NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

The following documents were seen by the Appraisal Committee at their meeting on 10 July 2018:

Following the Committee meeting on 10 July 2018 the company asked to submit additional evidence. To help the company, NICE shared a summary of the Committee's considerations contained within a draft ACD with the company. The additional evidence submitted by the company and the Evidence Review Group's critique were then seen by the Committee at their meeting on 15 January 2020.

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

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ID945 abiraterone for treating newly diagnosed high-risk hormone-sensitive prostate cancer

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Janssen	**Clarifying the decision problem and place of abiraterone in the treatment pathway** Janssen wish to clarify that the use of abiraterone as first-line treatment for adults newly diagnosed with high-risk metastatic hormone sensitive prostate cancer (mHSPC) is not intended to replace use of abiraterone or enzalutamide for the treatment of adults with metastatic castrate resistant prostate cancer (mCRPC) post-ADT as previously recommended by NICE (TA387 and TA377). Janssen believe it is essential that the decision problem be further clarified because debate regarding whether men receive 'abiraterone now' (when mHSPC) or 'abiraterone later' (when mCRPC) is only relevant to the small cohort of this indication. The treatment pathway for the majority of men with metastatic prostate cancer in the UK remains unchanged. Prostate cancer can be diagnosed at localised or metastatic stage. Since most new cases of prostate cancer (82%) in the UK are for men with localised disease, the treatment pathway of that cohort will not change; those who eventually progress to mCRPC would still be entitled to abiraterone or enzalutamide as per NICE guidance (TA327 and TA377). As such, for the majority, 'abiraterone later' is always the answer. Men newly diagnosed with high-risk mHSPC and relevant to this decision problem represent a small patient cohort accounting for approximately 8% of new prostate cancer cases (i.e. 3,500) each year in England. For these men, who have received the most severe type of diagnosis at first presentation of prostate cancer, 'abiraterone now or later' is a valid question. As highlighted by the Cancer Drugs Fund Lead (ACD Section 3.2, page 5), half of these men are unlikely to be fit for chemotherapy and thus 'abiraterone now' should always be the answer. Consequently, when discussing the metastatic prostate cancer pathway, it is essential to recognise that this indication would not displace abiraterone or enzalutamide in mCRPC (TA327 and TA377) for most of the men with metastatic prostate cancer in the UK. This indication only moves the use of abiraterone earlier to benefit the small cohort who would	Thank you for your comments. The committee understood that the population under appraisal was newly diagnosed high-risk hormone-sensitive prostate cancer, in line with the marketing authorisation.

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			be eligible when first diagnosed with high-risk metastatic disease. Please see pathway visualisation in Table 1 for further clarification. *[Figure provided but not reproduced here]*	
2	Consultee	Janssen	Addressing the comparison of AAP + ADT vs. ADT alone Janssen are concerned there has been very little consideration of the comparison of AAP + ADT vs. ADT alone in the Committee's preliminary decision, and we believe this is unreasonable in light of the evidence submitted to NICE. Both ADT alone and docetaxel + ADT are relevant comparators in this setting, yet significantly greater emphasis has been placed on the comparison with docetaxel + ADT, conveying an unbalanced assessment of the evidence. The ACD recognises: A patient expert explained that there is an unmet need for an alternative treatment option for people who cannot have docetaxel plus ADT. [Section 3.2] This statement signposts the high unmet need for an alternative life-extending therapy for men who cannot receive chemotherapy in the NHS. For these men, ADT alone is currently the only treatment option. Without AAP + ADT in mHSPC, men who cannot receive chemotherapy will remain sub-optimally treated, forcing them to wait for their cancer to progress before they can access a novel hormonal agent. Those men who do not wish to undertake chemotherapy will continue to face the difficult decision of whether to pursue docetaxel treatment regardless, adding to the psychological burden of this disease and its diagnosis. The proportion of men with newly diagnosed high-risk mHSPC who cannot receive chemotherapy is substantial, as highlighted by the ACD: The Cancer Drugs Fund's clinical lead noted that around 50% of people presenting with hormone-sensitive metastatic prostate cancer are not fit enough for docetaxel and have ADT alone. [Section 3.2] Real-world data on the usage of docetaxel + ADT indicates that, irrespective of its clinical benefit, only 40% of men actually receive chemotherapy for newly diagnosed mHSPC, indicating 60% remain on ADT alone2. Janssen also surveyed the broader clinical community to ascertain a balanced opinion on prescribing patterns in the NHS. Janssen conducted a survey with 27 clinical experts across the UK to better understand the current	Thank you for your comments. The committee concluded that abiraterone extends progression-free survival and overall survival compared with ADT alone. See section 3.6 of the FAD. The committee considered the proposal to consider abiraterone for people who can not have, or choose not to have docetaxel. The committee concluded that there are no clear-cut clinical criteria to define who could have abiraterone in combination, but not docetaxel in combination. It also agreed that there is no supporting evidence of the safety or effectiveness of abiraterone in combination for people who cannot have docetaxel in combination. The committee recognised

