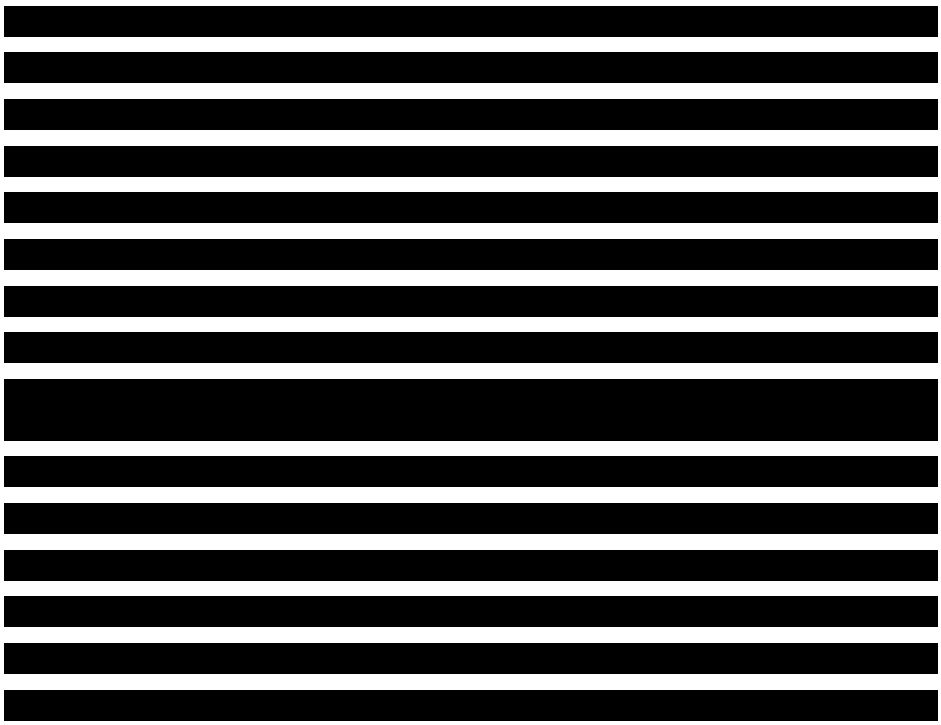
LATITUDE has provided the only evidence so far of AAP+ADT compared with ADT alone for the treatment of men with mHSPC. The ERG agree with LATITUDE results suggesting that AAP+ADT to be beneficial for the primary outcomes of OS and rPFS and for most of the secondary outcomes of safety and quality of life compared to

ADT. In terms of safety, AAP+ADT had a slight increased risk for hypertension and hypokalaemia. The results of LATITUDE are similar to those of the STAMPEDE trial. However, the STAMPEDE patient group was broader and while the company have conducted similar analyses on a *post hoc* subgroup profiled to be similar to the LATITUDE population, they rightly have not combined the results of these studies. Overall, the results from the LATITUDE trial provide evidence of benefits of AAP+ADT over ADT alone for the treatment of patients with mHSPC for the outcomes survival, progression and quality of life. The risk of some safety outcomes increased for AAP but the ERG agree that these may be well treated medically.

With no head-to-head trials assessing the effects and safety of abiratone versus the only other relevant comparator, DOC, identified for the patient group of interest, mHSPC, indirect treatment comparisons (ITC) were a sensible option. The company used a Bayesian network meta-analysis (NMA). The primary outcomes were based on three RCTs: LATITUDE, which compared AAP+ADT to ADT alone, and CHAARTED and GETUG-ARG 15, both of which compared DOC in conjunction with ADT to ADT alone. The Bayesian ITC showed that, when compared to DOC+ADT, AAP+ADT was highly likely to be superior in terms of rPFS, and at least as effective, but likely superior, in terms of OS. However, there is uncertainty about the size of effect as reflected in the credible intervals. Consistent results were attained through sub-group analyses using many combinations of patient groups in attempt to mirror the LATITUDE population. The results did not vary drastically but it is not clear which might be the most reliable.

