NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Abiraterone acetate for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy [ID503]

The following documents are made available to the consultees and commentators:

1. **Company Patient Access Scheme (PAS) submission** from Janssen
   - Patient Access Scheme submission
   - Additional data (final analysis of COU-AA-302) submitted by Janssen, 9 October 2015 (this is a spreadsheet, the spreadsheet is also available separately)

2. **Evidence Review Group addendum prepared in response to the new PAS submission** prepared by Kleijnen Systematic Reviews
   - Evidence Review Group addendum
   - ERG additional scenario analysis (shorter time between stopping first treatment and starting docetaxel)

3. **NICE request to the company for additional information following the 15 October 2015 Technology Appraisal Committee meeting**

4. **Company response to the request for additional information** from Janssen

5. **Evidence Review Group response to the Company's additional information** from Kleijnen Systematic Reviews
   - Evidence Review Group response
   - Evidence Review Group additional analyses (requested by the Chair of the Committee during the pre-meeting briefing)
   - Evidence Review Group additional analyses applying the existing patient access scheme to abiraterone used after docetaxel

6. **Email from the company to NICE clarifying the additional information (10 November 2015)**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template for Abiraterone Acetate

Date Revised: 13th April 2015

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

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

3.2 Please outline the rationale for developing the patient access scheme.

Abiraterone is already recommended by NICE for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen (under the end of life criteria), contingent upon a patient access scheme (PAS). The NICE TA259 (abiraterone for mCRPC previously treated with a docetaxel-containing regimen), issued in June 2012, states that “The manufacturer of abiraterone (Janssen) has agreed a patient access scheme with the Department of Health. This involves a single confidential discount applied to the list price of abiraterone.”

In August 2014, NICE issued a final appraisal determination (FAD) with a negative recommendation for abiraterone for the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated. This negative recommendation was made despite the same PAS (in the form of a simple discount) being applied to the pre-chemotherapy indication, with a similar level of cost-effectiveness estimated. The Appraisal Committee concluded that abiraterone did not meet the end of life criteria in the pre-chemotherapy indication and, as a result, was not cost-effective under the standard incremental cost effectiveness ratio (ICER) threshold used by NICE. Subsequently, the NICE single technology appraisal (STA) process was suspended in September 2014 as Janssen requested the opportunity to re-submit with an amended PAS. The Department of Health (DH) has since

referred the amended PAS on to PASLU, and NICE has since agreed to review abiraterone under the rapid review appraisal process.

We believe that the introduction of the amended PAS improves the cost-effectiveness of abiraterone in the pre-chemotherapy setting to a level that is acceptable to secure a positive recommendation by NICE, facilitating patient access to this important treatment option.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

Complex scheme (under the 2014 PPRS terminology)

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

Janssen have agreed to permanently reduce the official list price for abiraterone from £2,930 per 30 days to £2,300 per 30 days (-21.5%), and have proposed a new PAS under which the drug acquisition cost for abiraterone is accrued for a maximum of 10 months per patient. After 10 months on treatment, the cost of abiraterone is rebated to the NHS for each individual patient. This scheme provides certainty to the NHS as to the maximum amount the NHS will have to pay for an individual patient, regardless of whether a patient remains on treatment for longer than 10 months. This new proposal will result in the discontinuation of the existing confidential discount.

The newly proposed PAS will apply to all patients in both indications:

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

- The treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated.

The recommended posology of abiraterone is 1,000 mg (four 250 mg tablets) as a single daily dose. Abiraterone is to be taken with low dose prednisone or prednisolone at a recommended dose of 10 mg daily.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

This new PAS will apply to all patients with mCRPC who are prescribed abiraterone in the pre- and post-chemotherapy settings. The PAS proposes that the drug acquisition cost for abiraterone is rebated to the NHS after 10 months of treatment for each individual patient, meaning that the cost of abiraterone will be rebated from the 11th pack onwards for each patient (as each pack of abiraterone contains 30 days treatment). The new PAS, therefore, requires the recording of treatment duration for all abiraterone-treated patients.

This PAS was chosen as it materially improves the cost-effectiveness of abiraterone in the pre-chemotherapy setting and provides certainty to the maximum amount the NHS will have to pay for a particular individual patient. Janssen believes that the minimal increase in administrative burden should be weighed against the greater fiscal certainty and value for money afforded to the NHS through the implementation of this new PAS.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The PAS will apply to the entire population of adult men with mCRPC who are prescribed abiraterone in the post-chemotherapy and pre-chemotherapy settings, as per its licensed indications. There is no specific criterion a patient needs to satisfy for the PAS to be applied.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

Initially appraised in 2012 under the end of life criteria, abiraterone was only recommended for use in the post-chemotherapy setting following considerable efforts made by Janssen alongside the use of a confidential discount, in the form of simple PAS, to make the medicine available for prostate cancer patients in England and Wales.

[redacted]

In August 2014, the NICE appraisal committee decided that the end of life criteria could not be applied to abiraterone in the pre-chemotherapy setting and therefore the standard cost-effectiveness threshold would be applicable (i.e. £20K-£30K/QALY). In order to reduce the cost per QALY gained to this level, the actual purchase price of abiraterone for the NHS has to be substantially reduced below the current level. Since we are unable to determine whether an order for abiraterone is for the pre- or post-chemotherapy setting, any additional confidential discount would have to be applied to both indications, as well as for future indications. It is simply commercially unviable to offer a larger confidential discount to all current and future indications that is large enough to reduce the ICER in the pre-chemotherapy setting to below £30k/QALY.

Instead, Janssen has agreed to reduce the official list price for abiraterone from £2,930 per 30 days by 21.5% to £2,300 per 30 days, discontinue the

existing confidential discount and introduce the maximum treatment duration during which the NHS is charged for abiraterone both in the pre- and post-chemotherapy settings.

Janssen acknowledge that a 'complex' PAS may require more administrative burden than a simple discount. However, the newly proposed scheme for abiteratone is designed to enable the efficient treatment of mCRPC patients in parallel with the effective monitoring of the PAS across numerous Trusts/Hospitals in England and Wales, and involves the tracking of abiraterone prescriptions in both pre- and post-chemotherapy settings.

Under the proposed scheme, there is no change to how patients are managed, or to how abiraterone is prescribed and dispensed at the Trust/Hospital level. The scheme is based on the use of an internet-based Janssen PAS portal which enables the safe and efficient management of data to help the NHS and Janssen coordinate the reimbursement of abiraterone in accordance to the proposed PAS.

It is important to note that capping the duration of drug acquisition cost provides the NHS with full certainty as to the maximum spend on abiraterone for an individual eligible patient. As a result, an increase in administrative burden must be considered alongside the greater fiscal certainty and value for money offered to the NHS. In addition, Trusts/Hospitals will have clear financial incentive to enter data into the Janssen PAS portal because of the value associated with receiving a direct rebate to each Trust/Hospital or Homecare provider; thus, the additional administration required may be considered justifiable by the Trust/Hospital given the financial benefit of the new PAS.

The solution will be provided based on the following key principles:

- Simple and quick user interactions with the internet-based portal (offering either a manual inputting or data extract upload system).
- Application of a strict information governance policy

- Providing a platform that can be extended to other drugs
- No additional burden on existing NHS IT systems

Step 1 of using the internet-based Janssen PAS portal:

Trusts/Hospitals will be required to register each patient onto the internet-based PAS portal. This is a one-off exercise and registration can be completed by any member of the clinical team responsible for treating the patient.

Once the patient has been registered, the system will generate an anonymous unique reference code (the "URC") which will be used by Janssen for tracking time on treatment.

Step 2 of using the internet-based Janssen PAS portal:

Trusts/Hospitals will either continue to manually input monthly prescription information for each patient registered in the PAS portal or, alternatively, the hospital (or nominated Homecare provider) can select to upload prescribing data into the PAS portal.

All data required for the manual data entry is already available to local pharmacy staff. The data set is as follows: Patient Initials, NHS No, DoB, Prescription Date, Dispensing Date, Drug Name or BNF Drug Code and preferably (but not required) the start date of treatment.

Immediately following entry of prescription information, the PAS portal system will run a validation check and display the results in a summary report, highlighting any outstanding actions. If any of the patient entries are flagged with errors, the system will determine the next required action the user must take to rectify this, for example, if the report shows duplicate patients or patients are not registered but are eligible for registration (i.e. they have a valid prescription).

The Janssen PAS internet-based portal is underpinned by a sophisticated Role-Based Access Control (RBAC) functionality, clearly defining user roles

and associated access privilege to ensure that anonymised data is only visible at Trust/Hospital level. Through the robust security model within the portal there will be automatic and strict separation of data.

Table 1- Summary User Roles

Role	Description
Nurse	Ability to register patients
Doctor	Ability to register patients
Pharmacist	Ability to register patients Ability to provide prescription and dispensation information Ability to see aggregated and patient-level identifiable data reports
Homecare	Ability to provide prescription and dispensation information if nominated by Trust/Hospital Ability to see aggregated and patient-level identifiable data reports
Janssen	Ability to see aggregated and patient-level anonymised reports
AT/LHB	Ability to see aggregated reports
NHSE / NICE	Ability to see aggregated reports

Once validated by the Trust/Hospital pharmacist, information reported in the PAS portal will be used to generate a monthly 'PAS report' to Janssen (aggregated and patient-level anonymised reports) and to the Trust/Hospital (aggregated and patient-level with PID reports).

Once the milestone for rebate has been reached for a specific patient, Janssen will generate a credit note for subsequent repeat prescriptions to each NHS hospital.

The report will contain the following details:-

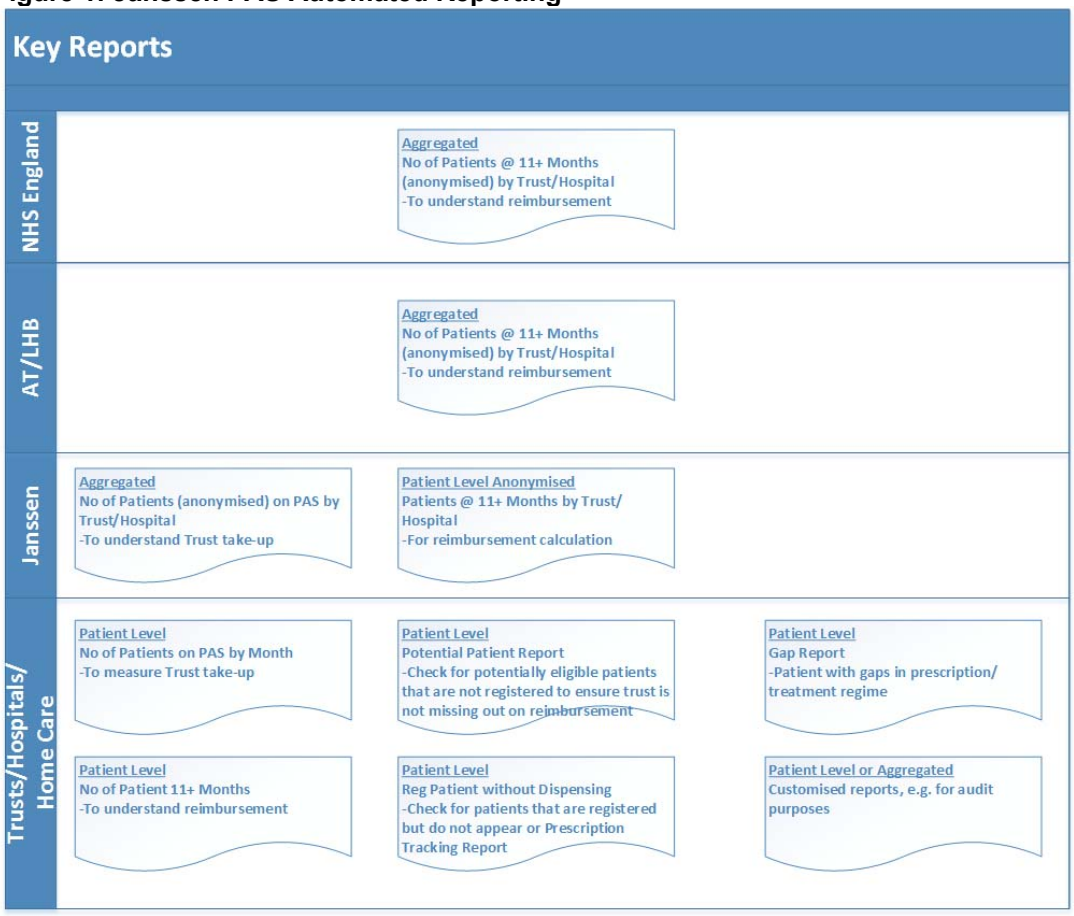
- Number of patients registered
- Number of patients receiving treatment with abiraterone
- Number of doses each patient has received
- Number of patients who have received abiraterone for more than 10 months

- Total amount Janssen is to rebate an individual NHS Trusts/Hospitals or Homecare provider in England, Wales and Northern Ireland.

A patient-level anonymised report of all patients registered in the PAS, detailing the treatment start date, the number of months on abiraterone at start of the report period, and the prescription dates covered by the report, will also be shared with Janssen.

The Janssen PAS portal will provide automated facilities to generate monthly/annual PAS reports, as presented in the table below.

Figure 1: Janssen PAS Automated Reporting



Based on these reports, Janssen will issue a credit note to each individual NHS Trust/Hospital or Homecare provider on a monthly basis. Whilst such a credit note could be used to offset against future purchase of Janssen products at Trust/Hospital level, it will be possible to settle the account via cash repayment, if necessary.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

Please refer to the flow charts in Section 3.9 below for the details of how the PAS will be administered and more details in section 3.7 of this submission. No data needs to be collected, above that which is already done so in current practice in order to administer the PAS, as the prescribing of abiraterone by hospital-based clinicians will trigger the data collection of treatment duration.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Figure 2: High-level process

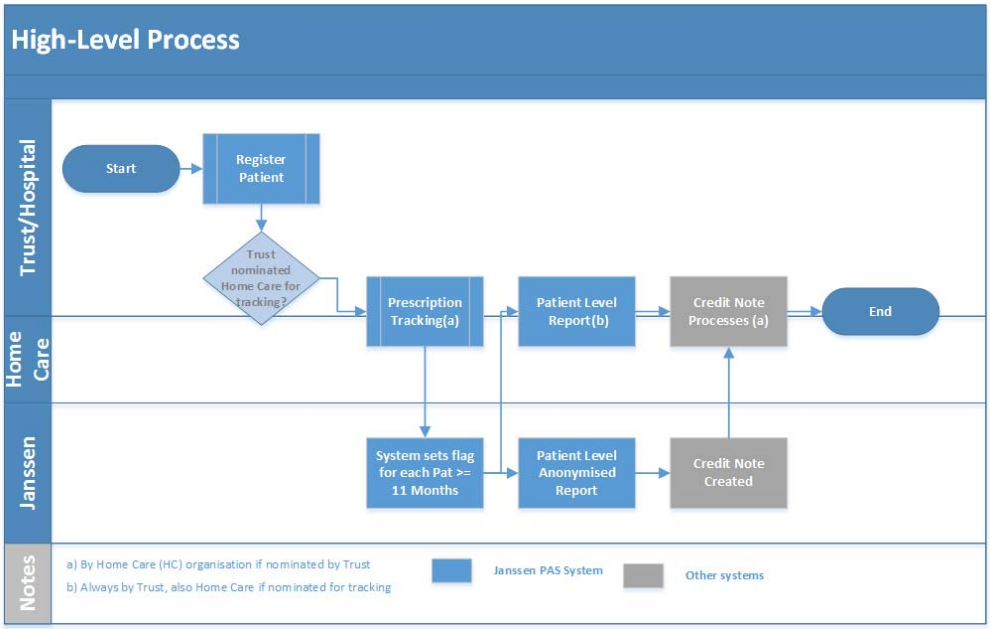


Figure 3: Patient registration detailed flow (HCP / Pharmacist)