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			split between docetaxel + ADT and ADT alone in men newly diagnosed with high-risk mHSPC. Whilst the UK Clinical Survey (Appendix A) showed varied use of docetaxel + ADT across the UK, the most common response (n=12) was that 50% receive docetaxel + ADT and 50% remain on ADT alone. An average of 52.5% of patients receive docetaxel + ADT when accounting for all 27 responses. It must be recognised that estimates provided by respondents in this survey are likely to be based on the total number of patients referred to oncology, as all respondents were practising oncologists. Some patients, who are clearly not fit for chemotherapy, may not be referred to an oncologist for further treatment, and will instead continue to be managed by a urologist with ADT alone. This may result in an under-estimation of the true proportion of newly diagnosed mHSPC patients who do not receive docetaxel + ADT for their disease. Whilst most men initially respond to ADT when given alone in mHSPC, the vast majority develop progressive disease within one to two years;3 progression to mCRPC is associated with further deterioration in health-related quality of life (HRQL), increased healthcare costs and reduced survival. Compared to ADT alone, AAP + ADT has shown unequivocal benefits in significantly delaying disease progression, improving (and sustaining) HRQL and extending survival, in men with newly diagnosed high-risk mHSPC. The ACD recognises this, stating: The clinical trial results show that, compared with ADT alone, AAP + ADT increases the time until disease progression and overall length of time people live. [Section 1.2] And, Abiraterone plus ADT statistically significantly improved both progression-free and overall survival compared with ADT alone in LATITUDE and in patients with metastatic disease in STAMPEDE, and the size of improvement was similar in the 2 trials. [Section 3.7] Without question, the Committee have concluded that AAP + ADT improved both progression-free and overall survival compared with ADT alone, however, there is very little consideration given to the cost-effectiveness of AAP + ADT in this setting. Results presented below show AAP + ADT is highly cost-effective vs. ADT alone yet this preliminary decision means that men who cannot receive chemotherapy in England will remain sub-optimally treated in the NHS.	the importance of patient choice when all the treatment options are clinically and cost-effective, but considered that it would be inappropriate to consider abiraterone only for those who currently choose to have ADT alone, and not those who currently chose to have docetaxel. See section 3.2 of the FAD. In updated analyses matching the committee's preferences and accounting for the confidential commercial arrangements of subsequent therapies, the resultant cost-effectiveness estimates compared with both ADT alone and docetaxel in combination are higher than £30,000 per QALY gained. The committee concluded that abiraterone did not represent a cost-effective use of NHS resources. See section 3.14 of the FAD.
3	Consultee	Janssen	**Addressing the economic modelling of AAP + ADT vs. ADT alone** Janssen acknowledge comments in the ERG Report and the ACD regarding the clinical data informing the comparison of AAP + ADT vs. ADT alone, as well as preference for	Thank you for your comments.

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			certain model assumptions which were not incorporated into the original base case analysis. In this section, we wish to address: *1.* Appropriateness of the clinical evidence base *2.* Cost-effectiveness of AAP + ADT vs. ADT alone **Appropriateness of the clinical evidence base** LATITUDE is the pivotal Phase III randomised controlled trial (RCT) which was conducted in the license-indicated population to specifically investigate AAP + ADT vs. ADT alone in the newly diagnosed, high-risk mHSPC patient population. As such, LATITUDE should be used as the primary source of clinical data for informing the cost-effectiveness of AAP + ADT vs. ADT alone. As highlighted in the submission [Section B.2.6], Janssen recognises that some subsequent therapies in LATITUDE would not have been permitted in the UK as only one novel hormonal agent in the metastatic pathway is currently funded by NHS England. The non-permitted sequences are presented in Table 2 and show the small number of patients who received a treatment sequence that may not be allowed in the NHS (n=[redacted] in the AAP + ADT arm and n=[redacted] in the ADT alone arm). In order to respond to the Committee's concerns, Janssen conducted an Inverse Probability of Censoring Weighted (IPCW) analysis which adjusted for these sequences to explore their impact on overall survival. These data were not presented in the submission and the caveat around uncertainty still applies; however, importantly, results showed an improved HR of [redacted] [95% CI: [redacted]]. *[Table provided but not reproduced here]* Janssen would like to address discussion within the ACD regarding the appropriateness of subsequent therapies in STAMPEDE: STAMPEDE was a trial in patients from the UK and was unblinded. This meant that follow-on treatments in STAMPEDE reflected what people would have in clinical practice in the UK because the choice of next treatment depends on the first treatment had, unlike in the blinded LATITUDE trial. [Section 3.5] And, The committee concluded that the estimates of survival from STAMPEDE after a	The committee recognised that in both LATITUDE and STAMPEDE, patients could have treatments that do not reflect NHS clinical practice. It concluded that the estimates from STAMPEDE were more relevant to clinical practice than those from LATITUDE. See section 3.8 of the FAD.