For the relapsing/progression patients, the mCRPC group, the ITC used were Bucher pairwise estimates comparing other treatments with AAP. This approach requires many independent steps and so, intuitively, seems less robust compared to the NMA above, but the ERG agree it was probably the only course of action to accommodate the lack of studies and comparison arms. Each study compared a treatment with a 'placebo' although not always the same one. The conclusion that AAP is comparable to other treatments with regard to OS and rPFS is probably reasonable. The ITC analyses for both the mHSPC and mCRPC patient groups, have basic assumption violations of contextual heterogeneity which the company discussed in some detail and acknowledge the subsequent limitations. However, no checks were provided for statistical heterogeneity or consistency. All of these mean that clinically,

<table>
<tr><td>List price and average cost of a course of treatment</td><td>The NHS list price of AA 500mg tablets x 56 = £2,735.00.

Treatment with AA is continued until disease progression. The median duration of treatment in men with newly diagnosed high-risk mHSPC is 24 months.[41]
<table><tr><td>Drug cost [list price]</td><td>£2,735 [28 days]</td></tr><tr><td>Packs per year</td><td>365/28 = 13</td></tr><tr><td>Drug cost per patient per year*</td><td>£35,652.68</td></tr></table>*Maximum drug cost presented, assuming all patients who are initiated on abiraterone acetate stay on treatment for a full year.</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>Abiraterone acetate is available to NHS customers through a confidential Commercial Access Arrangement (CAA) with NHS England. This CAA will extend to cover the use of AAP + ADT in patients with newly diagnosed high-risk mHSPC.
  </td></tr>
<tr><td colspan="2">Key: AA, abiraterone acetate; CYP17, 17α-hydroxylase; DHEA, dehydroepiandrosterone; EPAR, European Public Assessment Report; LHRH, luteinising-hormone-releasing hormone; PAS, patient access scheme; SPC, summary of product characteristics.</td></tr>
</table>

3.2.1 Safety

Abiraterone acetate (AA) may cause hypertension, hypokalaemia, fluid retention and cardiac failure due to increased mineralocorticoid levels. Caution is required in treating patients whose underlying medical conditions might be compromised by these contraindications (e.g. cardiac glycosides, severe renal impairment, heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia).

This is the only trial providing data specific to the target (i.e., licensed) population of interest, and thus is the primary evidence source for the company submission. The investigator-sponsored STAMPEDE study[45] represents the largest evidence base of data specific to UK clinical practice for AAP + ADT in early prostate cancer but include a broader patient population than LATITUDE and does not report data separately for HRD/HVD patients. Due to these limitations, data from the STAMPEDE trial are referenced as supportive evidence only in the company submission.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Characteristics and critique of the trials included in the systematic review of clinical effectiveness

As stated previously in section 4.1.5, the main evidence for the company submission is taken from the LATITUDE trial[41] with supporting evidence presented from the STAMPEDE trial[45]. A summary description of these two trials is presented in Table 9.

Table 12 Summary of secondary endpoints for the LATITUDE intention to treat population (reproduced from Table 11, Document B of the company submission)

	AAP + ADT (n=597)	ADT alone (n=602)
Time to pain progression		
Events, n (%)	233 (39.0)	289 (48.0)
Median months (95% CI)	NR (36.5, NR)	16.6 (11.1, 24.0)
HR (95% CI) [p-value]	0.70 (0.58–0.83) [<0.001]	
Time to subsequent prostate cancer therapy		
Events, n (%)	191 (32.0)	322 (53.5)
Median months (95% CI)	NR ([redacted])	21.6 ([redacted])
HR (95% CI) [p-value]	0.42 (0.35–0.50) [<0.001]	
Time to life-extending subsequent therapy for prostate cancer		
Events, n (%)	125 (20.9)	246 (40.9)
Median months (95% CI)	[redacted]	[redacted]
HR (95% CI) [p-value]	[redacted]	
Time to initiation of chemotherapy		
Events, n (%)	109 (18.3)	191 (31.7)
Median months (95% CI)	NR ([redacted])	38.9 ([redacted])
HR (95% CI) [p-value]	0.44 (0.35–0.56) [<0.001]	
Time to PSA progression		
Events, n (%)	241 (40.4)	434 (72.1)
Median months (95% CI)	33.2 (27.6, NR)	7.4 (7.2, 9.2)
HR (95% CI) [p-value]	0.30 (0.26–0.35) [<0.001]	
Time to next SRE		
Events, n (%)	[redacted]	[redacted]
Median months (95% CI)	NR (NR, NR)	NR (NR, NR)
HR (95% CI) [p-value]	0.70 (0.54–0.92) [0.009]	

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not reached; PSA, prostate specific antigen; SRE, skeletal-related event.
Source: Fizazi et al. 2017[41] LATITUDE CSR, 2017 European Public Assessment Report[37].