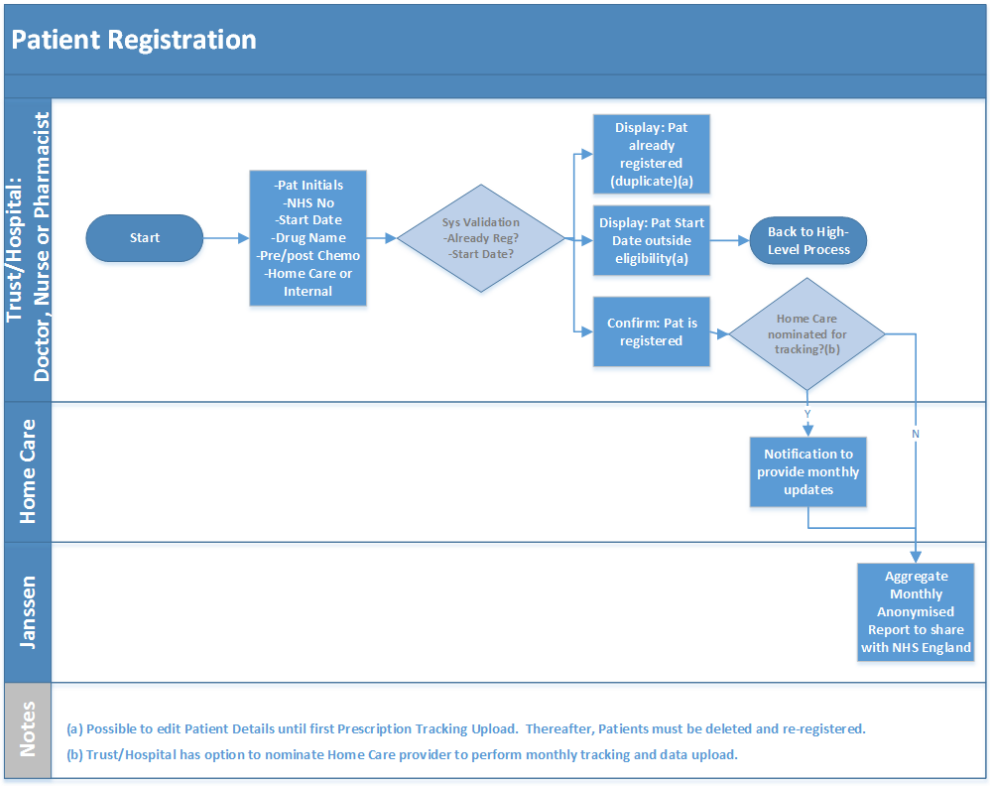
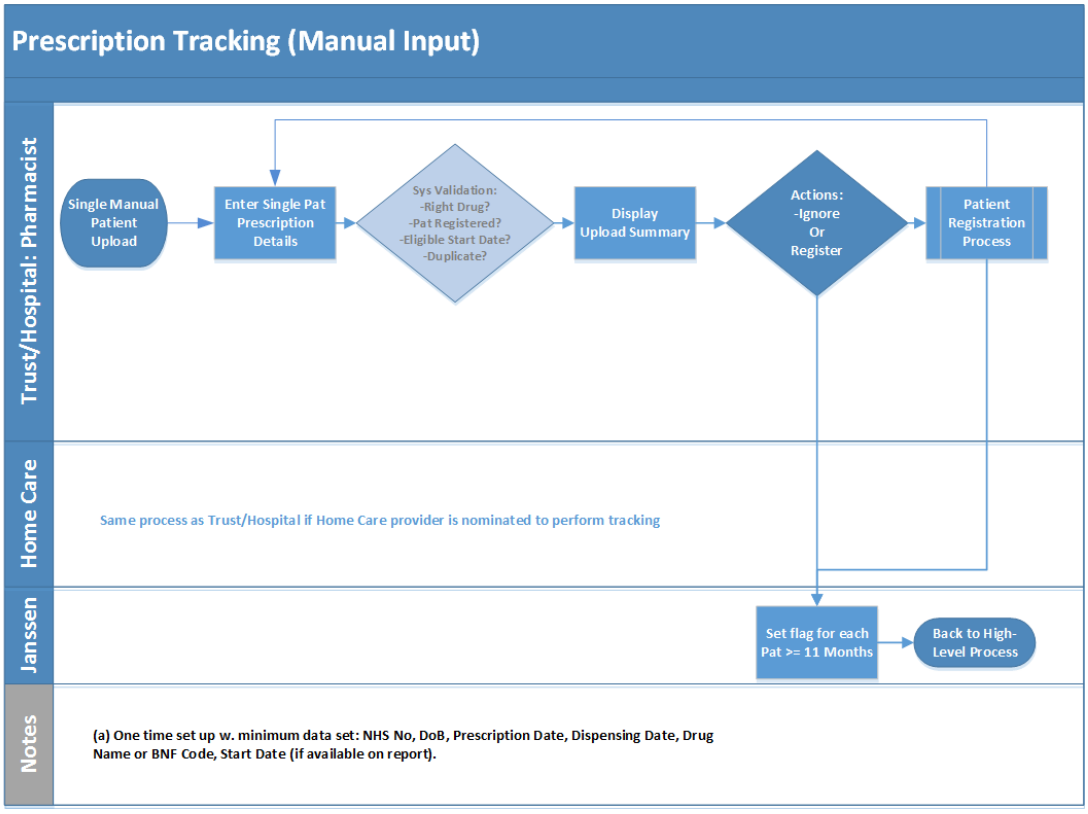
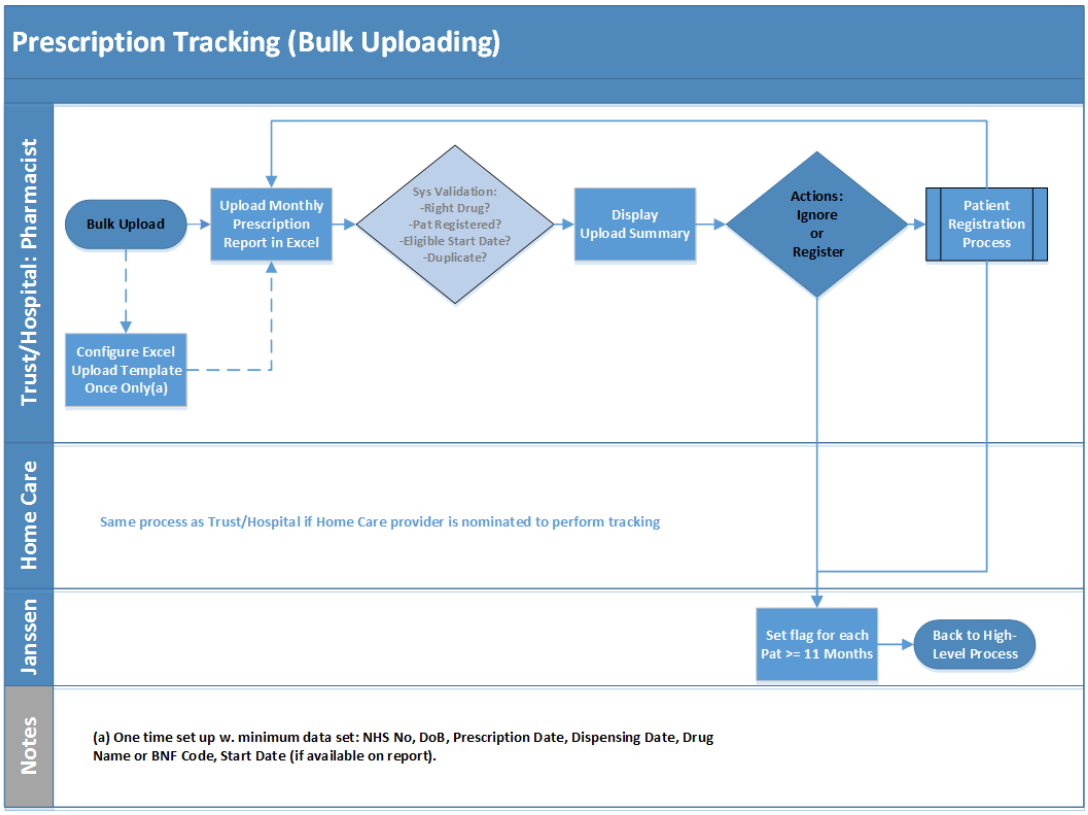


Figure 4: Prescription tracking detailed flow (Pharmacist);
OPTION 1 – manual uploading (default option)



OPTION 2 - Bulk uploading (if required by the Trust/Hospital pharmacist)



3.10 Please provide details of the duration of the scheme.

Janssen is committed to maintaining the scheme in association with NICE guidance related to abiraterone for the lifetime of the guidance.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

The PAS ensures that the drug acquisition cost is equal among all patients, regardless of the setting in which it is used, avoiding any potential inequality issues.

Whilst no potential equity issue was identified in relation to the proposed scheme itself, a positive outcome from the NICE STA process will mitigate some of the equity issues that may currently exist within the NHS in England, Wales and Northern Ireland.

Abiraterone is currently funded through the Cancer Drugs Fund (CDF), which may result in geographical variation in access to, and uptake of, the CDF-approved medicines, such as abiraterone. In addition, patients in Wales and Northern Ireland, where the CDF does not exist, do not have access to abiraterone in the pre-chemotherapy setting except when an individual patient funding request (IPFR) is approved. Therefore, there is not only a disparity within England but there is also inequality between England, Wales and Northern Ireland. The proposed scheme, and a resulting positive NICE recommendation, will remove such issues.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

Under the current PAS, there is no need to separate the PAS registration form, PAS order form or any type of PAS claim forms. Hospitals will continue to order abiraterone as they have always done.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The cost-effectiveness analysis in our first submission for abiraterone in the pre-chemotherapy setting [ID503] was conducted on the same population to whom the new PAS applies.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

The economic model has been updated to include assumptions that the Appraisal Committee considered as plausible within the context of this evaluation and which were thereafter reported in the cost-effectiveness section of the (FAD) report. The adjustments made to the model included:

- The utility increment of 0.021, applied to abiraterone-treated patients in the pre-chemotherapy setting was also applied to abiraterone-treated patients in the post-chemotherapy phase of the model.

- The docetaxel drug price was reduced by 20%: i.e. the docetaxel drug cost used in the original submission was multiplied by 0.8.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The proposed PAS uses a new abiraterone list price of £2,300 per 30 days and offers the drug free-of-charge after 10 months on treatment. In order to capture the new PAS in the economic model, the cost of abiraterone was only applied for 10 months of treatment to ensure drug costs were only accrued over the maximum duration defined by the new PAS, whilst not impacting Overall Survival (OS). This adjustment to abiraterone cost is applied when it is used in either the pre-chemotherapy or post-chemotherapy setting.

The only two updates to model parameters have been previously described in section 4.2, as per comments from the Appraisal Committee; all other parameters and assumptions remain unchanged with the introduction of the new PAS.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data used in the previous submission remains unchanged with the introduction of the new PAS, as it is not associated with any changes in clinical effectiveness relating to abiraterone, in either the post-chemotherapy or the pre-chemotherapy setting.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

There are negligible additional costs associated with the implementation and operation of the new PAS and hence its introduction will have virtually no impact on NHS budgets for England, Wales, and Northern Ireland, and only minimal adjustment to current processes. The impact on the ICER is also negligible.

Table 2: Costs associated with the implementation and operation of the proposed new PAS

	Calculation of cost	Reference source
Stock management	£0	The proposed scheme will not impact stock management
Administration of claim forms	£0	There is no need to issue any claim form because Janssen will proactively issue a credit note.
Staff training	£31	Hourly wage for nurse staff at £18 * 30 minutes for training on use of Janssen PAS portal to register patients & set up login details 'Agenda for change' pay rates for the mid-point on Band 6 £29,759 p.a., equivalent to £18 per hour: http://www.nhscareers.nhs.uk/working-in-the-nhs/pay-and-benefits/agenda-for-change-pay-rates/ Hourly wage for hospital pharmacist £22 * 60 minutes for training on use of Janssen PAS portal to track prescriptions and generate a monthly report from the pharmacy dispensing system. 'Agenda for change' pay rates for the mid-point on Band 7 £35,536 p.a., equivalent to £22 per hour: http://www.nhscareers.nhs.uk/working-in-the-nhs/pay-and-benefits/agenda-for-change-pay-rates/ We are assuming the time and cost at Homecare provider level will be consistent.
Tracking of supplies	£0	The proposed scheme will not impact tracking of supplies
Other costs	£2 per patient for patient registration	Hourly wage for nurse staff at £18 * 2 minutes to register a patient onto the PAS portal. The time to register one patient includes: Log in; Click on Register patient button; Fill in simple form (6 fields); Press the Submit Button; Log Off; Time estimate = 2 minutes 'Agenda for change' pay rates for the mid-point on Band 6 £29,759 p.a., equivalent to £18 per hour: http://www.nhscareers.nhs.uk/working-in-the-nhs/pay-and-benefits/agenda-for-change-pay-rates/ Hourly wage for administrative staff at hospital pharmacy £22 * 2 minutes per patient to manually input into the PAS internet-based system and then 2 minutes to

	£2 per patient per month for prescription tracking	generate the reports. The time to track monthly prescription per patient includes: Search for patient; Click on Prescription Tracking Button; Fill in simple form (6 fields); Press the Submit Button; Confirm / resolve any validation issues; Log Off Time estimate = 4 minutes However, we believe that a trained operator after a few weeks should be able to do this in 2 minutes 'Agenda for change' pay rates for the mid-point on Band 7 £35,536 p.a., equivalent to £22 per hour: http://www.nhscareers.nhs.uk/working-in-the-nhs/pay-and-benefits/agenda-for-change-pay-rates/ We are assuming the time and cost at Homecare provider level will be consistent.
Other [add more rows as necessary]		
Total implementation and operation costs	**£388**	**Yearly cost per hospital/Trust/Homecare provider assuming 5 new patients registered per month and 40 prescriptions tracked every month (excluding training costs)**

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

There are no additional treatment-related costs incurred by implementing the PAS.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

The cost-effectiveness results for the base case are presented without a PAS, with the original PAS and with the new proposed PAS. These analyses were conducted using the new assumptions recommended by the Committee as 4.2.

Table 3: Base case results without PAS

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 4: Base case results (original PAS - single confidential discount)

Technology	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,560	0.62	0.56	47,254

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 5: Base case results (new PAS)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	16,055	0.62	0.56	28,563

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

In the base case analysis, the estimated ICER for AAP vs. BSC (PP) is £28,563, based on incremental costs of £16,055 and incremental QALYs of 0.56. Although costs associated with the implementation of AAP were greater, the base case analysis generated an incremental life year gain of 0.62 as illustrated in Table 5 (increased from [redacted] years to [redacted] years) resulting in a cost per life year gained of £25,837. Hence, these results indicate that, under the standard threshold used by NICE, AAP is a cost-effective use of NHS resources in the post-ADT, pre-chemotherapy setting.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

BSC (PP) is the most appropriate comparator for AAP in adult men who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated. The base case economic analysis to be considered is that presented in Section 4.7 of this document.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Table 6: One-way sensitivity results (original PAS)

	Base case parameter	Proposed variation	ICER, £/QALY
Model base case ICER			**47,254**
Model settings			
Time horizon	Life time	10 years	[redacted]
Discount rate: health effects	3.5% for health effects & costs	0–5% for health effects 3.5% for costs	
Discount rate: costs	3.5% for health effects & costs	3.5% for health effects 0–5% for costs	[redacted]
Discount rate: for health effects & costs	3.5% for health effects & costs	0–5% for health effects & costs	[redacted]
Clinical settings			
Truncation of OS curve at 1%	Truncated	Non-truncated	[redacted]
Distribution for 1st-line treatment duration	Log-logistic (best fit)	Weibull only	[redacted]
		2-segment curve	
Cost inputs			
AA 1st-line compliance	98%	95–100%	[redacted]
Scheduled MRU	As per MRU study	25th–75th percentile on all scheduled MRU	
Unplanned MRU	As per COU-AA-302 trial	±20% on all unplanned MRU costs	[redacted]
Utility inputs			
Post-ADT baseline	0.830	±20% (0.664–0.996)	[redacted]
AA on-treatment utility increment	0.021	±20% (0.0168–0.0252)	
BSC (pre-docetaxel)	0.625	±20% (0.5–0.75)	[redacted]
Docetaxel	0.692	±20% (0.5536–0.8304)	
Post-docetaxel	0.700	±20% (0.56–0.84)	
BSC (before death)	0.500	±20% (0.4–0.6)	

[redacted]

AA, abiraterone acetate; ADT, androgen deprivation therapy; BSC, best supportive care; MRU, medical resource utilisation; N, no; PAS, patient access scheme; Tx, treatment; Y, yes.

Table 7: One-way sensitivity results (new PAS)

	Base case parameter	Proposed variation	ICER, £/QALY
Model base case ICER			**28,563**
Model settings			
Time horizon	Life time	10 years	31,722
Discount rate: health effects	3.5% for health effects	0–5% for health effects 3.5% for costs	23,784 – 30,674
Discount rate: costs	3.5% for costs	3.5% for health effects 0–5% for costs	29,851 – 28,283
Discount rate: for health effects & costs	3.5% for health effects & costs	0–5% for health effects & costs	24,855 – 30,373
Clinical settings			
AA treatment effect	Coefficients in prediction equations	±2 standard error (SE) around treatment coefficients in prediction equations	38,070 – 22,908
Truncation of OS curve at 1%	Truncated	Non-truncated	28,565
Distribution for 1st-line treatment duration	Log-logistic (best fit)	Weibull only	35,789
		2-segment curve	34,383
Cost inputs			
AA 1st-line compliance	98%	95–100%	27,499 – 29,273
Scheduled MRU	As per MRU study	25th–75th percentile on all scheduled MRU	28,002 – 29,597
Unplanned MRU	As per COU-AA-302 trial	±20% on all unplanned MRU costs	28,493 – 28,634
Utility inputs			
Post-ADT baseline	0.830	±20% (0.664–0.996)	23,261 – 36,995
AA on-treatment utility increment	0.021	±20% (0.0168–0.0252)	28,926 – 28,209
BSC (pre-docetaxel)	0.625	±20% (0.5–0.75)	28,534 – 28,593
Docetaxel	0.692	±20% (0.5536–0.8304)	28,270 – 28,862
Post-docetaxel	0.700	±20% (0.56–0.84)	27,537 – 29,668
BSC (before death)	0.500	±20% (0.4–0.6)	28,798 -28,332

Figure 5: Tornado diagram (new PAS)

AA, abiraterone acetate; ADT, androgen deprivation therapy; BSC, best supportive care; MRU, medical resource utilisation; N, no; PAS, patient access scheme; Tx, treatment; Y, yes.