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			patient needed a next treatment were likely to be more relevant to clinical practice in England than those from LATITUDE. [Section 3.5] Janssen are concerned that such statements do not recognise that STAMPEDE had a similar issue regarding subsequent therapies. Despite the study being unblinded and conducted in the UK, patients in STAMPEDE [Arm G] also received multiple novel agents in their pathway which would not be permitted by the NHS in normal practice. Whilst data on subsequent therapies specific to the metastatic cohort have not been published, of all those who had progressed in Arm G of STAMPEDE, 10% (25/248) received enzalutamide after AAP + ADT, and 3% (8/248) received abiraterone again.[4] In LATITUDE, these proportions were similarly 10% (30/314) and 3% (10/314), respectively.[5] Whilst the Committee suggest a preference for using data from STAMPEDE, specific data on subsequent therapies are not reported in sufficient detail to inform economic modelling; data (as currently reported) are not distinguished according to line of therapy in mCRPC,[4] or are only reported as time-to-event analysis for a sample few therapies.[6, 7] In this context, Janssen wish to highlight that patterns of subsequent therapies are not dissimilar between LATITUDE[5] and STAMPEDE[4] (in fact, some proportions appear to be identical as presented above), and the results of overall survival for AAP+ADT vs. ADT alone were also very similar between the two trials (i.e. HR=0.62 [0.51-0.76] and HR=0.61 [0.49-0.75], respectively). This supports the generalisability of the LATITUDE survival estimates to the UK population and reaffirms the clinical benefit of AAP + ADT over ADT alone. **Cost-effectiveness of AAP + ADT vs. ADT alone** Janssen maintain the relevance of LATITUDE as the primary source of clinical data for informing the cost-effectiveness of AAP + ADT vs. ADT alone, given the similarities between LATITUDE and STAMPEDE. Janssen also recognise that the treatment of men with newly diagnosed high-risk mHSPC is a sequential pathway and thus appropriate to model this way. Given the limited evidence available to inform the sequence of therapies received after a patient has progressed to mCRPC after first-line mHSPC, Janssen held an advisory board with five practising UK clinicians in prostate cancer to ascertain the most probable sequences which could be captured in the model. These proportions were subsequently validated on two separate occasions and Janssen are concerned there has been no recognition of this advisory board as a valid data source in the ACD.	In updated analyses matching the committee's preferences and accounting for the confidential commercial arrangements of subsequent therapies, the resultant cost-effectiveness estimates compared with both ADT alone and docetaxel in

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			Nevertheless, Janssen do acknowledge the ERG and Committee's preference for certain model assumptions which were not incorporated into the original base case analysis. Although we maintain that the assumptions made in the original base case analysis were robust, several ERG and Committee preferences have now been incorporated into an updated base case to address some of the concerns raised and better reflect the views of the Committee in order to aid decision making. To illustrate, the updated company base case has adopted the sequence shown in Figure 1, and two additional scenarios were also explored to capture the sequence of patients who would never receive a taxane chemotherapy. The key elements accounted for in the updated base case sequence for AAP + ADT and ADT alone and are detailed in Table 3. *[Table and Figure provided but not reproduced here]* Results of the updated base case for AAP + ADT vs. ADT alone, applying the confidential CAA and list prices for downstream therapies which are known to have patient access schemes (PASs), are presented in Table 5. Results show that, under the confidential CAA, AAP + ADT is a highly cost-effective use of NHS resources in men with newly diagnosed high-risk mHSPC. The incremental cost of using AAP (+ ADT) earlier in the treatment pathway is offset by its significant benefits in delaying disease progression, delaying chemotherapy, improving (and sustaining) HRQL and, ultimately, extending survival compared to ADT alone. Indeed, all ICERs related to the sensitivity analysis of AAP + ADT vs. ADT alone fall within the cost-effective threshold for the NHS. These results recognise the value of treating men with newly diagnosed high-risk mHSPC with a novel agent as early as possible. The series of scenario analyses conducted on the updated base case all consistently demonstrate that AAP + ADT remains a highly cost-effective use of NHS resources compared to ADT alone, irrespective of the model assumptions varied. *[Tables provided but not reproduced here]*	combination are higher than £30,000 per QALY gained. The committee concluded that abiraterone did not represent a cost-effective use of NHS resources. See section 3.14 of the FAD.
4	Consultee	Janssen	**Clarifying the level of access Janssen have to STAMPEDE data** There are multiple statements within the ACD that convey the Committee's preference for	Thankyou for your comments.

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			receiving clinical and quality of life data from STAMPEDE to inform the comparison of AAP + ADT vs. docetaxel + ADT; however, Janssen do not currently have access to these data. Janssen are concerned these statements imply we have actively chosen not to utilise these data in our submission which is not the case. The ACD states: The committee would have preferred data from patients with high-risk metastatic disease from STAMPEDE to have been included in the modelling. [Section 3.10] And, The committee further noted that the company could have used trial-based EQ-5D results for docetaxel plus ADT in its model because STAMPEDE collected these for the trial arms assessing abiraterone plus ADT, docetaxel plus ADT and ADT alone. [Section 3.12] Janssen do not have access to the individual patient data (IPD), nor any other unpublished data, from STAMPEDE. Whilst Janssen supported the STAMPEDE trial with the provision of abiraterone acetate free-of-charge for the entire duration in which the compound has been investigated, and additionally financially contributed to sponsorship of the trial, Janssen do not own the STAMPEDE data. Furthermore, patients enrolled in the STAMPEDE trial have not given consent for the manufacturer (i.e. Janssen) to access their data which has also restricted Janssen access to IPD. Finally, it is important to highlight that the key area of uncertainty lies with the comparative effectiveness of AAP + ADT [Arm G] and docetaxel + ADT [Arm C]. Since Janssen was not the manufacturer providing drug and additional financial support to Arm C, there are additional restrictions for Janssen to access the IPD related to patients who have received docetaxel + ADT and, to date, we have had to be reliant on published analyses. As such, strict data governance does not permit Janssen access to IPD from STAMPEDE to conduct additional analyses which would address the Committee's request for the use of direct evidence for AAP + ADT vs. docetaxel + ADT, specifically in those with high-risk metastatic disease. Of note, the identification and efficacy analysis of high-risk vs. low-risk (or similarly, high-volume vs. low-volume) patients from STAMPEDE has not yet been completed or published. 	Section 3.11 of the FAD has been updated to note that the company does not have access to health-related quality of life data from STAMPEDE.