In the LATITUDE trial, treatment with AAP+ADT significantly reduced the time to subsequent therapy for prostate cancer. The median time to subsequent therapy was not reached in the AAP + ADT group, it was 21.6 months for the ADT group (HR=0.415 [95%CI: 0.346–0.497], p<0.0001). Twice as many ADT alone patients required life-extending subsequent therapy (either docetaxel, enzalutamide, cabazitaxel, radium-233 or AAP) compared with those who received AAP+ADT (40.9% versus 20.9% respectively). The median time to life-extending subsequent therapy was not reached in the AAP + ADT group and was 29.5 months in the ADT

abiraterone in mHSPC, these data should only be considered as strong supporting evidence of AAP's clinical effectiveness, with the direct evidence from LATITUDE being the most appropriate source to inform the economic modelling in the licensed population.

Table 13 Meta-analyses of AAP+ADT versus ADT alone for the outcomes overall survival and disease progression (reproduced from Table 16, Document B of the company submission)

OS			
	Direct Evidence: AAP+ADT vs. ADT	**Direct Evidence: AAP+ADT vs. ADT**	**Meta-Analysis: AAP+ADT vs. ADT**
Trial Name	LATITUDE	STAMPEDE	Rydzewska et al. 2017[48]
Population	ITT	M1	
HR [95% CrI]	0.62 [0.51, 0.76]	0.61 [0.49, 0.75]	0.62 [0.53, 0.71]
Disease progression (i.e. rPFS or PFS)[a]			
	Direct Evidence: AAP+ADT vs. ADT	**Direct Evidence: AAP+ADT vs. ADT**	**Meta-Analysis: AAP+ADT vs. ADT**
Trial Name	LATITUDE	STAMPEDE	Rydzewska et al. 2017[48]
Population	ITT	M1	
HR [95% CrI]	0.47 [0.39, 0.55]	0.43 [0.36, 0.52]	0.45 [0.40, 0.51]
Key: AAP, abiraterone acetate prednisone/prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; CrI, credible interval; HR, hazard ratio; ITT, intent to treat; M1, metastatic; OS, overall survival; rPFS, radiographic progression-free survival. **Notes:** [a], PFS=radiological or clinical progression-free survival			

Adverse reactions

Treatment exposure

The median treatment duration in the safety population of the LATITUDE trial was 24 months in the AAP + ADT arm and 14 months in the ADT alone arm.[41]

[redacted] A total of 91.8% of patients in the AAP + ADT group and 86.0% of patients in the ADT alone group received ≥6 cycles of study drug; 54.5% and 29.7% of patients, respectively, received ≥24 cycles.

Dose reductions were reported for [redacted]% of patients treated with AAP + ADT and [redacted]% of patients treated with ADT alone, while dose interruptions were reported for

Statistical comparison of AAP versus docetaxel (DOC) for the primary outcomes OS and rPFS was only possible using ITC methods. The patient populations of two RTCs, CHAARTED (790 participants) and GETUG-AFU 15 (385 participants), which compared DOC +ADT with ADT alone using post-hoc selected sub-groups of newly diagnosed patients with high volume disease (HVD), were considered to be comparable with those in LATITUDE. The company used Bayesian network meta-analyses with fixed effects to find the indirect results of AAP+ADT versus DOC+ADT. The results presented in Table 21 demonstrate that, when compared with DOC+ADT, AAP+ADT has a 71.8% probability of being the better life prolonging treatment option (HR 0.92, 95% CrL 0.69-1.23) and a 92.9% probability of being better at delaying disease progression (HR 0.76, 95% CrL 0.53-1.10). Various sensitivity analyses examined the effect of post-hoc selection of the HVD patients rather than the high risk disease (HRD) group of LATITUDE; the inclusion of the M1 group from STAMPEDE (for both AAP+ADT and DOC+ADT) and the inclusion of those treated prior to current treatment or not. The results of the sensitivity analyses varied but there was a consistent trend in favour of AAP+ADT.