The deterministic sensitivity analyses using the new PAS indicated that the results were relatively stable across a range of assumptions. The model was most sensitive to AA treatment effect and post-ADT baseline utility, followed by discounting, 1st line treatment duration and a shorter time horizon. Parameters such as AA treatment effect and post-ADT baseline utility and duration of 1st line treatment, however, are underpinned by robust data extracted from the clinical trial COU-AA-302 and the bespoke UK patient utility study, and are therefore likely associated with a lower degree of uncertainty.

Nevertheless, the majority of analyses generated ICERs below the £30K/QALY threshold, with the maximum ICER derived throughout extensive sensitivity analyses being £38,070/QALY (of note, this upper estimate of £38,070 represents an extreme scenario).

The deterministic analysis also indicated that variation in parameters associated with larger degrees of uncertainty, such as scheduled and unscheduled MRU, had a limited impact on cost-effectiveness; varying these parameters from base case values showed the ICER for AAP vs. BSC (PP) to range only minimally, from £28,002–£29,597/QALY.

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Results from the PSA with the original PAS are as follows:

[redacted]

PAS, patient access scheme; QALY, quality-adjusted life year

[redacted]

BSC, best supportive care; PAS, patient access scheme

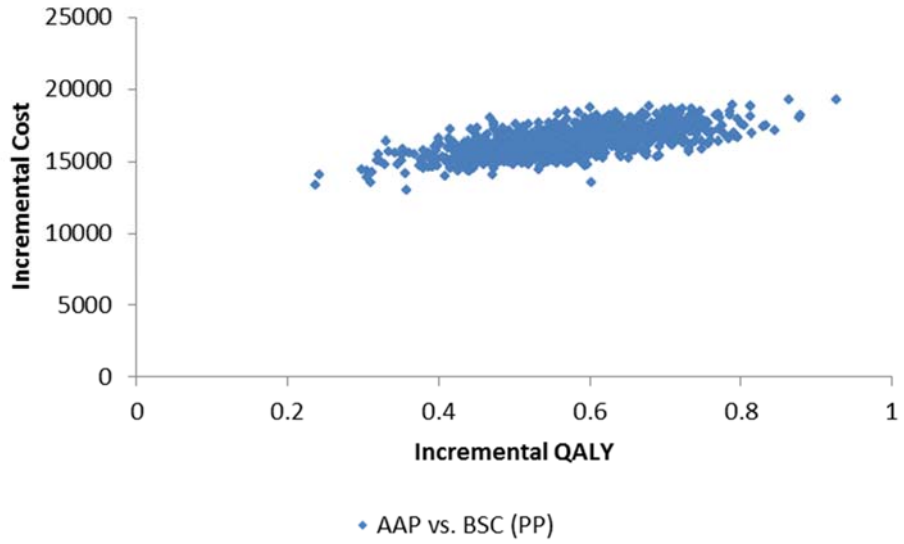
Table 8: Summary of the PSA (original PAS)

WTP threshold	AAP, %	BSC (PP), %
£40,000/QALY	[redacted]	[redacted]
£45,000/QALY	[redacted]	[redacted]
£50,000/QALY	[redacted]	[redacted]
£55,000/QALY	[redacted]	[redacted]

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness-to-pay

Results from the PSA with the new PAS are as follows:

Figure 6: Cost-effectiveness scatter plot (with new PAS)



PAS, patient access scheme; QALY, quality-adjusted life year

Figure 7: Cost-effectiveness acceptability curve (with new PAS)

BSC, best supportive care; PAS, patient access scheme

Table 9: Summary of the PSA for the base case (with new PAS)

WTP threshold	AAP, %	BSC (PP), %
£22,000/QALY	2	98
£26,000/QALY	20	80
£30,000/QALY	62	38
£34,000/QALY	83	17

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness-to-pay

At an ICER threshold of £30,000, the probability that AAP is the most cost-effective option when compared to BSC (PP) is 62%; at a threshold of £34,000, the probability increases to 83%.

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Scenario 1: Comparison against enzalutamide in the pre-chemotherapy setting

Enzalutamide (ENZ) is also indicated for the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated. Whilst this comparator was not included in the original submission for abiraterone in January 2014, enzalutamide is now also undergoing a NICE STA with abiraterone as a comparator, and has been listed on the CDF for several months. Thus, Janssen now considers that enzalutamide is an appropriate comparator for inclusion in a scenario analysis.

Whilst comparing these two interventions in terms of cost-effectiveness is of key interest to the efficient use of NHS resources in the UK, there are some important differences between the pivotal phase III trials (COU-AA-302 and PREVAIL) to be considered, as well as several analytical assumptions required, in order to ensure the comparison is valid and robust. It should be noted that the differences between these trials mean that a naïve (unadjusted, side by side) comparison of the two drugs would lead to an inaccurate and potentially misleading estimate of relative effectiveness. In light of such challenges, in order to incorporate enzalutamide into the economic model, clinical equivalence to abiraterone was assumed. Importantly, this is a conservative assumption; however, Janssen deems it to be the most appropriate approach given the uncertainty in estimating comparative clinical data. The rationale for assuming similar efficacy of abiraterone and enzalutamide is further supported by a recent matched adjusted indirect comparison (MAIC) comparing the final analysis from the COU-AA-302 trial with the PREVAIL trial (1).

In order to conduct the analysis of AAP vs. ENZ, the prediction equation and treatment coefficient for time to ENZ discontinuation was assumed to be the same as AAP (treatment coefficient = 0.4216; refer to Section 7.31 of the original submission). Whilst the PREVAIL trial protocol states that patients discontinuing ENZ should start chemotherapy or investigational treatment immediately, in order to conduct this analysis it was assumed they do not, as the same prediction equation and coefficients for AAP were used for ENZ in estimating time in BSC pre-docetaxel.

Table 10: Incremental results comparing AAP vs. ENZ assuming equivalent efficacy (original PAS)

	Total costs, £	Total LYG	Total QALYs	Increm. costs, £	Increm. LYG	Increm. QALYs	ICER, £/QALY
ENZ	[redacted]	[redacted]	[redacted]				
AAP				-36,220	0.00	0.00	n/a

AAP, abiraterone acetate + prednisolone; ENZ, enzalutamide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 11: Incremental results comparing AAP vs. ENZ assuming equivalent efficacy (new PAS)

	Total costs, £	Total LYG	Total QALYs	Increm. costs, £	Increm. LYG	Increm. QALYs	ICER, £/QALY

ENZ	[redacted]	[redacted]	[redacted]				
AAP	[redacted]	[redacted]	[redacted]	-45,530	0.00	0.00	n/a

AAP, abiraterone acetate + prednisolone; ENZ, enzalutamide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Results from this conservative analysis that assumes clinical equivalence shows in both cases, with the original or new PAS, AAP is a cost saving option compared with ENZ in the pre-chemotherapy setting. However, it is important to note that this scenario was conducted using the official list price for ENZ of £2,734.67 per 28 days. Given enzalutamide is currently supplied to the NHS at a simple discount under a confidential PAS; it is unlikely that results presented in Table 11 reflect the true ICER of AAP vs. ENZ.

[redacted]

Scenario 2: Urologist scheduled MRU costs

Table 12: Results when using scheduled urologist MRU costs (original PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,347	0.62	0.56	46,874

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 13: Results when using scheduled urologist MRU costs (new PAS)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	15,842	0.62	0.56	28,184

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Scenario 3: Oncologist and urologist scheduled MRU costs

Table 14: Results when using combined oncologist and urologist scheduled MRU costs (original PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,424	0.62	0.56	47,010

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 15: Results when using combined oncologist and urologist scheduled MRU costs (new PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	15,918	0.62	0.56	28,320

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Scenario 4: Utilities from the FACT-P to EQ-5D mapping study

Table 16: Results when using FACT-P to EQ-5D mapping utility values (original PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,560	0.62	0.52	50,640

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 17: Results when using FACT-P to EQ-5D mapping utility values (new PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	16,055	0.62	0.52	30,597

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Scenario 5: Utilities from the FACT-P to EQ-5D mapping study applied post-docetaxel

Table 18: Results when using utilities from the FACT-P to EQ-5D mapping study post-docetaxel (original PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,560	0.62	0.58	45,944

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 19: Results when using utilities from the FACT-P to EQ-5D mapping study post-docetaxel (new PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	16,055	0.62	0.50	27,772

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Scenario 6: Utility prior to death

Table 20: Results when utility of BSC before death is 0.615 (original PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,560	0.62	0.57	46,814

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 21: Results when utility of BSC before death is 0.615 (new PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	16,055	0.62	0.57	28,298

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Scenario 7: Substituting prednisolone use with dexamethasone use

Table 22: Results of substituting the cost of prednisolone with dexamethasone (original PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,554	0.62	0.56	47,243

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 23: Results of substituting the cost of prednisolone with dexamethasone (new PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	16,049	0.62	0.56	28,553

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Scenario 8: Testing prediction coefficients to generate comparable survival estimates

Table 24: Results when AAP/BSC (PP) patient distributions post-docetaxel are comparable (original PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,498	0.60	0.56	47,442

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 25: Impact of implementing scenario 8 on the distribution of patients in the model (with original PAS)

	AAP		BSC (PP)	
	% in each Tx phase[a]	Mean duration (years)	% in each Tx phase[a]	Mean duration (years)
Pre-docetaxel				
1st line active Tx	[redacted]	[redacted]	[redacted]	[redacted]
BSC (pre-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
On-docetaxel				
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
BSC (post-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
Post-docetaxel				
Post-docetaxel active Tx[b]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]

[a]Percentage (among the total starting population) who reach each 'state' in the treatment pathway.
[b]AAP arm: BSC (PP post-docetaxel); BSC (PP) arm: AAP (post-docetaxel).
AAP, abiraterone acetate plus prednisolone; PP, placebo plus prednisolone; Tx = treatment

Table 26: Results when AAP/BSC (PP) patient distributions post-docetaxel are comparable (new PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	15,992	0.60	0.56	28,633

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 27: Impact of implementing scenario 7 on the distribution of patients in the model (new PAS)

	AAP		BSC (PP)	
	% in each Tx phase[a]	Mean duration (years)	% in each Tx phase[a]	Mean duration (years)
Pre-docetaxel				
1st line active Tx	100%	1.97	100%	1.1
BSC (pre-docetaxel)	65%	0.68	70%	0.61
BSC (before death)	35%	1.55	30%	1.49
On-docetaxel				
Docetaxel	65%	0.41	70%	0.43
BSC (post-docetaxel)	30%	0.35	34%	0.48
BSC (before death)	22%	0.49	27%	0.65
Post-docetaxel				
Post-docetaxel active Tx[b]	30%	0.29	34%	0.48
BSC (before death)	30%	0.56	34%	0.48

[a]Percentage (among the total starting population) who reach each 'state' in the treatment pathway.
[b]AAP arm: BSC (PP post-docetaxel); BSC (PP) arm: AAP (post-docetaxel).
AAP, abiraterone acetate plus prednisolone; PP, placebo plus prednisolone; Tx = treatment

Scenario 9: Patients in the BSC (PP) arm do not receive an efficacious active treatment post-docetaxel

Table 28: Results when patients in BSC (PP) arm do not receive efficacious active treatment post-docetaxel (original PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	29,196	0.66	0.59	49,096

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 29: Results when patients in BSC (PP) arm do not receive efficacious active treatment post-docetaxel (new PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	19,886	0.66	0.59	33,440

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

It should be noted that this scenario is likely to be unrealistic as most mCRPC patients are expected to receive a NICE-approved novel agent post-docetaxel therapy in clinical practice if they did not receive a novel-agent pre-chemotherapy.

Scenario 10: Enzalutamide included as a post-docetaxel active treatment option in the BSC (PP) arm only

Of note, in the original submission for abiraterone in January 2014, this scenario was conducted to account for use of enzalutamide in the post-chemotherapy setting. The post-docetaxel treatment distribution was modelled so that 100% of patients received enzalutamide in the AAP arm, whilst 56.2% received enzalutamide and 43.8% received AAP in the BSC (PP). However, NICE guidance on enzalutamide [TA316], released in July 2014, has since recommended against the use enzalutamide in patients previously treated with abiraterone. As a result, this scenario is no longer valid and has been accordingly revised to reflect NICE guidance. Results presented in Table 30 and Table 31 reflect a scenario in which the post-docetaxel treatment distribution was modelled so that 100% received enzalutamide in the BSC (PP) arm, whilst no patients received enzalutamide in the AAP arm.

Table 30: Results of including enzalutamide as a post-docetaxel active treatment in the BSC (PP) arm only (original PAS)

	Total	Total	Total	Incremental	Incremental	Incremental	ICER,

	costs, £	LYG	QALYs	costs, £	LYG	QALYs	£/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	23,714	0.62	0.57	41,962

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 31: Results of including enzalutamide as a post-docetaxel active treatment in the BSC (PP) arm only (new PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	-	-	-	-
AAP	[redacted]	[redacted]	[redacted]	14,404	0.62	0.57	25,488

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Of note, this scenario is unlikely to reflect the true cost-effectiveness of AAP vs. BSC (PP) when enzalutamide is included as a post-docetaxel active treatment option because enzalutamide is currently supplied to the NHS at a simple discount under a confidential PAS.

Scenario 11: No restriction on patients ECOG status when switching to docetaxel after 1st-line treatment

Table 32: Results when no restriction on ECOG status when switching to docetaxel after 1st line treatment (original PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,163	0.57	0.54	48,723

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 33: Results when no restriction on ECOG status when switching to docetaxel after 1st line treatment (new PAS)

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	15,590	0.57	0.54	29,033

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo + prednisolone; PAS, patient access scheme; QALY, quality-adjusted life year.

Summary

The model base case ICER using the new PAS is £28,563/QALY gained and extensive sensitivity and scenario analyses demonstrate that the ICER is very stable to variation in model parameters with a higher degree of uncertainty. All scenarios with the new PAS resulted in ICERs varied between £28,184/QALY

and £33,440/QALY (note this upper limit of £33,440/QALY represents an unrealistic scenario from a clinical perspective).

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable – the patient access scheme is not related to clinical variables (see section 3.5).

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

When the new PAS is applied, abiraterone's ICER vs. BSC (PP) is below £30k/QALY in nearly all cases (as listed in Table 34), with the exception of scenario 4 and 9. Of note, Scenario 1 is not included in this table since the ICER is indeterminate given clinical equivalence of AAP vs. ENZ.

Under scenario 4, changing the utilities from the FACT-P to EQ-5D mapping study increased the ICER compared to the base case for AAP versus BSC (PP) with new PAS (£30,597 versus £28,563 in the base case with new PAS) Under scenario 9, where patients in the BSC (PP) arm do not receive an efficacious active treatment post-docetaxel, the ICER with the new PAS is £33,440 versus £28,563 in the base case. However, this scenario is not in line with clinical practice, as patients that do not receive a novel treatment prior to chemotherapy are eligible for either abiraterone or enzalutamide in line with

NICE guidance. Whilst Scenario 10 tested the effect of including enzalutamide as a post-docetaxel active treatment option in the BSC (PP) arm, it is unlikely to reflect the true cost-effectiveness of this situation in clinical practice because enzalutamide is currently supplied to the NHS at a simple discount under a confidential PAS. Overall, the ICER ranged from £27,772 to £33,440/QALY with new PAS and from £46,874 to £50,640/QALY with the original PAS.

Scenario 1 was added to acknowledge that enzalutamide is now an appropriate comparator to consider. Whilst assuming clinical equivalence showed that AAP was a cost saving option for the NHS, these results were derived using the enzalutamide list price and should be reviewed in that context.

The extensive scenario analyses demonstrate that, with the new PAS, abiraterone is a cost-effective treatment option compared against BSC (PP) in the pre-chemotherapy setting.

Table 34 Results showing the impact of PAS on ICERs

	With original PAS	With new PAS
Base case	£47,254	£28,563
Scenario 2: Urologist scheduled MRU costs	£46,874	£28,184
Scenario 3: Oncologist and urologist scheduled MRU costs	£47,010	£28,320
Scenario 4: Utilities from the FACT-P to EQ-5D mapping study	£50,640	£30,597
Scenario 5: Utilities from the FACT-P to EQ-5D mapping study applied post-docetaxel	£45,944	£27,772
Scenario 6: Utilities prior to death	£46,814	£28,298
Scenario 7: Substituting prednisolone use with dexamethasone use in BSC	£47,243	£28,553
Scenario 8: Testing prediction coefficients to generate comparable survival estimates	£47,442	£28,633
Scenario 9: Patients in the BSC (PP) arm do not receive an efficacious active treatment post-docetaxel	£49,096	£33,440
Scenario 10: Enzalutamide included as a post-docetaxel active treatment option	£41,962	£25,488
Scenario 11: No restriction on patients ECOG status when switching to docetaxel after 1st-line treatment	£48,723	£29,033

Of note: Scenario 1 is not included in this table as it uses a different comparator (ENZ) and the ICER is indeterminate due clinical equivalence

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS: patient access scheme; PP, placebo plus prednisolone; QALYs, quality-adjusted life years.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Not applicable

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Not applicable

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Reference List

1. Dearden L, Majer I, Heeg B, Liwing J, Sandstrom K, Diels J. PCN12 - Comparison of Mean Overall Survival (OS) and Radiographic Progression Free Survival (RPFS) Based on Matching Adjusted Indirect Comparison of Abiraterone Acetate and Enzalutamide for the Treatment of Castration-Resistant Prostate Cancer in Chemotherapy Naïve Patients. Value in Health. 2014 11//;17(7):A616.