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			[redacted]	
5	Consultee	Janssen	**Addressing the comparison of AAP + ADT vs. docetaxel + ADT** Janssen wish to highlight that conclusive statements in the ACD regarding the generalisability of STAMPEDE data to the licensed population are currently unsubstantiated by evidence. The ACD also contains conflicting statements regarding the comparative effectiveness of AAP + ADT vs. docetaxel + ADT and Janssen do not believe the Committee's preliminary decision has accounted for the full evidence base. In this section we wish to address: *1.* Generalisability of STAMPEDE data to the licensed indication *2.* Appropriateness of utilising NMA **1. Generalisability of STAMPEDE data to the licensed indication** Janssen acknowledge there is a degree of uncertainty around the relative difference in overall survival for patients treated with AAP + ADT vs. docetaxel + ADT and therefore believe it is essential to consider all available evidence which is comparable to the licensed indication. Janssen do recognise the prominence of STAMPEDE, its unique design and relevance to the UK; however, we also wish to re-emphasise that the metastatic patient cohort in STAMPEDE is broader than the licensed indication for AAP + ADT. The ACD states: The clinical experts explained that results for the licensed population (that is, the subgroup of patients with high-risk disease) had been collected, but not yet published. Two clinical experts, who were also investigators in STAMPEDE, explained that there was no reason to believe that there was any subgroup of people for whom abiraterone was more or less effective; abiraterone appeared similarly effective in localised, metastatic and high-risk hormone-sensitive prostate	Thank you for your comments. The committee has considered all of analyses presented in response to this consultation exercise and subsequently as addenda to this response. Please see sections 3.5 and 3.7 of the FAD for the committee's considerations.

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			cancer. [Section 3.4] Therefore, The committee agreed that, although STAMPEDE assessed treatments in a broader population than the population covered by the marketing authorisation for abiraterone, data from STAMPEDE are broadly generalisable to the population for whom abiraterone plus ADT is being appraised. [Section 3.4] To Janssen's knowledge, the identification and efficacy analysis of high-risk vs. low-risk (or similarly, high-volume vs. low-volume) patients of STAMPEDE [Arm G] has not yet been fully completed; [redacted]. Under these conditions, Janssen were unable to definitively state that the metastatic population from STAMPEDE is generalisable to the licensed indication for AAP + ADT in newly diagnosed high-risk mHSPC. For this reason, we chose to focus the clinical base case of AAP + ADT vs. docetaxel + ADT on the network meta-analysis (NMA) which utilised LATITUDE and the subgroups of patients with newly diagnosed high-volume disease from the CHAARTED and GETUG-AFU 15 studies as these were most similar to the LATITUDE population. The NMA utilised in the original base case derived a HR of 0.92 [0.69-1.23]; Bayesian probability in favour of AAP + ADT of 71.8%. Recognising the importance of STAMPEDE, these data were included in the NMA as a key scenario analysis and indeed results were very similar (HR=0.91 [0.76-1.09]; Bayesian probability 84.5% in favour of AAP + ADT). **2. Appropriateness of utilising NMA** In discussing the STAMPEDE data, the ACD states: [The committee] preferred direct evidence from patients with high-risk metastatic disease from STAMPEDE for the comparison between abiraterone plus ADT with docetaxel plus ADT to indirect evidence from the company's network meta-analysis. [Section 3.4] This statement is misleading because this analysis was conducted in all metastatic patients, not specifically for the high-risk subgroup in which abiraterone is licensed; as mentioned above, the high-risk analysis has not yet been completed. Furthermore, Janssen do not believe it appropriate (nor consistent with NICE precedent) to solely focus on a single subgroup analysis of 342 metastatic patients from STAMPEDE which was not	