Results of sensitivity analyses of time to skeletal-related events (SRE) were similar in the indirect comparison between AAP+ADT and DOC+ADT, [redacted] but with a Bayesian pairwise probability of [redacted].

Only two RCTs, LATITUDE (AAP+ADT versus ADT) and GETUG-AFU 15 (DOC+ADT versus ADT, presumably newly diagnosed HVD patients) could be included into an ITC for the assessment of secondary outcome measures of safety. No sensitivity analyses were reported. When the AAP+ADT group (n=597) was indirectly compared to the DOC+ADT group (n=189), [redacted]

However, AAP+ADT was found [redacted]

significantly lower at 3 months (-3.09, p=0.02) but significantly higher at 12 months compared to ADT (+2.85, p=0.04). But differences did not exceed the minimum clinically meaningful change at any time point, which was taken to be a change of 6 to 10 points. Both arms reported significantly poorer FACT-Taxane scores compered to baseline. Brief pain inventory scores were similar between the arms. The authors conclude that "*Although ADT+D was associated with statistically worse QOL at 3months, QOL was better at 12months for ADT+D patients than for ADT patients. Both arms reported a similar minimally changed QOL over time, suggesting that ADT+D is not associated with a greater long-term negative impact on QOL*".

[redacted]The company do not reference minimum clinically meaningful changes and conclude that "*Results of the ITC showed treatment with AAP+ADT was associated with notable benefits in HRQL compared to DOC+ADT. These benefits were observed from three months and sustained for at least one year after treatment*".

A crude reading of the company ITC and the results of Morgans et al[54] suggests that the 12 month FACT-P improvement from AAP+ADT compared to ADT is roughly double that of the improvement from DOC+ADT compared to ADT.

The model requires estimates for quality of life increments or decrements relative to ADT for patients in rPFS. For rPFS specific estimates of FACT-P changes there may be some confounding between both AAP+ADT and ADT and DOC+ADT and ADT in the RCT data due to more progression with ADT than with either AAP+ADT or DOC+ADT.

However, given the greater rPFS superiority for AAP+ADT over ADT compared to DOC+ADT over ADT, any such confounding might be expected to benefit AAP+ADT more than DOC+ADT. Yet, it cannot be unambiguously stated that the literature concludes that FACT-P changes for those remaining in rPFS are better among AAP+ADT patients than among ADT (post DOC+ADT) patients, or that they are better among ADT (post DOC+ADT) patients than among ADT patients.

Table 40 Unplanned medical resource use: mHSPC

	Unit cost	AAP+ADT	ADT
Radiotherapy procedure	£101	[redacted]	
Radiotherapy preperation	£288		
MRI	£180		
CT scan	£120		
X-ray	£171		
Hospitalisation	£307		
Oncologist	£173		
Urologist	£103		
Surgery	£12,778		
Emergency room	£148		
General practitioner	£38		
Annual cost		£1,192	£1,513

This is augmented with the adverse event frequencies taken from the LATITUDE trial for AAP+ADT and ADT, and from Gravis et al[58] for DOC+ADT which result in additional annual costs of around £630, £580 and £1,105 respectively. The higher cost for DOC+ADT is due to 32% having neutropenia, which may be reasonable to apply to those receiving docetaxel but may be less reasonable to those who have completed their course of docetaxel, i.e., ADT (post DOC+ADT) patients, which is why the model applies the AE rates related to ADT during the off-treatment period following completion of treatment with docetaxel.

mCRPC drug and administration costs

The 1st line mCRPC compliance ratios for abiraterone and enzalutamide are assumed to be 100%[1]. This seems appropriate due to the curves that they are applied to being labelled discontinuation curves. However, for docetaxel, cabazitaxel and radium-223 the company uses treatment completion rates to estimate compliance rates of 73%, 64% and 79%. Given the discontinuation curves these are applied to, they underestimate the direct drug costs of docetaxel, cabazitaxel and radium-223 for 1st line mCRPC.

[1] As reviewed later, an adjustment is applied to the costs of abiraterone for 1st line mCRPC with the intention of allowing for the [redacted], but this has little to no effect and can be ignored.