Comparative clinical data - COU-AA-302 (including final analysis)

Treatment exposure

	Interim analysis 2	
	AAP (N=546)	PP (N=542)
Median follow-up, months	8.3	
Median treatment duration, months (range)	13.8 (0.3, 29.9)	8.28 (0.1, 28.1)

SOURCES: Ryan et al. N Engl J Med 2013;368:138-48 (IA2), Rathkopf et al. Eur Urol. 2014 Nov;66 analysis).

Discontinuation and cross-over

Treatment discontinuations (Safety population)

	Interim analysis 2	
	AAP (N=542)	PP (N=540)
Patients treated, n (%)	542 (100.0)	540 (100.0)
Treatment discontinued	376 (69.4%)	454 (84.1%)
Treatment ongoing	166 (30.6%)	86 (15.9%)
Reasons for discontinuation, n (%)		
Radiographic and unequivocal clinical progression	57 (10.5%)	53 (9.8%)
Radiographic progression only	115 (21.2%)	162 (30.0%)
Unequivocal clinical progression only	111 (20.5%)	136 (25.2%)
AE	40 (7.4%)	29 (5.4%)
Withdrawal of consent to treatment	32 (5.9%)	46 (8.5%)
Other	20 (3.7%)	28 (5.2%)
Lost to follow-up	1 (0.2)	0

SOURCES Clinical study reports for IA2, IA3 and final analysis

Subsequent therapy

Selected subsequent therapy for prostate cancer – ITT population

	Interim analysis 2	
	AAP (N=546)	PP (N=542)
Number of subjects with selected subsequent therapy for prostate cancer	242 (44.3%)	327 (60.3%)
Docetaxel	207 (37.9%)	287 (53.0%)
Cabazitaxel	45 (8.2%)	52 (9.6%)
Ketoconazole	39 (7.1%)	63 (11.6%)
AAP	26 (4.8%)	54 (10.0%)
Sipuleucel-T	27 (4.9%)	24 (4.4%)
Radium-223		
Enzalutamide		

SOURCES: Ryan et al. N Engl J Med 2013;368:138-48 (IA2), Rathkopf et al. Eur Urol. 2014 Nov;66
analysis).

Co-primary efficacy outcome – rPFS and OS

rPFS in patients treated with either AAP or PP - ITT population

	Interim analysis 2	
	AAP (N=546)	**PP (N=542)**
Number of patients with PFS event, n (%)	271 (49.6)	336 (62.0)
Time-to-event[a] (months), median (95% CI)	16.5 (13.8, 16.8)	8.3 (8.1, 9.4)
HR (95% CI)[a]	0.53 (0.45, 0.62)	
p value[b]	<0.0001	

a HR is from a stratified proportional hazards Cox model. HRs <1 favour AAP.
b p-value is from a log-rank test stratified by ECOG PS score (0 or 1).
Legend: AAP, abiraterone acetate plus prednisone/prednisolone; CI, confidence interval; HR, haz
prednisone/prednisolone.
SOURCES: Ryan et al. N Engl J Med 2013;368:138-48 (IA2), Rathkopf et al. Eur Urol. 2014 Nov;
analysis).

Overall survival of patients treated with either AAP or PP - ITT population

	Interim analysis 2	
	AAP (N=546)	**PP (N=542)**
Number of deaths, n (%)	147 (26.9)	186 (34.3)
OS[a] (months), median (95% CI)	NR (NR, NR)	27.2 (26.0, NR)
HR (95% CI)[b]	0.75 (0.61, 0.93)	
p value[c]	0.0097	
p value required for significance	0.0005	

a Survival time of living patients was censored at the last date a patient was known to be alive or
b HRs from a stratified proportional hazards Cox model. HRs <1 favour AAP.
c p value from a log-rank test stratified by ECOG PS score (0 or 1).
Legend: AAP, abiraterone acetate plus prednisone/prednisolone; CI, confidence interval; HR, haz
plus prednisone/prednisolone.
SOURCES: Ryan et al. N Engl J Med 2013;368:138-48 (IA2), Rathkopf et al. Eur Urol. 2014 Nov;
analysis).

Of note, any effect of cross-over on the third interim analysis results is expected to be minimal du
third interim analysis. However, the OS outcome at final anlaysis was obtained in the context of s
enzalutamide and radium-223 in the placebo group; with 53% of placebo subjects having receive
proven to have a positive impact on OS, including docetaxel (57-61%), cabazitaxel (18-19%) and
groups.

OS analyses of PP patients receiving subsequent therapy with AA at IA3 and final analysis

	Interim analysis 2	
	AAP (N=546)	**PP (N=542)**
Iterative Parameter Estimate, HR (95%CI)		

CI, confidence interval; HR, hazard ratio.
SOURCES: Report of updated data from study COU-AA-302 22 May 2012 data cut-off - 3IA (unp

Other secondary endpoints at final analysis

Time to use of opiates for pain from prostate cancer - ITT population

	Interim analysis 2	
	AAP (N=546)	**PP (N=542)**
Number of events, n (%)	183 (33.5%)	235 (43.4%)
Median (95% CI)	NE (28.25, NE)	23.66 (20.24, NE)
Hazard ratio (95% CI)*	0.686 (0.566, 0.833)	
p value**	0.0001	

* Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors AA.
** p value is from a log-rank test stratified by ECOG PS score (0 or 1).
SOURCES: Ryan et al. N Engl J Med 2013;368:138-48 (IA2), Rathkopf et al. Eur Urol. 2014 Nov;6(analysis).

)

Interim analysis 3		Final analysis	
AAP (N=546)	PP (N=542)	AAP (N=546)	PP (N=542)
27.1		49.2	
13.8 (0.3, 34.9)	8.28 (0.1, 32.4)	13.8 (0.3, 56.7)	8.28 (0.1, 54.3)

5(5):815-25 (IA3), Ryan et al. Lancet oncology, 2015, 16(2):152-60 (final

Interim analysis 3		Final analysis		
AAP (N=542)	PP (N=540)	AAP (N=542)	PP (N=540)	PP to APP (N=93)
542 (100.0)	540 (100.0)	542 (100.0%)	540 (100.0%)	93 (100.0%)
419 (77.3)	482 (89.3)	500 (92.3%)	540 (100.0%)	58 (62.4%)
123 (22.7)	58 (10.7)	42 (7.7%)	0	35 (37.6%)
66 (12.2)	56 (10.4)	68 (12.5%)	56 (10.4%)	1 (1.1%)
126 (23.2)	172 (31.9)	160 (29.5%)	172 (31.9%)	13 (14.0%)
118 (21.8)	141 (26.1)	138 (25.5%)	142 (26.3%)	6 (6.5%)
45 (8.3)	33 (6.1)	50 (9.2%)	33 (6.1%)	9 (9.7%)
36 (6.6)	52 (9.6)	41 (7.6%)	56 (10.4%)	2 (2.2%)
27 (5.0)	28 (5.2)	42 (7.7%)	30 (5.6%)	19 (20.4%)
1 (0.2)	0	1 (0.2%)	0	0

Interim analysis 3		Final analysis	
AAP (N=546)	PP (N=542)	AAP (N=546)	PP (N=542)
274 (50.2)	348 (64.2)	365 (66.8%)	435 (80.3%)
239 (43.8)	304 (56.1)	311 (57.0%)	331 (61.1%)
60 (11.0)	70 (12.9)	100 (18.3%)	105 (19.4%)
39 (7.1)	63 (11.6)	87 (15.9%)	54 (10.0%)
38 (7.0)	78 (14.4)	69 (12.6%)	238 (43.9%)
33 (6.0)	28 (5.2)	45 (8.2%)	32 (5.9%)
		20 (3.7%)	7 (1.3%)
		87 (15.9%)	54 (10.0%)

5(5):815-25 (IA3), Ryan et al. Lancet oncology, 2015, 16(2):152-60 (final

Interim analysis 3		Final analysis	
AAP (N=546)	**PP (N=542)**	**AAP (N=546)**	**PP (N=542)**
292 (53.5)	352 (64.9)		
16.5 (13.8, 16.8)	8.2 (8.0, 9.4)		
0.52 (0.45, 0.62)			
<0.0001			

zard ratio; ITT, intent-to-treat; PFS, progression-free survival; PP, placebo plus

;66(5):815-25 (IA3), Ryan et al. Lancet oncology, 2015, 16(2):152-60 (final

Interim analysis 3		Final analysis	
AAP (N=546)	**PP (N=542)**	**AAP (N=546)**	**PP (N=542)**
200 (36.6)	234 (43.2)	354 (65)	387 (71)
35.3 (31.2, 35.3)	30.1 (27.3, 34.1)	34.7 (32.7, 36.8)	30.3 (28.6, 33.3)
0.79 (0.66, 0.96)		0.81 (0.70, 0.9)	
0.0151		0.0033	
0.0034		0.0384	

lost to follow-up as of the cut-off date for the interim analysis.

zard ratio; ITT, intent-to-treat; NR, not reached; OS, overall survival; PP, placebo

;66(5):815-25 (IA3), Ryan et al. Lancet oncology, 2015, 16(2):152-60 (final

e to the few patients involved and the short time between unblinding and the
ignificant crossover and subsequent treatment with abiraterone acetate,
d AAP or enzalutamide at some time in follow-up. Moreover, other therapies
enzalutamide (10-16%), were widely used as subsequent therapy in both study

; (ITT population)

Interim analysis 3		Final analysis	
AAP (N=546)	**PP (N=542)**	**AAP (N=546)**	**PP (N=542)**
0.78 (0.63, 0.93)		0·74 (0·60–0·88)	

ublished), Ryan et al. Lancet oncology, 2015, 16(2):152-60 (final analysis)

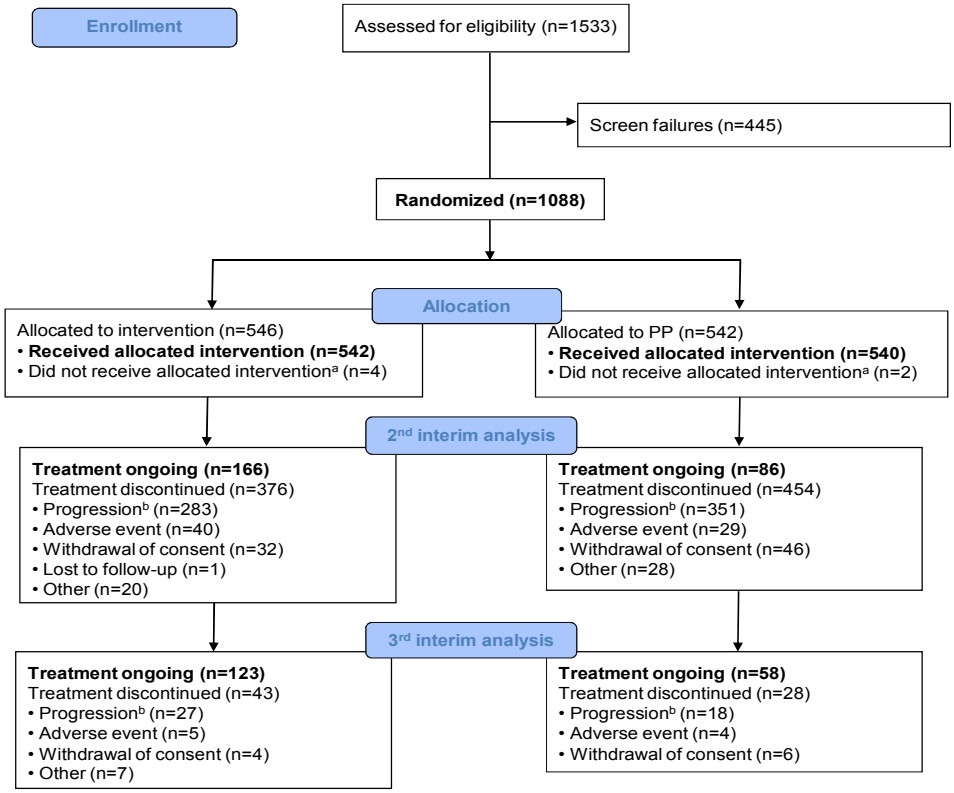
Interim analysis 3		Final analysis	
AAP (N=546)	**PP (N=542)**	**AAP (N=546)**	**PP (N=542)**
210 (38.5%)	259 (47.8%)	278 (50.9)	322 (59.4)
NE (28.25, NE)	23.66 (20.40, 30.26)	33.38 (30.23, 39.75)	23.39 (20.27, 27.53)
0.710 (0.592, 0.852)		0.721 (0.614, 0.846)	
0.0002		< 0.0001	

5(5):815-25 (IA3), Ryan et al. Lancet oncology, 2015, 16(2):152-60 (final

Third Interim Analysis (3IA)

Patient Flow

Figure 3: COU-AA-302 study patient flow diagram - data from third interim analysis (sec



SOURCE: COU-AA-302 study clinical study reports (unpublished) [18;65].

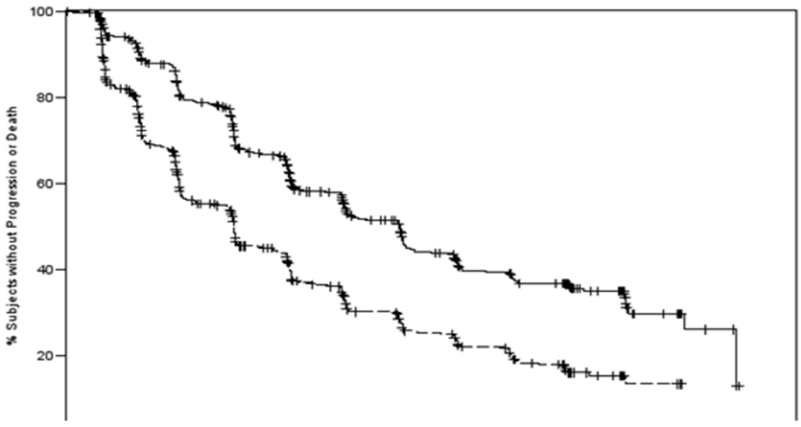
a. Five patients were mistakenly randomised instead of indicating them as screening failures withdrew consent after randomisation but before starting treatment.

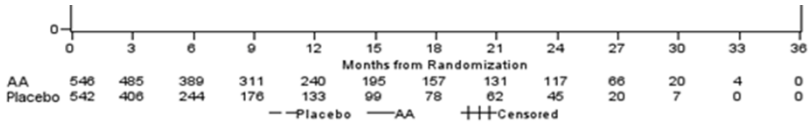
b. Radiographic and/or unequivocal clinical progression.

Legend: AAP, abiraterone acetate plus prednisone/prednisolone; ITT, intent-to-treat; PP, pla prednisone/prednisolone.

Co-primary efficacy outcome – rPFS

Figure 5: Kaplan–Meier curve of rPFS – ITT population (third interim analysis – 22.05.12

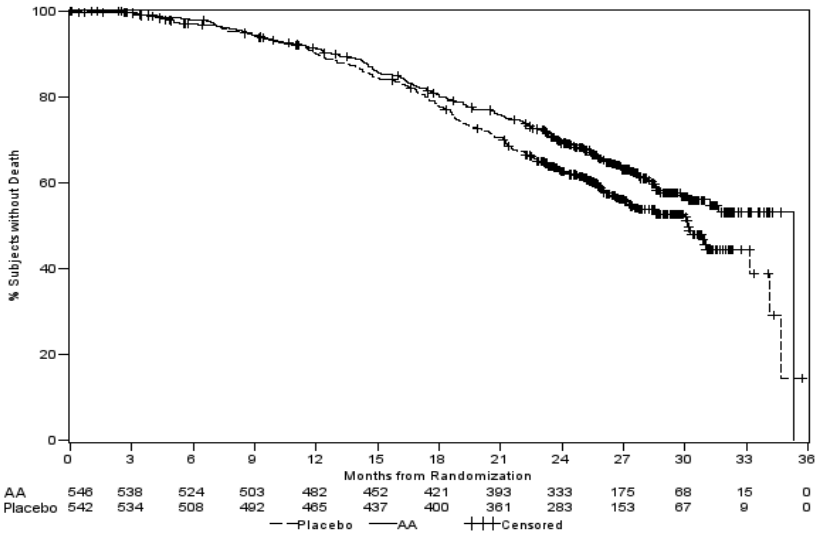




SOURCE: COU-AA-302 study clinical study report (unpublished) [18] and conference poster [7
AA, abiraterone acetate plus prednisone/prednisolone; ITT, intent-to-treat; Placebo, placebo pl

Co-primary efficacy outcome – OS

Figure 6: Kaplan–Meier curve of OS – ITT population (COU-AA-302 study third interim a



SOURCE: COU-AA-302 study clinical study report (unpublished) [18] and conference poster [7
AA, abiraterone acetate plus prednisone/prednisolone; ITT, intent-to-treat; OS, overall survival

tion 6.3.8. of the original submission)

; one patient (AAP arm)

cebo plus

, **55% data cut-off)**

74].
lus prednisone/prednisolone; rPFS, radiographic progression-free survival.