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			powered to detect any differences in overall survival between the two arms. It should also be noted that the *post-hoc* subgroup analysis of AAP + ADT vs. docetaxel + ADT from STAMPEDE derived a HR of 1.13 (0.77-1.66) with a confidence interval indicating sizable uncertainty and lacking statistical significance (p=0.53). This result does not draw a consistent conclusion with the two larger cohort analyses of STAMPEDE that were powered to detect differences in overall survival. Indeed, the reported treatment effect on survival for AAP + ADT vs. ADT alone in metastatic patients from STAMPEDE (HR=0.61 [0.49-0.75])[4] was larger than the previously-reported treatment effect on survival for docetaxel + ADT vs. ADT alone in metastatic patients (HR=0.76 [0.62-0.92).[7] This suggests the direct analysis may not be reliable. Given the uncertainty in the direct analysis of patients contemporaneously randomised in STAMPEDE to AAP + ADT or docetaxel + ADT, Janssen believe it is most appropriate to consider the wider evidence base to assess the comparative effectiveness of AAP + ADT vs. docetaxel + ADT. The ACD in fact concurs with Janssen in this regard as it subsequently states: > The committee concluded that the direct evidence could be further supported by a network meta-analysis including evidence from patients with high-risk metastatic disease from STAMPEDE, CHAARTED, GETUG-AFU 15 and LATITUDE. This would combine evidence from a larger number of people and potentially decrease the uncertainty about the relative effectiveness of abiraterone. [Section 3.6] Janssen wish to highlight that an NMA of this composition was presented in the submission and used in a scenario analysis although it has not been recognised in the ACD. The value of NMA is recognised by NICE DSU TSD 4, and of particular importance when inconsistency is detected in the clinical evidence base.[8] Assuming the entire metastatic group from STAMPEDE is generalisable to the licensed indication, as previously inferred, and the Committee agrees that the direct analysis could be supported by an NMA, Janssen must emphasise the relevance of results already presented in the original submission and highlight these results is unlikely to change with additional data for high-risk patients. The result of the NMA which includes STAMPEDE are presented again in Table 2 and demonstrate a positive trend towards AAP + ADT being the better treatment compared to docetaxel + ADT in terms of overall survival, with a HR=0.91 (CrI: 0.76-1.09) and Bayesian probability of 84.5%. In order to address the Committee's preference for STAMPEDE data, Janssen has also	

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			conducted another NMA using only STAMPEDE data from the three relevant published analyses. The result of this analysis, also presented in Table 2, show a consistent HR=0.91 (CrI: 0.72-1.15) and thus derives the same conclusion in favour of AAP + ADT vs. docetaxel + ADT with a Bayesian probability of 79.2%. These results could be explained by the size of the trial populations included in the network, and the power of each analysis. Since the comparison of AAP + ADT vs. ADT alone (HR=0.61 [0.49-0.75]) included 1,002 metastatic patients and the comparison of docetaxel + ADT vs. ADT alone (HR=0.76 [0.62-0.92] included 1,086 metastatic patients, these are given greater weight in the network than the unpowered analysis of AAP + ADT vs. docetaxel + ADT (HR=1.13 [0.77-1.66]) which only included 342 metastatic patients. Two alternative, independent NMAs have also been published investigating the relative effectiveness of ADT alone, AAP + ADT and docetaxel + ADT in this setting, both of which have drawn similar conclusions: • The Systemic Treatment Options for Cancer of the Prostate (STOPCAP) NMA of aggregate data aimed to establish the optimal treatment from all available studies of ADT in combination with AAP, docetaxel or celecoxib.[9] The results showed that AAP + ADT was most likely to be the optimal treatment with regards to overall survival (94% probability), with docetaxel + ADT second best (35% probability).[9] In addition, the results showed that AAP + ADT was most likely to be optimal for failure-free survival (FFS) (100% probability), with docetaxel + ADT second best; however, results for FFS should be interpreted with caution due to variation in the definitions across included trials.[9] • The NMA by Wallis et al. further supported these results, concluding that, while there was no statistically significant difference between AAP + ADT and docetaxel + ADT for overall survival based on Frequentist NMA, Bayesian analysis showed a high likelihood (89% probability) that AAP + ADT was the preferred approach for patients with newly diagnosed mHSPC.[10] It is important to recognise that separate research groups have conducted independent analyses and reached similar conclusions regarding the difference in overall survival between AAP + ADT and docetaxel + ADT. Considering the trend in a series of published analyses adds greater weight to considering just one in isolation. It should also be noted	

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			that the authors of Sydes et al (2018)[6] signposted the importance of NMA and the necessary next step for taking all published data from STAMPEDE, alongside all other data from RCTs reported in metastatic prostate cancer, to derive an NMA which would enable an assessment of potential ranking of effective therapies.[6] The NMA on "PFS-like" endpoints that Janssen have conducted is also presented in Table 2 for both the wider evidence base as well as an NMA based solely on STAMPEDE which utilises FFS only. These results show treatment with AAP + ADT is highly likely to be the better treatment compared to docetaxel + ADT in terms of delaying disease progression (HR=[redacted] [redacted] and HR=0.53 [0.44-0.93]), with Bayesian probability [redacted]% and 100%, respectively. ***[Table provided, not reproduced here]***	
6	Consultee	Janssen	**Addressing discussion around the subsequent therapies and post-progression survival** There are multiple statements in the ACD that suggest AAP + ADT and docetaxel + ADT have equal survival benefit, despite the progression-free survival benefit reported with AAP + ADT. Janssen are concerned the rationale for such claims are unsubstantiated by clinical evidence. In this section we wish to address: *1.* Evidence for post-progression survival *2.* Relevance of docetaxel re-challenge **3. Evidence for post-progression survival** As the Committee have focused on the unpowered analysis of AAP + ADT vs. docetaxel + ADT from STAMPEDE, the ACD suggests there is no difference in survival benefit between AAP + ADT and docetaxel + ADT, despite the progression-free survival benefit with AAP + ADT. On several occasions the ACD suggests that men treated with docetaxel + ADT in mHSPC have longer post-progression survival compared to those treated with AAP + ADT because of the number of treatment options available to them in mCRPC. The ACD states: Two of the clinical experts explained that the reason for a progression-free survival benefit but lack of overall survival benefit with abiraterone plus ADT compared with docetaxel plus ADT in STAMPEDE was that patients may have had fewer	Thank you for your comments. The committee's conclusion on the effectiveness of docetaxel is based on the results of both the direct comparison and the network meta-analysis. See section 3.7 of the FAD.