As far as the ERG can ascertain, the 1st line mCRPC treatment costs are calculated as the prevalent 1st line mCRPC on treatment population multiplied by a time invariant arm specific

Table 46 Scenario analyses around MSM start point: AAP+ADT cost effectiveness

	MSM/TA387 model		MSM model	
KM cut-off	vs ADT	vs DOC + ADT	vs ADT	vs DOC + ADT
4 months	£16,936	£17,180	£19,884	£26,001
5 months (BC)	£17,418	£17,828	£20,438	£26,909
6 months	£17,638	£18,358	£20,636	£27,619
7 months	£17,825	£19,326	£21,001	£28,545

5.2.11 Model validation and face validity check

DOC+ADT vs ADT estimates

The NICE summary of DOC+ADT compared to ADT for mHSPC states that "*In men with hormone-sensitive metastatic prostate cancer at 4 years, estimates based on a meta-analysis of the 3 RCTs (STOpCaP, n=2992)… a 9% absolute improvement in overall survival with docetaxel compared with ADT alone (49% compared with 40%, p<0.0001)… a 16% absolute improvement in time to disease progression with docetaxel compared with ADT alone (treatment failure 64% compared with 80%, p<0.0001)* ".

The company base case predicts survival at 4 years of 47% for DOC+ADT compared to 34% for ADT, so a similar absolute survival for DOC+ADT but somewhat lower for ADT and hence a larger net gain of 13%. The company outline that this comparison is based upon the STOpCaP NMA and in a broader population that the licensed indication for AAP+ADT in newly diagnosed high-risk mHSPC. Taking rPFS as the measure of progression the company base case predicts progression at 4 years of 75% for DOC+ADT and 87% for ADT suggesting that the model overestimates progression for both arms and particularly for DOC+ADT. Linking the OS and rPFS together may suggest that the model overestimates the time that DOC+ADT patients spend in post progression survival. Given the importance of post progression mCRPC costs in the DOC+ADT arm for the company base case, any overestimation of the time spent in post progression in the DOC+ADT arm may of concern.

Additional ERG structural analysis

The company scenario analysis that uses the MSM model rather than the MSM/TA387 model also revises the mCRPC treatment proportions to be those of the LATITUDE trial. The company argument is that the LATITUDE data were generated by these mCRPC treatment proportions. The results of this scenario analysis can be compared with the results of a

Most of the values in the above are in line with intuition when compared with the TPMs of AAP+ADT and ADT. However, the probability of dying among those who have progressed is anomalous and is now lower than that of both AAP+ADT and ADT. It can be argued that this anomaly is worse than that of the DOC+ADT TPM of the company base case.

Application of the above TPM considerably worsens the deterministic MSM/TA387 model cost effectiveness estimate for AAP+ADT compared to DOC+ADT from £17,828 per QALY to £25,530 per QALY. The ERG implementation of sampling of this within the probabilistic modelling may be formally incorrect and may not properly take into account confidence intervals and correlations. Nonetheless, this results in a smaller change in the central probabilistic estimate, it only worsening from £18,168 per QALY to £20,867 per QALY. The non-linearity of the model may relate to the DOC+ADT versus ADT OS hazard ratio being somewhat further from unity than the DOC+ADT versus AAP+ADT hazard ratio.

The above does not argue that the company choice is incorrect. It only highlights that it is a choice which has not been justified, another choice could equally well have been made and that the most reasonable estimate may lie somewhere between the two.

MSM/TA387 model: Differentiation of 1st line mCRPC treatment effects

As already highlighted, the company comparison of 1st line mCRPC treatments' effectiveness estimates an OS hazard ratio central estimate which [redacted]

The company MSM/TA387 model structure is largely justified by the company on the basis of the need to properly model the effects of extending rPFS upon OS; i.e., the LATITUDE data for rPFS are reliable but thereafter the modelling needs to depart from the LATITUDE data.

The only means of approximating this within the MSM/TA387 model is to differentiate 1st line mCRPC treatments by the company central estimates of the OS hazard ratios. The ERG will apply this as a sensitivity analysis.

Aberdeen HTA Group

Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer

ADDENDUM to the ERG report

Completed on 30 April 2018

This report was commissioned by the NIHR HTA Programme as project number 16/108/08.