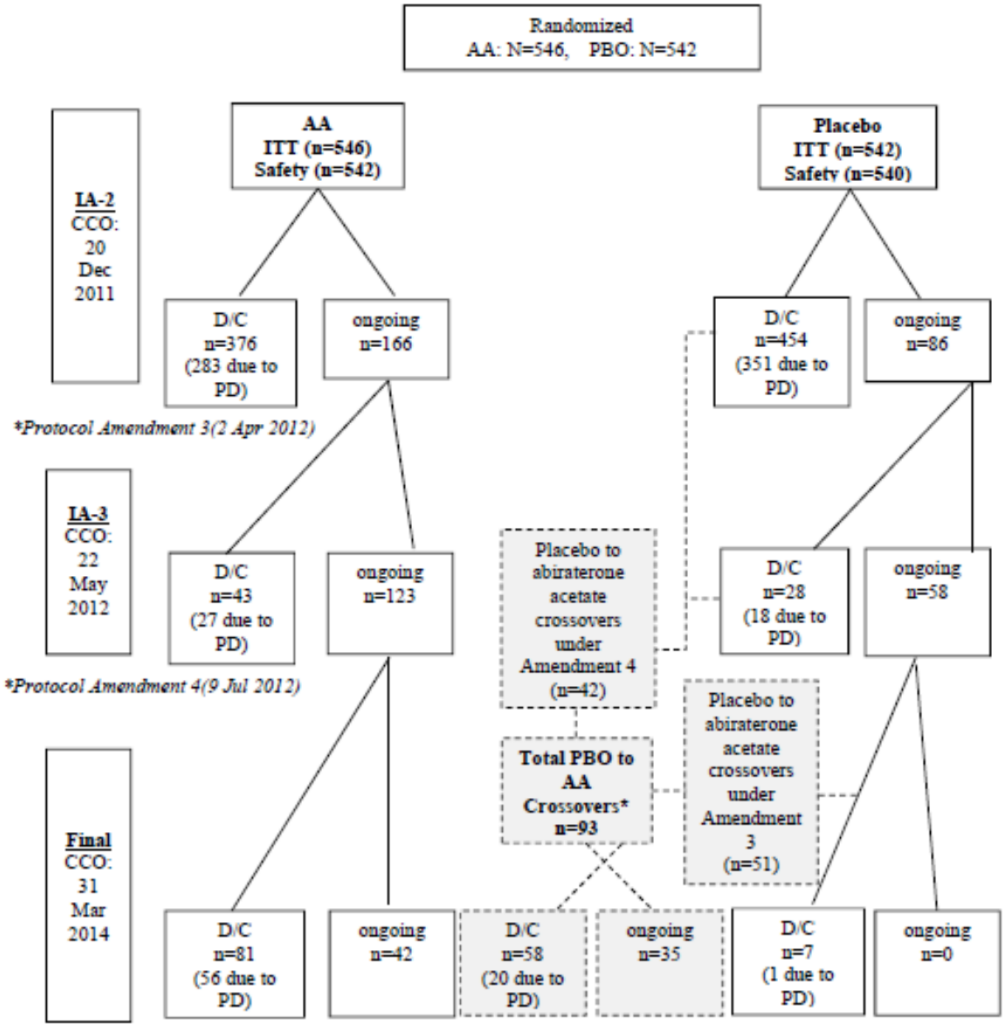
nalysis)

74].
; Placebo, placebo plus prednisone/prednisolone.

Final Analysis

Patient Flow

Figure 1. Subject disposition (Study COU-AA-302)

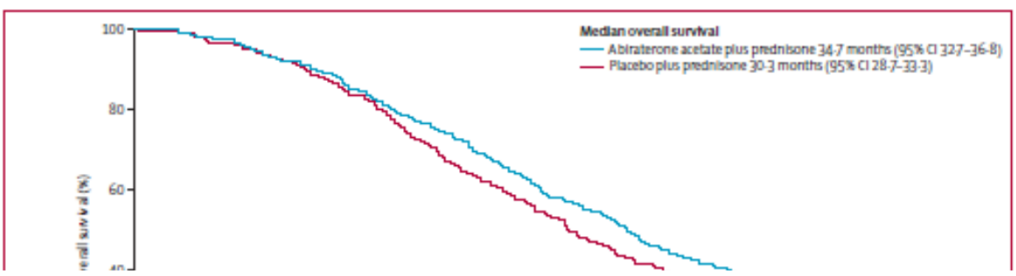


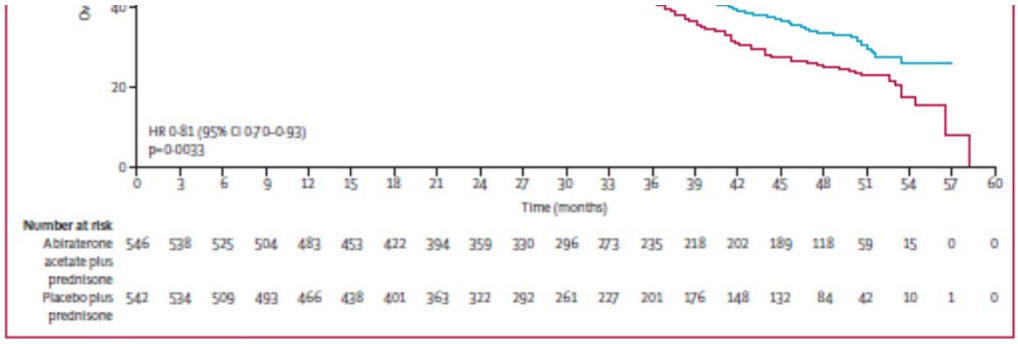
*After IA-2, the protocol was amended to allow subjects receiving placebo (Amendment 3) or those who were discontinued from placebo, but continuing in long-term follow up (Amendment 4) to crossover to abiraterone acetate treatment.
CCO=clinical cutoff date; D/C=discontinued; PBO=placebo; IA=interim analysis; ITT=intent to treat; PD=disease progression

Source: IA2 CSR, IA3 CSR, Final Analysis CSR

Co-primary efficacy outcome –OS

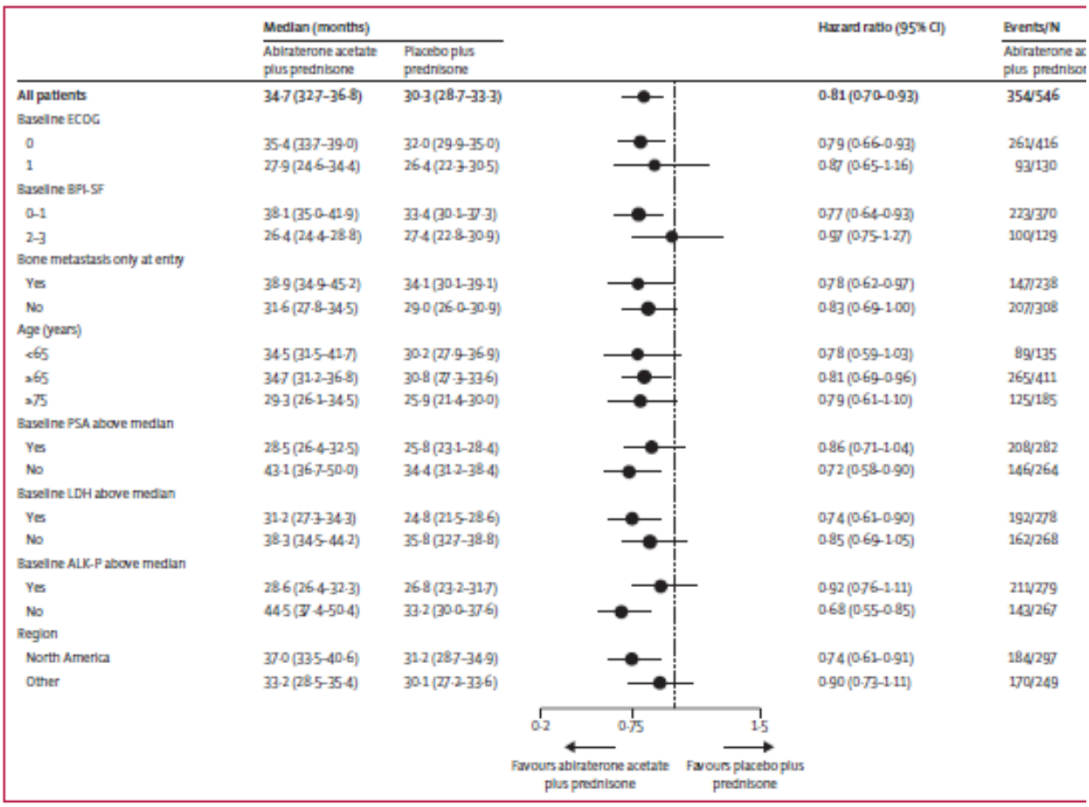
Figure 2 - Kaplan-Meier curve of OS at final analysis - ITT population (i.e. all patients a





Source: Ryan et al. Lancet oncology, 2015, 16(2):152-60

Figure 3 - Sub-group analysis of OS - ITT population

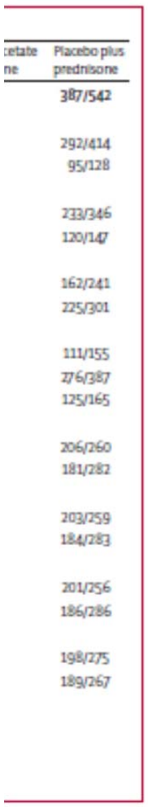


	Median (months)		Hazard ratio (95% CI)	Events/N
	Abiraterone acetate plus prednisone	Placebo plus prednisone		Abiraterone ac plus prednisor
All patients	**34·7 (32·7–36·8)**	**30·3 (28·7–33·3)**	**0·81 (0·70–0·93)**	**354/546**
Baseline ECOG				
0	35·4 (33·7–39·0)	32·0 (29·9–35·0)	0·79 (0·66–0·93)	261/416
1	27·9 (24·6–34·4)	26·4 (22·3–30·5)	0·87 (0·65–1·16)	93/130
Baseline BPI-SF				
0–1	38·1 (35·0–41·9)	33·4 (30·1–37·3)	0·77 (0·64–0·93)	223/370
2–3	26·4 (24·4–28·8)	27·4 (22·8–30·9)	0·97 (0·75–1·27)	100/129
Bone metastasis only at entry				
Yes	38·9 (34·9–45·2)	34·1 (30·1–39·1)	0·78 (0·62–0·97)	147/238
No	31·6 (27·8–34·5)	29·0 (26·0–30·9)	0·83 (0·69–1·00)	207/308
Age (years)				
<65	34·5 (31·5–41·7)	30·2 (27·9–36·9)	0·78 (0·59–1·03)	89/135
≥65	34·7 (31·2–36·8)	30·8 (27·3–33·6)	0·81 (0·69–0·96)	265/411
≥75	29·3 (26·1–34·5)	25·9 (21·4–30·0)	0·79 (0·61–1·10)	125/185
Baseline PSA above median				
Yes	28·5 (26·4–32·5)	25·8 (23·1–28·4)	0·86 (0·71–1·04)	208/282
No	43·1 (36·7–50·0)	34·4 (31·2–38·4)	0·72 (0·58–0·90)	146/264
Baseline LDH above median				
Yes	31·2 (27·3–34·3)	24·8 (21·5–28·6)	0·74 (0·61–0·90)	192/278
No	38·3 (34·5–44·2)	35·8 (32·7–38·8)	0·85 (0·69–1·05)	162/268
Baseline ALK-P above median				
Yes	28·6 (26·4–32·3)	26·8 (23·2–31·7)	0·92 (0·76–1·11)	211/279
No	44·5 (37·4–50·4)	33·2 (30·0–37·6)	0·68 (0·55–0·85)	143/267
Region				
North America	37·0 (33·5–40·6)	31·2 (28·7–34·9)	0·74 (0·61–0·91)	184/297
Other	33·2 (28·5–35·4)	30·1 (27·2–33·6)	0·90 (0·73–1·11)	170/249

Legend: ECOG=Eastern Cooperative Oncology Group. BPI-SF=brief pain inventory—short fo
specific antigen. LDH=lactate dehydrogenase. ALK-P=alkaline phosphatase. Efficacy analyse
intention-to-treat populations (ie, all patients assigned to abiraterone acetate or placebo), i
subsequent crossover.

Source: Ryan et al. Lancet oncology, 2015, 16(2):152-60

assigned to abiraterone acetate or placebo, irrespective of subsequent crossover)



cetate ne	Placebo plus prednisone
	387/542
	292/414
	95/128
	233/346
	120/147
	162/241
	225/301
	111/155
	276/387
	125/165
	206/260
	181/282
	203/259
	184/283
	201/256
	186/286
	198/275
	189/267

rm. PSA=prostate-
s were done in the
irrespective of

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF
HEALTH POLICY & MANAGEMENT

Maastricht University

ADDENDUM TO

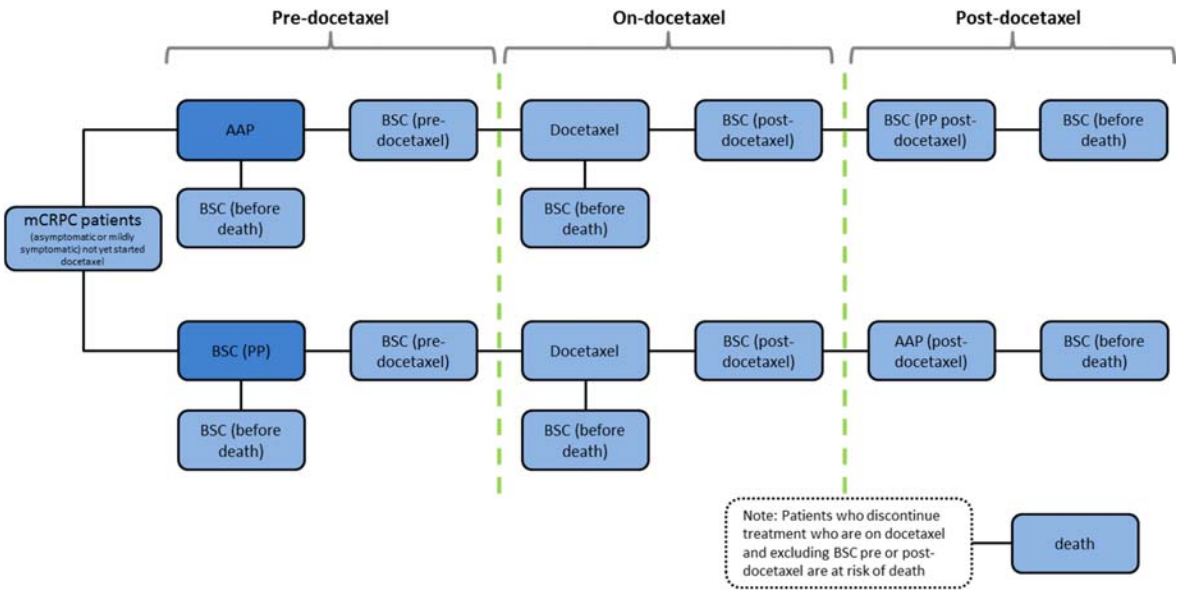
Abiraterone for the treatment of chemotherapy naïve metastatic castration-resistant prostate cancer

Addendum by the ERG in response to the new PAS submission

PATIENT ACCESS SCHEME AND COST-EFFECTIVENESS RESULTS PRE-DOCETAXEL

In the initial submission the Company presented a comparison of AAP versus BSC, by means of a discrete event simulation (DES) model, tracking patients at the individual level. The model follows patients until age 100, which is assumed to reflect a lifetime time horizon. Patients entering the model were assigned to either the AAP or the BSC strategy (see also Figure 1). Patients who discontinue pre-docetaxel active treatment or progress are monitored in a BSC phase before starting docetaxel. After the docetaxel treatment phase, patients are monitored in a BSC phase for progression again upon which they could receive active treatment (AAP) if deemed appropriate. However, patients who had already received AAP in the 1st line were not eligible for re-treatment with AAP post-docetaxel. After all treatment options had been explored and disease has progressed, patients then enter a palliative stage (before death).

Figure 1: Model pathway



Note: AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone.
The size of the boxes does not reflect active treatment/BSC duration.
Patients only receive licensed products or those with positive reimbursement appraisal.

The ERG received the patient access scheme (PAS) submitted by the Company, excluding the economic model, on January 19th. This submission considered abiraterone (Zytiga®) for the treatment of metastatic castrate-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.