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			treatment options after abiraterone plus ADT than after ADT alone or docetaxel plus ADT. The clinical experts involved in STAMPEDE explained that post-progression survival was reduced after abiraterone plus ADT compared with after ADT alone in this trial. [Section 3.9] And, The committee concluded that the first-choice treatment option for hormone-sensitive metastatic prostate cancer affects the follow-on treatments a person may have, and that having abiraterone plus ADT results in fewer follow-on treatment options than having ADT alone or docetaxel plus ADT. [Section 3.3] Janssen are concerned these claims are unsubstantiated by clinical evidence. It should be noted that neither post-progression survival or 'PFS2' were included as pre-specified analyses within the STAMPEDE protocol. Furthermore, follow-up (FU) of patients in that study has been of insufficient length so far to make definitive statements around the sequence of treatment in mCRPC or the length of post-progression survival. The length of follow-up for patients who received docetaxel + ADT in STAMPEDE [Arm C] has been much longer (median FU=43 months) than for those who received AAP + ADT [Arm G] (median FU=40 months) as Arm C finished recruiting earlier. This could potentially result in additional bias in results. **4. Relevance of docetaxel re-challenge** The ACD states the reason the Committee believe patients have fewer treatment options after AAP + ADT is solely due to the use of docetaxel re-challenge after docetaxel + ADT. The ACD highlights: The clinical experts explained that people who have previously had docetaxel as first-line treatment can be given docetaxel again (for up to 10 cycles) because the benefit of docetaxel is not exhausted when used with ADT for only 6 cycles. [Section 3.3] To our knowledge, there is no robust clinical evidence to suggest that docetaxel re-challenge has significant clinical benefit or would be widely used in the NHS following docetaxel + ADT in mHSPC. This was also recognised by NICE TA101[11] which specially states that "repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy."	

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			Whilst the ACD states that STAMPEDE could be more reflective of what subsequent therapies men in the UK receive in clinical practice, only 14% (i.e. 44/315) received docetaxel re-challenge in mCRPC after docetaxel + ADT in mHSPC as part of STAMPEDE [Arm C].[7] That said, Janssen do acknowledge that no longer term follow-up of STAMPEDE has been published to inform whether this percentage has subsequently changed. A follow-up analysis of GETUG-AFU 15 has, however, been published in which the effectiveness of docetaxel re-challenge after docetaxel + ADT in mHSPC has been discussed.[12] To our knowledge, this is the only published evidence discussing the clinical benefit of docetaxel re-challenge in the relevant sequence and setting. Data in the publication showed that docetaxel re-challenge, following progression to mCRPC after upfront docetaxel + ADT in mHSPC was of limited clinical benefit and only active in a small number of patients (irrespective of being used first- or second-line mCRPC).[12] The authors go on to suggest that taxane re-challenge with cabazitaxel, instead of docetaxel, could be the preferred strategy for patients with mCRPC who were treated with upfront docetaxel + ADT in mHSPC.[12] Indeed, this was also the opinion reflected at the advisory board that Janssen held in preparation for submission and, as a result, we included taxane re-challenge with cabazitaxel in the economic modelling. Janssen sought advice from five practising UK clinicians at this meeting to inform the most likely sequence/proportions of subsequent therapies after treatment in mHSPC and docetaxel re-challenge was not prominent in discussions. Janssen have also surveyed 27 clinical experts across the UK to ascertain whether docetaxel re-challenge is common practice in the NHS. Whilst some experts (n=5) suggested there is not enough data/experience of this yet in the UK, most of the respondents agreed that docetaxel re-challenge is uncommon. The most frequent reason provided for not re-challenging was the availability of other treatments for mCRPC (including abiraterone/enzalutamide and cabazitaxel) that were considered more appropriate at this stage of disease progression. Where numbers were provided, the proportion of patients who would be re-challenged was estimated to be between zero and <25% (n=12). Respondents further advised that docetaxel re-challenge would only ever be in patients who have had a very good response on it previously, and most likely only after other agents have been given first. Cabazitaxel was identified as preferred option for re-challenge with a taxane due to the lower risk of neuropathy seen with it (n=2). The UK Clinical Survey report has been provided in Appendix A to this response.	