Contains CIC/AIC

This addendum has been created to address some issues raised by the company at error check as well as some comments raised during the PMB

ERG comments and analyses

SAE+SRE QoL decrement in DOC+ADT arm

The company has at error check identified an additional error in the company model. The models submitted by the company do not apply the QoL decrements for SAEs and SAEs for mHSPC in the DOC+ADT arm. The mHSPC quality of life values in the DOC+ADT arm omit the [redacted] when the values are based upon applying the full LATITUDE QoL regression and the [redacted] when the decrements are based upon values drawn from the literature.

Note that the intention of the company model, presumably due to the efficacy of DOC+ADT more closely resembling AAP+ADT than ADT, is that when applying the full LATITUDE QoL regression the SAE and SRE decrement of [redacted] for AAP+ADT should be applied rather than the [redacted] decrement for ADT. The intention is to apply these decrements in addition to the TTO DOC+ADT specific decrements of [redacted] for DOC+ADT on treatment and [redacted] for ADT (post DOC+ADT).

The company base case relies upon the SAE and SRE decrements derived from the literature rather than using the LATITUDE QoL regression values. The SAE and SRE QoL decrements derived from the literature are very small, so the model bias is small. The SAE and SRE QoL decrements that apply when the full LATITUDE QoL regression is applied are an order of magnitude larger. The bias is correspondingly larger as outlined below.[1]

Table 1. Effect of omission of SAE/SRE QoL decrements for DOC+ADT on ICERs

SAE/SRE QoL source	LATITUDE	Literature
DOC+ADT SAE/SRE decrement excluded	£21,389	£17,828
DOC+ADT SAE/SRE decrement included	£18,185	£17,594
Bias against AAP+ADT	15%	1%

[1] These biases are also present in the first company submission Document B and the associated model.

The ERG did not identify this error. But the ERG revised base case relies upon the application of the full LATITUDE QoL regression. As a consequence, this error biases the ERG revised base case and most of the ERG sensitivity analyses in favour of DOC+ADT.

mCRPC treatment costs

The ERG report outlines that the company model does not take into account the time dependent nature of treatment costs for mCRPC. This mainly affects the treatments in the APP+ADT arm. Patients receiving docetaxel for mCRPC are limited to a maximum of ten 3-weekly cycles of treatment. Similarly, radium-223 is limited to a maximum of six 4-weekly cycles. However, for the AAP+ADT arm the company model assumes that among those on 1st line mCRPC treatment, 60% incur the 3-weekly docetaxel treatment costs including the £260 administration cost and 30% incur the 4 weekly radium-223 costs indefinitely[2].

There is a similar bias in the ADT arm and the DOC+ADT arm, but it considerably smaller due to fewer patients receiving docetaxel or radium-223 for their mCRPC.

At error check the company has made extensive revisions to the model to account for the time varying cost profile of the mCRPC treatments. The ERG has not cross checked any of the company model revisions to mCRPC treatment costs but reports the effects of these revisions below.

Table 2. Effect of company revision to mCRPC costing

Comparator	ADT	DOC+ADT
Original ICER	£17,418	£17,828
ICER with company revised mCRPC costs	£14,513	£13,595
Bias against AAP+ADT	17%	24%

Note that the company does not extend this analysis to take into account the time dependent quality of life of mCRPC treatments, i.e. it makes no attempt to apply the quality of life decrements for docetaxel treatment of mCRPC that it applies for docetaxel treatment of mHSPC.

[2] These costs are qualified by time invariant proportions of patients completing their course, but the basic aspect of indefinite mCRPC treatment and costs applies.

Abiraterone CAA for mCRPC

The ERG report outlines how applying the abiraterone CAA for mCRPC has minimal impact upon the mCRPC abiraterone costs that the model estimates. The company accepts that there is an error and has provided a model with revised calculations. The revised company approach appears to be a modified version of the previous approach. This can be critiqued on the same grounds as the previous approach by examining the estimated reduction in mCRPC abiraterone drug costs when the CAA is applied and when it is not. This results in the following estimates.

Table 3. Effect of company revision to mCRPC abiraterone CAA on drug costs

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

The effects of applying the abiraterone CAA for mCRPC are very much more in line with what would be expected given the mCRPC TA387 adjusted discontinuation curves. The company revision has similar effects upon the abiraterone mCRPC costs in the MSM model.

For the company submitted base case cost effectiveness estimates the effect of the revision to the costing of the mCRPC is as follows.