In addition to introducing a new PAS, the Company made two adjustments to the economic model in an effort to respond to some of the comments that were reported in the cost-

effectiveness section of the Final Appraisal Determination (FAD) document. The adjustments made to the model included:

1. A utility increment of 0.021, as observed in the abiraterone-treated chemotherapy-naïve population, was applied to the post-docetaxel active treatment phase of the model.
2. The docetaxel drug price was reduced by 20%: i.e. the docetaxel drug cost was multiplied by 0.8.

The Company permanently reduced the official list price for abiraterone by 21.5%, resulting in a price of £2,300 per 30 days pack (instead of [redacted] with the original PAS). In addition, as part of the new PAS, the drug acquisition costs of abiraterone are rebated to the NHS after 10 months (30.4 doses) of treatment for each individual patient (maximum costs per patient are thus £23,335). The new PAS applies to patients with metastatic castrate-resistant prostate cancer both pre- and post-chemotherapy as well as for future indications (since the Company stated it is unable to determine whether an order for abiraterone is for pre- or post-chemotherapy). The company estimates the annual implementation and operation costs of the new PAS to be £388 per hospital/Trust/Homecare provider assuming 5 new patients registered per month and 40 prescriptions tracked every month (excluding training costs). These costs were not included in the economic model.

Incorporating the two adjustments mentioned above, the cost-effectiveness results based on the original and new PAS are presented in Tables 1 and 2. Compared with the original PAS, the total costs for the best supportive care arm increased, while the total costs for the abiraterone arm decreased, resulting in a decreased ICER of £28,563 with the new PAS.

Table 1: Base-case results (with original PAS - single confidential discount)[a]

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,560	0.62	0.56	47,254

LYG, life-year gained; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone.
[a]Source: Table 3 of Patient access scheme submission

Table 2: Base-case results with new PAS[a]

	[redacted]	[redacted]	[redacted]	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	16,055	0.62	0.56	28,563

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP,

placebo plus prednisolone.
[a]Source: Table 4 of Patient access scheme submission

In addition to the base-case results, the Company provided multiple scenario analyses (Appendix 1). The ERG did not attempt to replicate all scenario analyses (given the time available), rather a sample of the sensitivity analyses presented by the Company was successfully replicated by the ERG.

ERG critique

Besides the two adjustments described above, all other parameters and assumptions remained unchanged in the model used to calculate the outcomes with the introduction of the new PAS. Hence, most of the critiques listed in the ERG report and mentioned in the "Consideration of the evidence" section of the FAD document still apply. The main critiques on the economic model are summarized in Table 3.

Table 3: Summary of critique from the ERG report and FAD

	Description	Reference	ERG comment on PAS submission
1	The model lacks transparency.	ERG report section 5.2.2 and FAD section 4.10	No changes were indicated in the PAS submission.
2	The model structure lacks face validity as the DES model does not include the possibility of dying during 1st line active and post-docetaxel treatment. This cannot be regarded as a conservative assumption.	ERG report section 5.2.2 and ERG report section 5.2.6	No changes were indicated in the PAS submission.
3	The model outcomes lack face validity as the post-docetaxel survival in the model seems very low compared to survival reported in TA259. Moreover, the Committee noted that the model predicted that patients wait 6 months to start docetaxel after having stopped with abiraterone while clinical specialists described that patients would switch treatment within a week of progression.	ERG report section 5.2.10, FAD sections 4.10 and 4.17	No changes were indicated in the PAS submission.
4	The use of a subset of patients (N=902) instead of the intention-to-treat population (N=1088) introduces bias to both time to treatment discontinuation (TTD) and overall survival (OS) in favour of abiraterone.	ERG report section 5.2.6 and FAD section 4.12	No changes were indicated in the PAS submission.
5	The Company was inconsistent in the steps for estimating the prediction equations for the DES model. This included: • The inconsistent use of stratified prediction equations. • The inconsistent use of candidate covariates. • The inconsistent use of candidate interaction terms. • The inconsistent inclusion of covariates and	ERG report section 5.2.6 and FAD section 4.10	No changes were indicated in the PAS submission.

	interaction terms that were not statistically significant. Moreover, the Committee noted that "the company made a large number of judgements when determining which variables to include in the prediction equations, which covariates to retain in the equations, and which parametric distribution to choose for extrapolation". The ERG would prefer consistent use of non-stratified models, (candidate) covariates and (candidate) interaction terms when estimating the prediction equations.		
6	The log-logistic and log-normal distributions are often criticised for its long tail potentially offering an unrealistic survival benefit. Therefore, this would preferably be explored by the Company, for instance by replacing all log-logistic and log-normal distributions by Weibull distributions in an explorative analysis.	ERG report section 5.3 and FAD section 4.13	No changes were indicated in the PAS submission.
7	The ERG believes that the on-treatment utility increment for abiraterone is questionable and that instead separate utility decrements for all adverse events should be incorporated in the model.	ERG report section 5.2.7	No changes were indicated in the PAS submission.
8	The ERG suggested a utility increment of 0.046 for the post-docetaxel active treatment phase, consistent with TA259 (considering the post-docetaxel phase).	ERG report section 5.2.7	Although the Company did incorporate a utility increment of 0.021 (observed pre-docetaxel) for the post-docetaxel active treatment phase in their updated model for the PAS submission, the ERG would prefer a value that is consistent with previous TA259.
9	Skeletal related events (SREs), which are probably present in the post-docetaxel phase, were not considered in the model (in contrast with TA259). It can be questioned whether not including SREs is a conservative approach.	ERG report section 5.2.6	No changes were indicated in the PAS submission.

In addition to the critique outlined in Table 3 above, the reduced docetaxel drug price of £855.60 per 160mg vial (reduction of 20% to the BNF price) might still overestimate the actual docetaxel price. The electronic market information tool (eMit) database indicated that a docetaxel drug price of £35.35 per 160mg vial could be plausible.

ERG additional analyses

Based on the initial PAS submission (without economic model), it was unclear to the ERG how the PAS was exactly incorporated in the model. However, on the 26th of March, the ERG did receive a revised model that was used by the Company to calculate the cost-effectiveness of 1st line abiraterone plus prednisone versus best supportive care (BSC) in patients with mCRPC using the new PAS. The PAS was incorporated by using a duration of 0.83 years (10/12) to limit the maximum time on abiraterone both in 1st line (abiraterone plus prednisone strategy) and post-docetaxel (in BSC; the comparator strategy) for the cost calculation. This parameter is listed in the cost inputs worksheet (cell E45), and defined in the parameter worksheet (cells F261 (cDrug_Dur_AA) and F263 (cDrug_Dur_2ndAA)) for 1st line and post-docetaxel use of abiraterone, respectively. These parameters are used in the model worksheets to limit the costs of the use of abiraterone, by using the minimum of the actual duration of use and 0.83 years to calculate the costs of abiraterone (model AA worksheet rows 1028 and 1035, and Model Pred worksheet row 1007). The ERG thinks the PAS is implemented correctly. However, the ERG was not able to replicate the exact results of the company by using the model originally submitted by the Company (see Tables 2 and 4; difference of £19 in the incremental costs). This is consistent with the ERG report, where the ERG was also unable to replicate the exact costs that were presented by the Company (see ERG report P. 98).

Table 4: ERG's attempt to replicate the results presented by the Company (Table 2)

Technology	[redacted]	[redacted]	Incremental costs, £	Incremental QALYs	ICER, £/QALY
Company Base case					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	16,074	0.56	28,598

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone.

Consistent with the ERG report, the additional analyses performed by the ERG were based on the model originally submitted by the Company. While examining the new PAS, the ERG noticed that in the 1st line aberaterone, the drug costs are multiplied by 98% compliance, while for post-docetaxel abiraterone a compliance of 100% was assumed. This assumes that the abiraterone costs due to non-compliance in the 1st line are completely recoverable (the maximum costs per patient are £22,869 instead of £23,335). The ERG thinks it is questionable that these costs are fully recoverable. Hence, all additional analyses performed by the ERG (except the analysis presented in Table 4) were conservatively based on abiraterone costs in the 1st line and post-docetaxel without correction for non-compliance.

Tables 5 and 7 provide the overview of additional (sensitivity) analyses presented in the ERG report (ERG report Tables 6.1 and 6.2) while implementing the new PAS. Please note that the adjustments (utility increment of for post-docetaxel active treatment and reduced docetaxel price)

adopted by the Company are also incorporated in these analyses. Moreover, Table 8 provides an additional scenario analyses (based on the ERG preferred base case) wherein the docetaxel drug price was further reduced to £35.35 per 160mg vial (based on the eMit database).

Table 5: Overview of additional analyses undertaken by the ERG using the new PAS

Technology	[redacted]	[redacted]	Incremental costs, £	Incremental QALYs	ICER, £/QALY
Company Base case (calculated by ERG)					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	16,074	0.56	28,598
No recoverable AAP costs[a]					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	16,473	0.56	29,307
Post-docetaxel on treatment utility[a,b]					
BSC (PP)	[redacted]	[redacted]			
AAP	[redacted]	[redacted]	16,473	0.56	29,498
Updated prediction equations[a,c]					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	15,089	0.43	35,191
ERG Base case[d]					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	15,089	0.43	35,486

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

[a] This scenario assumes that the abiraterone non-compliance in the 1st line does not lead to recoverable drug costs.

[b] A utility increment of 0.046 instead of 0.021 was applied in the post-docetaxel phase for patients on active treatment (i.e. receiving abiraterone).

[c] Prediction equations based on the ITT population and including treatment as only covariate were used (based on the "302 mode Parametric Functions Parameters" file provided by the manufacturer in response to clarification question B4a).

[d] Combination of the 'Post-docetaxel on treatment utility' and 'Updated prediction equations' scenarios while assuming that the abiraterone non-compliance in the 1st line does not lead to recoverable drug costs.

Probabilistic sensitivity analyses were performed for the ERG base case (using 2000 iterations) and the probability that AAP is cost-effective compared to BSC for thresholds of £30,000, £40,000 and £50,000 is 5%, 88% and 100% respectively (see Figure 2 and Table 6).

Figure 2: Cost-effectiveness acceptability curve (ERG base case including new PAS)

Table 6: Summary of the PSA (ERG base case including new PAS)

WTP threshold	AAP, %	BSC (PP), %
£30,000/QALY	5	95
£35,000/QALY	44	56
£40,000/QALY	88	12
£45,000/QALY	99	1
£50,000/QALY	100	0

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone; QALY, quality-adjusted life year.

Table 7: Additional sensitivity analyses (based on ERG base case) using the new PAS

Technology	[redacted]	[redacted]	Incremental costs, £	Incremental QALYs	ICER, £/QALY
ERG Base case[a]					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	15,089	0.43	35,486
Remove cabazitaxel negative treatment effect					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	15,153	0.44	34,771
Equal post-docetaxel survival compared to TA 259					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	14,491	0.36	39,722
Weibull instead of Log-logistic					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	14,368	0.26	55,616
Weibull instead of Log-normal					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	14,855	0.43	34,928

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

[a] See Table 5.

Table 8: Scenario analysis (based on ERG base case) using the new PAS and docetaxel price based on eMit dtabase

Technology	[redacted]	[redacted]	Incremental costs, £	Incremental QALYs	ICER, £/QALY
ERG Base case[a]					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	15,089	0.43	35,486
Docetaxel price of £35.35 per 160mg vial					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	15,924	0.43	37,448

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

[a] See Table 5.

CONSEQUENCES OF PATIENT ACCESS SCHEME FOR POST-DOCETAXEL ABIRATERONE

The PAS is not limited to pre-docetaxel abiraterone, but also applies to abiraterone administered post-docetaxel (TA259). This ERG has no detailed knowledge on TA259. However, it can be speculated that despite the total costs decreased with the new PAS (opposed to the original PAS) when abiraterone is administered pre-docetaxel, this new PAS may very well increase these costs if abiraterone is administered post-docetaxel (consequently increasing the ICERs presented in TA259). This speculation is based on the increase in total costs for the best supportive care arm (Tables 1 and 2). To our knowledge, the only plausible explanation for this increase in costs is an increase in total abiraterone costs given post-docetaxel in the best supportive care arm. Moreover, the speculation is supported by Table 68 of the initial submission by the Company, showing that the pre-docetaxel active treatment period ([redacted] months) is substantially longer than the post-docetaxel active treatment period ([redacted] months). Hence, it is likely that pre-docetaxel more patients will be on abiraterone for more than 10 months (after which the costs of abiraterone are rebated to the NHS) accumulating to a higher total discount compared with post-docetaxel. These findings are however speculative and it is recommended to consider the impact of the new PAS for post-docetaxel abiraterone administration in more detail.

APPENDIX 1: OVERVIEW OF SCENARIO ANALYSES PROVIDED BY THE COMPANY

Table: ICERs for Scenario analyses presented by the Company (based on Company PAS submission Table 34)

	With original PAS	With new PAS
Base case	£47,254	£28,563
Scenario 1: Comparing AAP and ENZ administered pre-chemotherapy	NA[a]	NA[a]
Scenario 2: Using urologist scheduled MRU costs	£46,874	£28,184
Scenario 3: Using oncologist and urologist scheduled MRU costs	£47,010	£28,320
Scenario 4: Utilities from the FACT-P to EQ-5D mapping study	£50,640	£30,597
Scenario 5: Utilities from the FACT-P to EQ-5D mapping study applied post-docetaxel	£45,944	£27,772
Scenario 6: Adjusting utilities prior to death	£46,814	£28,298
Scenario 7: Substituting prednisolone use with dexamethasone use in BSC	£47,243	£28,553
Scenario 8: Testing prediction coefficients to generate comparable survival estimates	£47,442	£28,633
Scenario 9: Patients in the BSC (PP) arm do not receive an efficacious active treatment post-docetaxel	£49,096	£33,440
Scenario 10: Enzalutamide included as a post-docetaxel active treatment option	£41,962	£25,488
Scenario 11: No restriction on patients ECOG status when switching to docetaxel after 1st-line treatment	£48,723	£29,033

AAP, abiraterone acetate plus prednisolone; ENZ, enzalutamide; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS: patient access scheme; PP, placebo plus prednisolone; NA, not applicable

[a] For scenario 1 (using ENZ instead of BSC as comparator), it is not possible to calculate an ICER given that this scenario consists of a cost-minimisation analysis, assuming equal effectiveness for AAP and ENZ.

Table: Using the ERG preferred base case and calibrating the time between end 1st line treatment and docetaxel start to 1-2 weeks[a]

Technology	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER, £/QALY
Using the ERG preferred base case					
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	13,986	0.46	30,581

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone.

[a]The time between end 1st line treatment and docetaxel start was calibrated by reducing the intercept of the following prediction equation by 90%: Time from AAP/BSC (PP) treatment discontinuation to docetaxel start. The resulting time between end 1st line treatment and docetaxel start was 1.2 weeks for both AAP and BSC (PP) respectively.

Abiraterone acetate for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy [ID503]

Following the discussion of abiraterone acetate for metastatic hormone relapsed prostate cancer not previously treated with chemotherapy on15th October 2015 the Appraisal Committee has asked NICE to request the following data and analyses from Janssen.

Please can you send this data to us by **5pm Friday 30th October** and can you upload it to the following NICE Docs link:

1) Priority: Using the final data cut for COU-AA-302, please provide Kaplan-Meier curves for time to treatment discontinuation of initial treatment (with either abiraterone or placebo) for:

- ITT population
- Analysable subset with covariates
- On both graphs, please also plot the modelled time to treatment discontinuation curves with a log-logistic extrapolation and a Weibull extrapolation for comparison.

If any data is available from CDF prescribing to show the length of time people take abiraterone in clinical practice, please supplement the above with those data.

Rationale for request 1:
The Committee noted that a key driver of the model was the choice of parametric distribution for modelling the duration of initial treatment. A Weibull distribution gave a higher ICER than the log-logistic distribution used in the company's base case. The Committee heard from the company that the final analysis of the COU-AA-302 trial supported their choice of a log-logistic distribution. Accordingly, the Committee has asked to see these data.

2) Using the final data cut for COU-AA-302, please provide overall survival Kaplan-Meier curves for:

- ITT population
- Analysable subset with covariates
- On both graphs, please also plot the modelled survival curve (using data from the third interim analysis and the analysable subset with covariates) for comparison

At each time point, please provide:

- the number of trial patients at risk
- the number who died,

- the number who were censored.

Please also specify the number of people who crossed over from placebo to receive abiraterone pre-docetaxel and the number who received subsequent treatments (please state what these treatments were). Please split into treatments available on the NHS and those not available that is, cabazitaxel, sipuleucel-T and abiraterone and enzalutamide (when abiraterone or enzalutamide have been received previously).

Rationale for request 2:
During the meeting on 15 October 2015, the Committee heard from the company that the final overall survival data validated the extrapolation curves in the company's model. Although the Committee had been presented with the final data for the ITT population, it had not seen Kaplan-Meier curves for the subgroup used in the modelling, nor could it compare the curves from the trial with the curves from the model.

3) Please provide further information about the method used to adjust for cabazitaxel given after docetaxel in the model and why it was chosen over other methods. Please also explain why this adjustment was only made for cabazitaxel and no other subsequent treatments. Please provide a scenario analysis in which a different adjustment method is used.

Rationale for request 3:
The Committee was informed that this aspect of the modelling is described on page 99 of the company submission. However, the Committee found this part of the submission unclear and has requested further information about the methods used and the rationale for their use.