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			It is important to also highlight that if docetaxel re-challenge is relevant after docetaxel + ADT then it could also be relevant downstream at third-line mCRPC after AAP + ADT. As such, an equal number of follow-on treatments would be available after AAP + ADT and docetaxel + ADT in mHSPC. There is however scarce evidence for the clinical benefit of docetaxel re-challenge irrespective of its position in the pathway. As a result, Janssen do not believe there is a valid, or evidence-based, rationale for concluding patients have a much shorter post-progression survival after AAP + ADT which would ultimately result in equal overall survival benefit with docetaxel + ADT.	
7	Consultee	Janssen	**Discussing the interpretation of HRQL data for docetaxel + ADT** Janssen are concerned that the ACD contains conflicting statements regarding the health-related quality of life (HRQL) of patients treated with docetaxel + ADT and such statements are unsubstantiated by any evidence. *1.* Evidence for patients' HRQL on docetaxel *2.* Factual inaccuracy regarding model utility decrements **5. Evidence for patients' HRQL on docetaxel + ADT** To date, no EQ-5D utility data associated with docetaxel + ADT in mHSPC have been published, however, the ACD states: The committee further noted that the company could have used trial-based EQ-5D results for docetaxel plus ADT in its model because STAMPEDE collected these for the trial arms assessing abiraterone plus ADT, docetaxel plus ADT and ADT alone. [Section 3.12] And, [The committee] concluded that it was preferable to use EQ-5D data from the subgroup of people from STAMPEDE with metastatic and high-risk hormone-sensitive prostate cancer to assess quality of life because comparable data were available for abiraterone plus ADT, docetaxel plus ADT and ADT alone. [Section 3.12] As highlighted above, Janssen have not yet been able to access these data. We understand that HRQL analyses have been conducted on the EQ-5D data collected in STAMPEDE by the University of York, however, the results of these analyses have not yet	Thank you for your comments. The committee took into account an ERG scenario modelling a utility decrement associated with docetaxel. See section 3.11 of the FAD.

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			been published and are not accessible to Janssen. As a result, Janssen consulted the HRQL data published from the CHAARTED study which showed patients' HRQL over the course of treatment on and after docetaxel in mHSPC. These data assessed the change in patients' prostate cancer-specific functional status (measured by the FACT-P) as well as their level of pain (measured by the Bone Pain Index, BPI) over the course of a year.[13] Results showed that patients' HRQL was significantly impacted while on-treatment with docetaxel and that patients did take a long time to recover from treatment (i.e. 12 months).[13] These data validate the rationale for including a utility decrement on-treatment with docetaxel in the model, as well as a smaller decrement in the off-treatment phase to capture the fact that patients are still recovering. Janssen believe that the ACD considerably downplays the relevance of these data by suggesting the impact of docetaxel on patients' quality of life is small, transient, and without long-lasting effect: The clinical expert noted that, in CHAARTED (a trial of docetaxel plus ADT compared with ADT), quality of life slightly declined on docetaxel in the first 3 months but then returned to normal. [Section 3.13] Janssen wish to highlight that, in the ACD, discussion of patients' quality of life are currently unsubstantiated by evidence and appear to contradict earlier statements made in the report. We believe this may be due to a misinterpretation of the evidence base which has translated into misleading statements regarding HRQL. The ACD states: The clinical experts explained that they did not consider it plausible that quality of life would be worse while having docetaxel plus ADT because any treatment that improves prostate cancer symptoms would improve quality of life. [Section 3.13] And, The clinical experts involved in STAMPEDE stated that quality of life was improved on docetaxel plus ADT in that trial. [Section 3.13] These statements are confusing and contradict previous statements made earlier in the ACD regarding adverse events on docetaxel. The ACD had stated previously: The committee heard that some people prefer having abiraterone first, rather than docetaxel, because it has fewer adverse effects and is better tolerated. However, it also heard that some people choose to have docetaxel first because of its shorter treatment. [Section 3.2] Whilst we fully agree with this assertion as it emphasises the importance of patient	

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			preference in this setting, Janssen are concerned the inconsistent statements within the ACD regarding the impact docetaxel has on patients' HRQL do not portray an appropriate assessment of the evidence. Indeed, the patient voice within the NICE submission from Prostate Cancer UK clearly highlights how impactful the prospect of chemotherapy is to patient's lives: *"It was such a relief not to have to have chemo. The side effects of chemo would have made it much tougher for me to continue to work effectively which I needed to do in order to get my business in order and in a position where it can function effectively without me." [Prostate Cancer UK submission to NICE]* **6. Factual inaccuracy regarding model utility decrements** Janssen wish to highlight a factual inaccuracy in discussion around the relevance of including disutilities for AEs as the ACD states: The committee noted that although adverse effects were worse during treatment with docetaxel plus ADT than with abiraterone plus ADT or ADT alone, the effect of adverse effects on quality of life had been accounted for separately in the company model thereby potentially double counting the utility loss from adverse events. [Section 3.13] Due to the application of the utility decrements for on- and off-docetaxel, Janssen chose not to apply the AE utility decrements in the docetaxel + ADT arm in order to avoid double-counting the utility loss. The above statement is therefore factually incorrect.	
8	Consultee	Janssen	**Addressing the economic modelling of AAP + ADT vs. docetaxel + ADT** Janssen are concerned that the Committee's rationale for disagreeing with the validity of the economic model stem from a series of assumptions that have been addressed in above sections and as such, are not supported by robust evidence, given the ACD states: The committee stated that, because the company's model structure did not reflect the treatment pathway for metastatic hormone-sensitive prostate and gave implausible survival estimates. [Section 3.16] In this section we wish to address: *1.* Modelled treatment pathway	Thank you for your comments. The committee considered the updated model submitted by the company. See sections 3.9 and 3.13 of the FAD.