Table 4. Effect of company revision to mCRPC abiraterone CAA

Comparator	ADT	DOC+ADT
Original ICER	£17,418	£17,828
ICER with company revised mCRPC CAA	£18,233	£19,394
Bias in favour of AAP+ADT	5%	9%

PMB comment: quality of life values

The NICE secretariat noted that it would aid Committee if there was a slide on quality of life values in the model as applied by the company in its submissions, by the ERG in its report and as applied by the ERG following the model error identified by the company at error check.

The three sets of values are based upon the same basic sets of inputs for a given LATITUDE QoL regression, the differences between them being:

- Deriving the SAE and SRE QoL decrements from values in the literature or by applying the full LATITUDE regression.
- Including or excluding the SAE and SRE QoL decrement in the DOC+ADT arm.
- Including or excluding the [redacted] ADT (post DOC+ADT) decrement estimated by the company TTO study.
- Including or excluding the mHSPC SAE and SRE QoL decrement for the ADT arm in the mCRPC quality of life values to avoid these being inconsistent with the mHSPC values.

The mCRPC quality of life values from TA387 of 0.830 for 1st line mCRPC, 0.625 for 2nd line mCRPC and 0.500 for 3rd line mCRPC are used to derived ratios of 75% for 2nd line mCRPC and 60% for 3rd line mCRPC compared to 1st line mCRPC.

Table 5. Quality of life inputs

				Company	ERG	Corrected
General inputs						
Intercept	[redacted]			✓	✓	✓
mCRPC (rPFS)				✓	✓	✓
	AAP+ADT	ADT	DOC+ADT			
On Tx	[redacted]			✓	✓	✓
% On Tx				✓	✓	✓
Post Tx				✓	×	×
SAE/SRE decrement						
LATITUDE	[redacted]			✓	✓	✓
Literature				✓	✓	✓
Include SAE/SRE decrement for DOC+ADT mHSPC				×	×	✓
mCRPC treatment specific effects						
1st line	[redacted]			✓	✓	✓
2nd line				✓	✓	✓
3rd line				✓	✓	✓
ERG mCRPC adjustment				×	✓	✓

The following table omits the quality of life values for mCRPC prior to 1st line treatment and mCRPC after 1st line treatment but prior to 2nd line treatment.

Table 6. Quality of life values: Full LATITUDE regression applied

	mHSPC		mCRPC		
	On Tx	Post Tx	1st line	2nd line	3rd line
Company					
AAP+ADT	[redacted]				
ADT					
DOC+ADT					
ERG					
AAP+ADT	[redacted]				
ADT					
DOC+ADT					
Corrected					
AAP+ADT	[redacted]				
ADT					
DOC+ADT					

Table 7. Quality of life values: SAE and SRE decrements from literature

	mHSPC		mCRPC		
	On Tx	Post Tx	1st line	2nd line	3rd line
Company					
AAP+ADT ADT DOC+ADT	[redacted]				
ERG					
AAP+ADT ADT DOC+ADT	[redacted]				
Corrected					
AAP+ADT ADT DOC+ADT	[redacted]				

PMB discussion: effectiveness against DOC+ADT

It was requested that analyses varying the effectiveness of AAP+ADT compared to DOC+ADT be undertaken, incorporating the STAMPEDE results of Table 9 of Document B and assuming no benefit of treatment. It has not been possible for the ERG to revise the model to introduce a waning post trial treatment effect as per the NICE methods guide section 5.1.16. The ERG performs the following scenario analyses.

Table 8. Additional scenarios on AAP+ADT vs DOC+ADT effectiveness

	rPFS HR	OS HR
Base case: Table 18 DocB	0.76	0.92
ITC inc. STAMPEDE[3]: Table 19 DocB	0.71	0.91
STAMPEDE: Table 9 DocB	0.69	1.13
No OS effect	0.76	1.00
No effect	1.00	1.00

Cost effectiveness estimates

No ICERs will be presented during Part 1 of the meeting due to the cPAS appendix. In a revised cPAS appendix the ERG presents the same set of analyses as in the ERG report, plus

[3] Note that the company scenario of this applies the AIC PFS HR of [redacted] rather than the rPFS HR of 0.71.

the additional four scenarios outlined above and scenarios including the company revisions to the mCRPC costs and the abiraterone mCRPC CAA implementation.