4) In a scenario analysis, the ERG shortened the period between stopping the first treatment and starting docetaxel to 1.2 weeks. Please provide the results of this scenario applied to the company's base case.

Rationale for request 4:
The Committee noted that this scenario reduced the ERG's ICER. The Committee has not seen how this affected the ICER when applied using the Company base case assumptions

5) Please supply data/analyses to support use of the COU-AA-302 trial to model survival after docetaxel (used in company's base case) rather than COU-AA-301 trial (used in ERG's scenario analyses)

Rationale for request 5:

The company stated in the meeting that the population from COU-AA-301 differed from COU-AA-302 because people had received docetaxel earlier in COU-AA-301 and were therefore fitter at the point they received treatments after docetaxel. The Committee would like to see data supporting the company's comments. Please provide the patient characteristics for both trials at the point patients stopped taking docetaxel. Please also provide the sample size at this time point, and the subsequent number of deaths and patients who were censored. This will help the Committee to assess the validity of the modelling of survival after docetaxel in the current appraisal.

Please could you provide the requested data by 5pm Friday 30th October to enable the Appraisal Committee to discuss these data at its November committee meeting.

Single Technology Appraisal (STA)

Abiraterone acetate for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy [ID503]

1) Priority: Using the final data cut for COU-AA-302, please provide Kaplan-Meier curves for time to treatment discontinuation of initial treatment (with either abiraterone or placebo) for:

- ITT population
- Analysable subset with covariates
- On both graphs, please also plot the modelled time to treatment discontinuation curves with a log-logistic extrapolation and a Weibull extrapolation for comparison.

If any data is available from CDF prescribing to show the length of time people take abiraterone in clinical practice, please supplement the above with those data.

Figure 1 (ITT population) and Figure 2 (analysable population) presented below compare the observed Kaplan-Meier (KM) curves for time to treatment discontinuation from the COU-AA-302 trial (at time of the final analysis) to the extrapolated time to treatment discontinuation curves from the base case model (based on the 3rd interim analysis of COU-AA-302) using either the log-logistic [best-fit] extrapolation or the Weibull extrapolation of first line AAP and PP.

From inspection of Figures 1 and 2, the extrapolated time to treatment discontinuation curves from the base case model fit the Kaplan-Meier curves for AAP and PP arm of COU-AA-302 at time of the final analysis, for both the ITT and the analysable populations respectively:

- The log-logistic modelled curve of AAP (yellow curve) remains a better fit versus the Weibull modelled curve (green curve) when compared with the observed KM curve (orange curve).

- Predictions for PP with log-logistic (purple curve) or Weibull (grey curve) are not as strong a match to the observed KM curve (blue curve). Patients who were treated with PP remain on treatment longer with either extrapolation approach than the observed data suggests. Consequently, the relative treatment benefit of AAP is underestimated by the predictive equations based on the final data cut for COU-AA-302.

Janssen believes that the choice of the log-logistic curve originally justified by the use of AIC, BIC and visual inspection, and the standard methodology used to determine parametric fit in modelling (as recommended by the Decision Support Unit, DSU) remains justifiable based on the comparison of the extrapolated model curves with the final analysis KM curves.

Figure 1. . Comparison of KM versus Modelled Time to Treatment Discontinuation, ITT Population

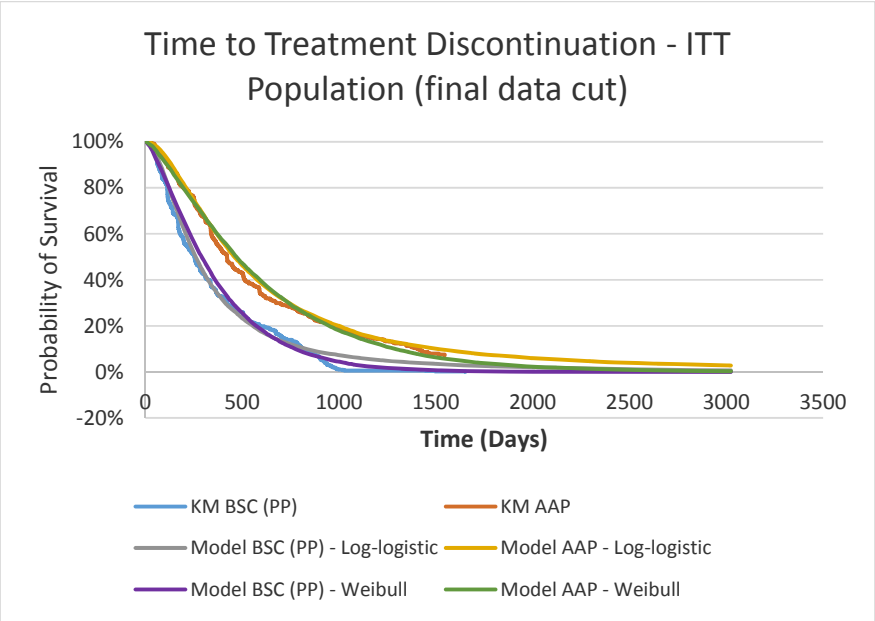
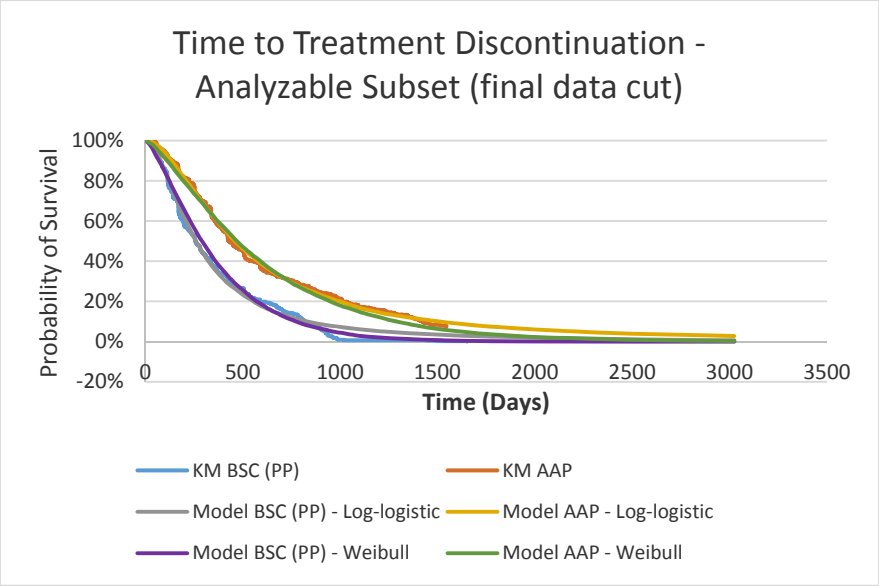


Figure 2. Comparison of KM versus Modelled Time to Treatment Discontinuation, Analysable Subset



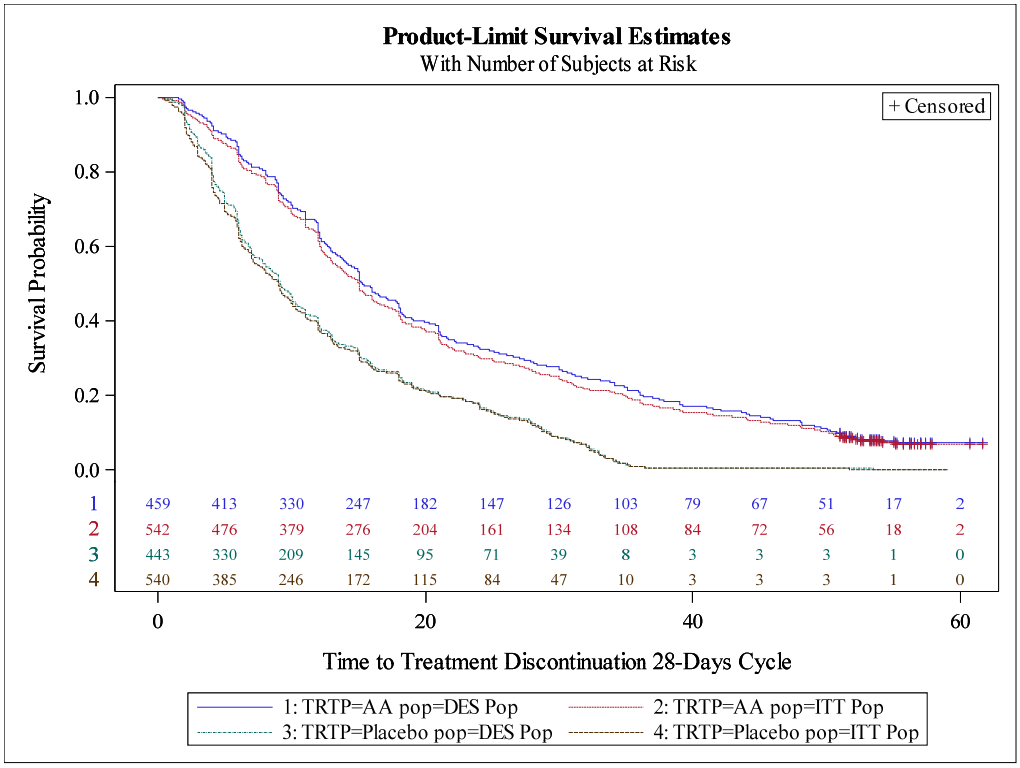
Note that KM curves are based on the final data cut; modelled curves with log-logistic [best-fit] extrapolation and Weibull extrapolation are based on the 55% interim data cut.

It should also be noted that the KM curves for time to treatment discontinuation are very similar between the analysable and the ITT populations (See Figure 1 and Figure 2), as previously presented in our response to the ERG's clarification questions and the response to the ACD. The same can be said when comparing the log-logistic and Weibull curves for both populations.

Figure 3 shows the time to first line treatment discontinuation in 28-day cycles for the ITT and analysable populations, with patients at risk displayed in the graph (every 5 cycles, for readability), and demonstrates that the KM curves and extrapolated curves of time to treatment discontinuation are very similar between the ITT and the analysable population.

We therefore maintain that using the analysable sub-population to generate the predictive equations does not overestimate the survival benefit of AA over PP, and that the analysable sub-population remains the best dataset to use within the economic model.

Figure 3. Kaplan Meier Curves of Time to Treatment Discontinuation for the ITT and Analysable Subset Populations



Note: the same data sets were used in Figures 1, 2 and 3. The "DES Pop" references the analysable subset.

Lastly, Janssen has reviewed the CDF dataset for abiraterone, as requested by NICE. Unfortunately, the CDF reporting of drug usage (i.e. total number of notifications received by drug for each indication) does not provide any insight as to the duration of treatment, as it is only possible to determine the number of notifications per drug, not duration of treatment.

2) Using the final data cut for COU-AA-302, please provide overall survival Kaplan-Meier curves for:

- ITT population
- Analysable subset with covariates
- On both graphs, please also plot the modelled survival curve (using data from the third interim analysis and the analysable subset with covariates) for comparison

At each time point, please provide:

- the number of trial patients at risk
- the number who died,
- the number who were censored.

Please also specify the number of people who crossed over from placebo to receive abiraterone pre-docetaxel and the number who received subsequent treatments (please state what these treatments were). Please split into treatments available on the NHS and those not available that is, cabazitaxel, sipuleucel-T and abiraterone and enzalutamide (when abiraterone or enzalutamide have been received previously).

At the final analysis cut-off, 741 death events had been observed (354 [65%] in the AAP group and 387 [71%] in the PP group). The final analysis overall survival (OS) results met the stringent pre-specified statistical significance level of 0.0384, although the point estimate for the HR (0.81) was marginally higher than the treatment effect size of 0.80 hypothesised to represent a clinically meaningful result. However, the OS outcome at final analysis was obtained in the context of significant crossover and subsequent treatment with novel therapies in the PP arm (See Table 1); with 238 (44%) PP patients having received AAP during follow-up including 93 (17%) who crossed over to AAP prior to docetaxel. Moreover, patients also received other therapies that have a proven positive impact on OS, including docetaxel (57% and 61% of AAP and PP arms respectively), cabazitaxel (18% and 19%) and enzalutamide (10% and 16%).

Table 1. Selected subsequent therapy for prostate cancer – ITT population (COU-AA-302, final analysis)

	Interim analysis 3		Final analysis	
	AAP (N=546)	PP (N=542)	AAP (N=546)	PP (N=542)
Number of subjects with selected subsequent therapy for prostate cancer	274 (50.2)	348 (64.2)	365 (66.8%)	435 (80.3%)
Docetaxel	239 (43.8)	304 (56.1)	311 (57.0%)	331 (61.1%)
Cabazitaxel	60 (11.0)	70 (12.9)	100 (18.3%)	105 (19.4%)
Ketoconazole	39 (7.1)	63 (11.6)	87 (15.9%)	54 (10.0%)
AAP	38 (7.0)	78 (14.4)	69 (12.6%)	238 (43.9%)
Sipuleucel-T	33 (6.0)	28 (5.2)	45 (8.2%)	32 (5.9%)
Radium-223			20 (3.7%)	7 (1.3%)
Enzalutamide			87 (15.9%)	54 (10.0%)

References: Rathkopf et al. Eur Urol. 2014 Nov;66(5):815-25 (IA3), Ryan et al. Lancet oncology, 2015, 16(2):152-60 (final analysis).

The final analysis OS results adjusted to subsequent AAP therapy also met statistical significance, but with a point estimate for the **HR of 0.74.** This represents a much larger treatment effect size than the 0.80 hypothesised to represent a clinically meaningful result, and a larger treatment effect than the 3rd interim analysis HR (0.79) upon which the economic model is based. On this basis, Janssen believes that using the 3rd interim analysis data in the economic model can be considered conservative, as it underestimates the overall OS benefit of AAP over PP.

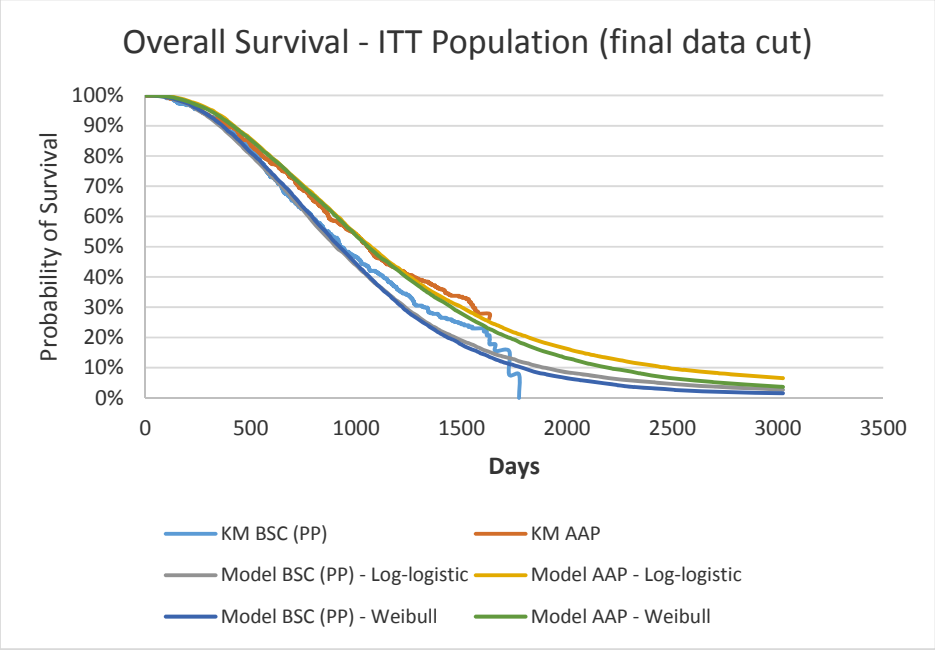
Figure 4 (ITT population) and Figure 5 (analysable subset) below compare the OS Kaplan-Meier curves observed in the COU-AA-302 trial to the modelled OS curves for AAP and PP (using log-logistic and Weibull survival extrapolated curves).

From inspection of the graphs, the model prediction of OS using log-logistic (yellow line) for AAP remains a better fit versus using the Weibull model (green line), although the log-logistic curve slightly under-estimates the OS benefit for AAP. Review of the graphs also shows that the model prediction of OS using log-logistic (grey line) for the PP arm slightly under-estimated the observed OS Kaplan-Meier curve for the PP arm at the final analysis data cut. The underestimate of OS for the PP arm based on the 3rd interim data cut compared to final data cut is likely due to the high number of PP patients who had received subsequent therapy with AAP between the 3rd interim analysis and the final analysis.

As a result of the above, Janssen believe that the choice of the log-logistic curves to extrapolate the OS of AAP and PP, originally made based on the AIC, BIC, visual inspection, and the standard methodology used to determine parametric fit in modelling (as recommended by the DSU), remains justified.

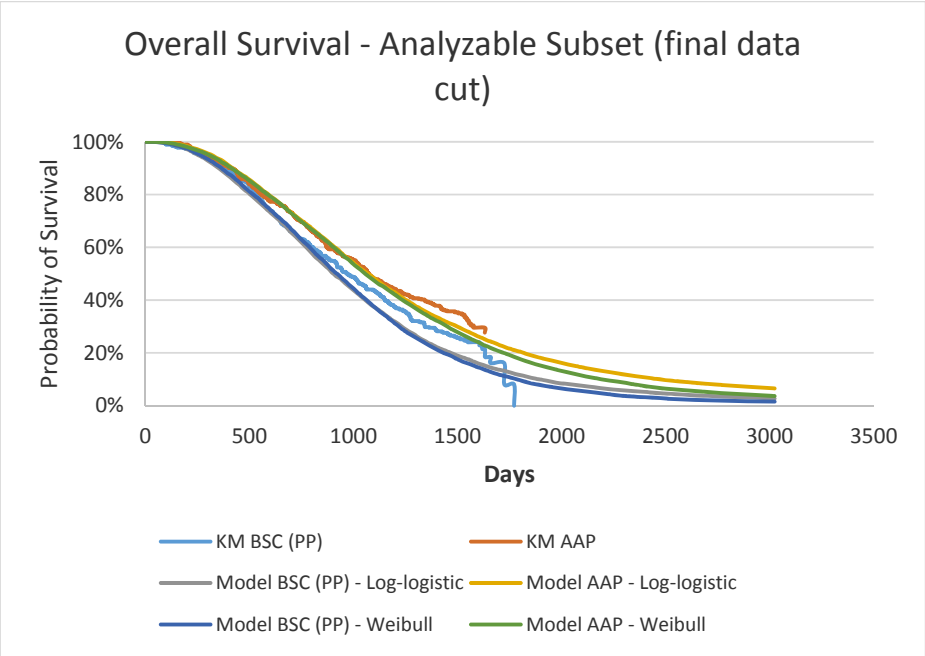
As for the time to treatment discontinuation, the population chosen to determine the predictive equations does not impact the OS curves, as presented in Figure 6.

Figure 4. Comparison of KM versus Modelled OS, ITT Population



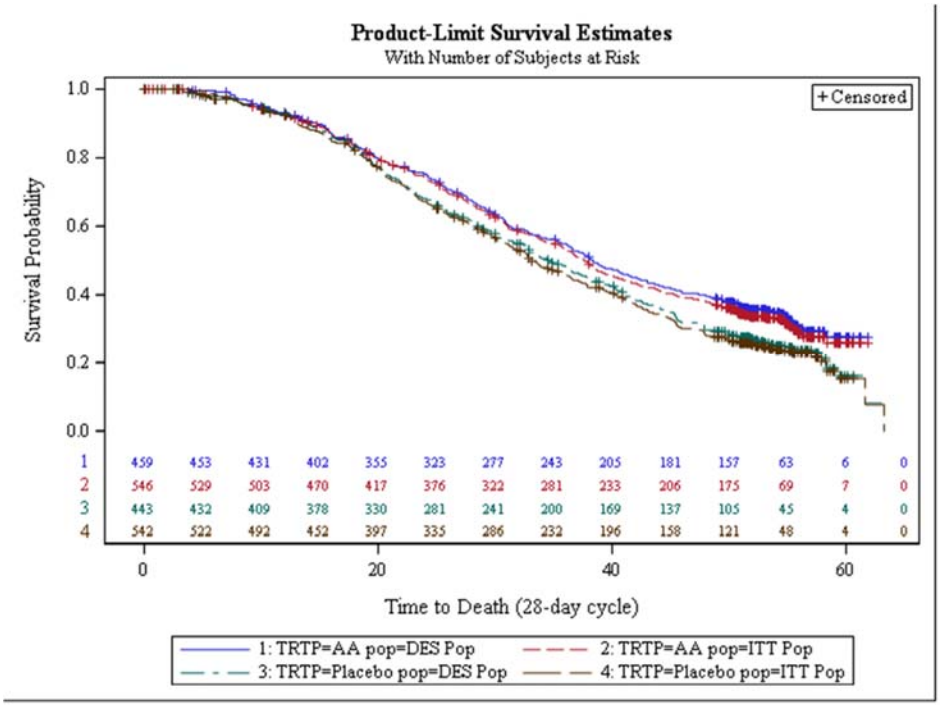
Note that KM curves are based on the final data cut; modelled curves with log-logistic [best-fit] extrapolation and Weibull extrapolation are based on the 55% interim data cut.

Figure 5. Comparison of KM versus Modelled OS, Analysable Subset



Note that KM curves are based on the final data cut; modelled curves with log-logistic [best-fit] extrapolation and Weibull extrapolation are based on the 55% interim data cut.

Figure 6. Kaplan Meier Curves of Overall Survival for the ITT and Analysable Subset Populations



Note: the same data sets were used in Figures 1, 2 and 3. The "DES Pop" references the analysable subset.

3) Please provide further information about the method used to adjust for cabazitaxel given after docetaxel in the model and why it was chosen over other methods. Please also explain why this adjustment was only made for cabazitaxel and no other subsequent treatments. Please provide a scenario analysis in which a different adjustment method is used.

In the COU-AA-302 trial, a proportion of patients in both arms were treated with cabazitaxel (post-docetaxel), and a proportion of AAP patients also received post-chemotherapy AAP/enzalutamide after docetaxel failure. However, cabazitaxel use post-docetaxel is not recommended by NICE (TA255) and use of enzalutamide / AAP post-chemotherapy in patients who already received AAP post-ADT is not recommended by NICE or NHS England. Therefore, we adjusted our base case analysis for subsequent use of cabazitaxel, enzalutamide and AAP in the AAP arm. No adjustments were made to the PP predictive equations in order to remain conservative, and apply as little deviation from the clinical trial results as possible.

In order to adjust for novel therapy (including cabazitaxel) use post-docetaxel in the COU-AA-302 study, a 'negative' treatment effect was applied to the AAP arm for 2 of the predictive equations: time to post-docetaxel active treatment discontinuation and time from end of third treatment to death. We had to estimate the benefit expected of an active post-docetaxel treatment and data from the AAP arm of COU-AA-301 trial was used as a proxy to determine the effect of active post-docetaxel treatment for COU-AA-302 patients who received such active therapy post-docetaxel.

The 2 predictive equations were estimated as a function of prior treatments and current patient characteristics, to which we added a new term (i.e. adjustment to the intercept based on AAP treatment effect in COU-AA-301) accounting for the clinical benefits of receiving active treatment following docetaxel in the COU-AA-302 trial, Table 2:

- The intercept of the AAP arm for 'time to post-docetaxel active treatment discontinuation' was reduced by –0.5174 (AAP coefficient) in order to adjust for the additional time AAP patients in the trial who received cabazitaxel (post-docetaxel) might have gained.
- The intercept of the AAP arm for 'time from end of third treatment to death' was increased by 0.1493 (AAP coefficient) to adjust for the longer time AAP patients might have at the end of docetaxel treatment until death if we assume they did not receive cabazitaxel.

Table 2. Adjusting the survival of patients treated with cabazitaxel after docetaxel failure

	Time from post-docetaxel start to end	**Time from end of third-line treatment to death**
Intercept	5.2241	7.1534
Calibration term for clinical benefits of post-docetaxel cabazitaxel use	–0.5174	0.1493
Adjusted intercept	**4.2981**	**7.3027**

Note: this table corresponds to Table 35 in the original submission to NICE in January 2014.

It should be noted that use of cabazitaxel post-docetaxel, although not being recommended by NICE (TA255), has been funded through the national Cancer Drug Fund, and is being re-appraised by NICE

[anticipated guidance publication date: May 2016]. On this basis, it could be argued that adjusting for cabazitaxel use post-docetaxel should not be considered.

Table 3 below shows an ICER of £27,738 if no adjustment for subsequent active therapy is made, which is lower than the base case ICER of £28,563 (with adjustment). The current base case analysis adjusting for subsequent active therapy use is therefore conservative.

Table 3. Results Without Adjustment to Post-Docetaxel Active Treatment Effect

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	16,255	0.66	0.59	27,738

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

4) In a scenario analysis, the ERG shortened the period between stopping the first treatment and starting docetaxel to 1.2 weeks. Please provide the results of this scenario applied to the company's base case.

Table 4 below displays the ICER when time from end of first line treatment to start of docetaxel is fixed at 1.2 weeks. Under this scenario, a lower ICER of £26,640 is estimated compared to the base case ICER (£28,563).

The 1.2 week pre-docetaxel period is much lower than the time period estimated by the prediction equations for modelled patients in the AAP arm (21 weeks on average) and BSC (PP) arm (22 weeks on average) of COU-AA-302, giving lower LYs and QALYs in the scenario analysis compared to the base case analysis. While the reduced pre-docetaxel time period lowers the pre-docetaxel phase costs, on- and post-docetaxel phase costs (particularly drug and unplanned MRU costs) increase by a greater magnitude. The reduction in the ICER is due to total costs in both the AAP and BSC (PP) arms increasing in the scenario analysis versus the base case, while QALYs in both arms decrease by a lower magnitude.

Table 4. Results When Time from 1st Line Treatment End to Docetaxel Start is 1.2 weeks

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	14,735	0.62	0.55	26,640

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

5) Please supply data/analyses to support use of the COU-AA-302 trial to model survival after docetaxel (used in company's base case) rather than COU-AA-301 trial (used in ERG's scenario analyses)

The patient population from the COU-AA-301 trial (TA259) is fundamentally different to the population in the COU-AA-302 trial at start of post-docetaxel treatment. Importantly, the treatment histories at that point, which are known to impact outcomes, are also very different between the two populations. In the COU-302 trial, a significant proportion of patients have already received effective active treatment with AAP and docetaxel, while in the COU-AA-301 trial most patients (70%) had received only one line of treatment with chemotherapy. Earlier treatments also have an important impact on the time from post-docetaxel treatment to death.

While the COU-AA-302 trial does not track all of the potentially evolving patient characteristics from baseline to allow a meaningful comparison between the two trials at the start of post-docetaxel treatment, the graph below shows the differences in OS between the two trials from the start of post-docetaxel treatment (Figure 7). The review of the graph clearly establishes that the COU-AA-301 and COU-AA-302 cohorts are not the same in terms of their Kaplan-Meier overall survival curves. Patients in the COU-AA-301 trial have longer survival times, and using these data in the model would provide an overestimation of survival during this phase for patients who had received earlier active therapy. Given patients are likely to experience less benefit with each subsequent therapy, the overall survival differences presented in Figure 7 are therefore clinically plausible.

Figure 7. OS from start of post-docetaxel active treatment in the COU-AA-302 trial versus COU-AA-301 trial

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

ERG response to:
the Company's response to NICE request for additional information on 22 October 2015

Abiraterone acetate for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy

In the Company's response to question one, the Kaplan-Meier curves (using the final data cut data) for time to treatment discontinuation (TTD) were provided. These curves were compared with the TTD using the 55% interim data cut data, as used in the original submission as an input in the economic model (Figures 1 and 2 presented in the Company's response). Visual inspection of these Figures is difficult due to the thick lines, the crude scales, and the lack of summary data (see for instance Table 67 of the original Company submission). Based on this hampered visual inspection of Figures 1 and 2 presented in the Company's response, the Log-logistic curve seems to have the best fit to the Kaplan-Meier curves for abiraterone. Perhaps unnecessary to add, but this does not verify the extrapolation with the Log-logistic curve beyond the trial period. Also, the statement by the Company that "the relative treatment benefit of AAP is underestimated by the predictive equations based on the final data cut for COU-AA-302" is speculative and should be validated. Moreover, it seems that the final data cut data is similar to the 55% interim data cut data for TTD. Therefore, the conclusions and reflections of the ERG as discussed in the ERG report and the addendum by the ERG remain unchanged. This also holds true for the comparison between the ITT population and the analysable subset.

In the Company's response to question two, the Kaplan-Meier curves (using the final data cut data) for overall survival (OS) were provided (see Figures 4 and 5 presented in the Company's response). These were compared with OS curves retrieved from the economic model (using the 55% interim data cut data, fitting different distributions for TTD). Again visual inspection of these Figures is difficult due to the thick lines, the crude scales, and the lack of summary data. Based on this hampered visual inspection of Figures 4 and 5 presented in the Company's response, the Weibull and Log-logistic curves seems to result in similar OS in the short term while in the long-term the Kaplan-Meier curves deviates from the predicted OS in the model (for both the Weibull and Log-logistic curves). We would also like to point out that the ERG did not replace- the Log-logistic curves with the Weibull curves in the ERG base case (only in sensitivity analyses). Therefore, the conclusions and reflections of the ERG as discussed in the ERG report and the addendum by the ERG remain unchanged. Moreover, the statement by the Company that "using the 3rd interim analysis data in the economic model can be considered conservative" is speculative and should be validated (e.g. by informing the economic model using the final data cut data). To enhance the comparison of the observed OS using the final data cut data and the OS in the economic model, the OS retrieved from the Kaplan-Meier curves (Figures 4 and 5 presented in the Company's response) and the economic model (ERG base case) are presented in Table 1.

Table 1: OS comparison of observed OS (KM curves; final data cut) and modelled OS (ERG base case)

	Economic model (ERG base case)		Observed (ITT population)		Observed (analysable subset)	
	Abiraterone	BSC	Abiraterone	BSC	Abiraterone	BSC
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS, overall survival; KM, Kaplan-Meier; BSC, best supportive care.

In the Company's response to question three, further information regarding the correction for cabazitaxel was provided. Although, it is still not entirely clear how the prediction equations (presented in Table 2 in the Company's response) were estimated (e.g. which parametric function, which covariates), the correction for cabazitaxel seems reasonable given the data available and given that it is a conservative approach compared to not correcting for cabazitaxel. Nevertheless, the N used to estimate the prediction equations is relatively low, and the assumption that the "calibration term for clinical benefits of post-

docetaxel cabazitaxel use" reflects the treatment effect of cabazitaxel might be biased by confounding by indication. Therefore, the magnitude of the impact of the adjustment on the ICER remains uncertain. The direction of change regarding the ICER with and without the adjustment for cabazitaxel is however as expected and in line with the ERG report and the addendum by the ERG. It should be noted that the Company did not respond to the question why this adjustment was only made for cabazitaxel.

In the Company's response to question four, the results of an additional analysis was provided, changing the period between stopping the first treatment and starting docetaxel to 1.2 weeks. The direction of change regarding the ICER presented in the analysis (compared with the base case) is as expected and in line with the additional analysis provided by the ERG (October 2015; requested during the pre-meeting briefing).

Finally, in response to question 5, OS from COU-AA-301 and COU-AA-302 are compared (Figure 7 presented in the Company's response). This observational comparison was in line with the expectations of the ERG. Moreover, the Company's argument that the populations from COU-AA-301 and COU-AA-302 differ due to the treatment histories might only be partly true. It is argued that the majority of patients in the COU-AA-301 trial had received only one line of treatment with chemotherapy, this might also be applicable to the best supportive care group in COU-AA-302. Hence, the best supportive care group in COU-AA-302 and the experimental group in COU-AA-301 might be comparable regarding treatment history. However, the ERG does not have access to data to validate this statement. We would also like to point out that the ERG has used the COU-AA-302 data in the ERG base case (the COU-AA-301 data was only used in sensitivity analyses).

		Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
ERG base case						
+reduce time to switch to docetaxel to 1.2 weeks						
+eMit price for docetaxel	BSC	[redacted]	[redacted]			
+set post-docetaxel survival equal to TA259	Abiraterone			£14,057	0.379	£37,137
ERG base case						
+eMit price for docetaxel	BSC	[redacted]	[redacted]			
+set post-docetaxel survival equal to TA259	Abiraterone			£15,326	0.365	£42,009

Note from NICE technical team: these analyses were requested by the Chair during the pre-meeting teleconference. The model uses the new complex PAS in both arms.

		Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
ERG base case	BSC					
	Abiraterone			£16,098	0.425	£37,859
ERG base case + Weibull instead of log-logistic	BSC					
	Abiraterone			£15,389	0.258	£59,567
ERG base case + set post-docetaxel survival equal to TA259	BSC					
	Abiraterone			£15,500	0.365	£42,488

Note from NICE technical team: these analyses applied the old simple discount PAS to the comparator arm and the new complex PAS to the intervention arm.

Email from Janssen to NICE clarifying the additional information

Sent – 10 November 2015

Dear Jeremy

Apologies for the lateness of this email. Whilst I appreciate you have requested that we raise any factual errors tomorrow during the Committee meeting, I am very concerned about the ERG's response to the requested analyses (attached). It appears that there is a simple misunderstanding, and I would just like to clarify it ahead of tomorrow's meeting, as I am concerned that the meeting could be de-railed by something that can very easily be addressed via email. Quite simply (and I apologise that we didn't make this more clear in our response), the KM curves that we sent (that NICE requested) in a Word doc (also attached) were sent as interactive graphs, and could have very easily been enlarged. Had the ERG done this, they would have been able to quite clearly see the extrapolations, and upon visual inspection, could see which extrapolation better fit the data (ie log-logistic, as opposed to Weibull). I have attached enlarged versions of the curves, as well as the background data.

Given that this topic was scoped in by NICE in 2011 and we have all been working on it for nearly 5 years now, I would just request at this eleventh hour, particularly since the ERG response was only sent to us late on Friday night, that the existence of these enlarged curves and files with the data (to allow the ERG to validate) be made known to the Committee tomorrow.

Kindest regards

[redacted]

[redacted]

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