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			2. Modelled survival estimates 3. Cost-effectiveness of AAP + ADT vs. docetaxel + ADT 4. Exploratory analysis of OS for AAP + ADT vs. docetaxel + ADT **7. Modelled treatment pathway** Janssen wish to highlight that the current model does account for different sequences that may be received in the metastatic prostate cancer pathway, through the application of a matrix of subsequent therapies based on their market shares. These percentages depict the differing likelihoods of alternative treatments in each health state, given the distributions applied in the previous health state. This was considered the best way of capturing sequential treatments within the structure of a Markov model. We believe it is essential we clarify this to show that the current model is fit-for-purpose. The ACD however states: The committee disagreed with the company's assumptions on follow-on treatments because: it did not model a second treatment course with docetaxel after docetaxel plus ADT; and it did not reflect that people having abiraterone plus ADT for hormone-sensitive prostate cancer have fewer treatment options available for hormone-refractory prostate cancer. [Section 3.11] And, The committee would have preferred to have seen analyses on the effect of different sequences and numbers of follow-on treatments to understand the relationship between progression-free survival and overall survival in high-risk metastatic hormone-sensitive prostate cancer. [Section 3.9] It is clear that the rationale for having fewer follow-on treatments after AAP + ADT is solely attributed to the use of docetaxel re-challenge after docetaxel + ADT. Given the expert clinical feedback attained from a sample of 27 practising clinical experts across the UK suggesting that docetaxel re-challenge is uncommon, Janssen maintain that the assumptions for subsequent therapies used in the original base case (i.e. utilising estimates attained from the advisory board and including cabazitaxel as a means of taxane re-challenge) were not inaccurate. Nevertheless, we acknowledge the Committee's	

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			preferences and, since the model is already suited to modelling different compositions of subsequent therapies, have presented scenario analyses in which a) docetaxel re-challenge is included after docetaxel + ADT and b) explicit sequences are explored. The sequence included as the updated company base case is illustrated in Figure 2 below, alongside two additional, clinically plausible scenario analyses that have been explored in Table 10. The key elements accounted for in the updated base case sequence for AAP + ADT and docetaxel + ADT are detailed in Table 8. Of note, docetaxel re-challenge is now included following the Committee's preference but, as guided by the UK Clinical Survey, only after exposure to a novel agent and at a maximum of 25%. Cabazitaxel re-challenge is still included, as validated by the UK Clinical Survey with a maximum of 25%. ***[Table and figure provided but not reproduced here]*** **Modelled survival estimates** The ACD suggests the reason the Committee do not think the model derives plausible survival estimates is due to their focus on the single unpowered analysis from STAMPEDE. Janssen do not however believe the model derives implausible survival estimates because of the concordance in results from all three independent NMAs, which indicates that there is a very high probability of AAP + ADT being superior with regards to overall survival compared to docetaxel + ADT. The economic model also captures the progression-free survival benefit of AAP + ADT vs. docetaxel + ADT, which is a significant driver of cost and cost-effectiveness. Furthermore, Janssen wish to highlight that the model still holds face validity with regards to the duration of time spent pre- and post-progression across treatment arms. The ACD highlights that: > The committee expected that, if the model reflected the treatment pathway, the benefits of abiraterone plus ADT in delaying progression might be balanced by the potential benefits of the availability of more treatment options after a person's prostate cancer has become hormone-relapsed after ADT alone or docetaxel plus ADT. [Section 3.16] Combined with discussion in the ACD which suggests the length of time a person lived after progressing on treatment for mHSPC was kept similar in the model regardless of	

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			treatment, Janssen are concerned these statements present an inaccurate summary of the model outcomes because the model did not assume equal post-progression survival between treatment arms. Modelled post-progression survival was dependent upon the subsequent therapies applied in mCRPC. As illustrated in Figure 3, post-progression survival for the docetaxel + ADT arm was indeed longer than AAP + ADT for the base case. Figure 3 shows that the model captured the longer time spent in mHSPC (i.e. pre-progression) with AAP + ADT compared to docetaxel + ADT (3.64 LYs vs. 2.93 LYs) whilst a shorter time in mCRPC (i.e. post-progression) with docetaxel + ADT compared to AAP + ADT (1.43 LYs vs. 1.40 LYs). It also shows that AAP + ADT derives an overall survival benefit because the longer time spent in mCRPC after docetaxel + ADT is not sufficient to offset the gains in mHSPC with AAP + ADT. The longer patients can remain hormone-sensitive, the longer they can retain a better quality of life which is of utmost importance to the patients themselves, their family, their carer and, ultimately, the NHS. ***[Figure provided but not reproduced here]*** Nevertheless, Janssen recognise the Committee's concern over the uncertainty in the relative survival benefit of AAP + ADT vs. docetaxel + ADT and have thus conducted a threshold analysis to show that AAP + ADT remains a cost-effective use of resources whilst varying the HR against docetaxel + ADT. The results of this threshold analysis can be found in Table 12. **Cost-effectiveness of AAP + ADT vs. docetaxel + ADT alone** Janssen acknowledge the ERG and Committee's preference for certain model assumptions which were not incorporated within the original base case analysis. Although we maintain that the assumptions made in the original base case analysis were robust, several ERG and Committee preferences have now been incorporated into an updated base case to address some of their concerns and better reflect the views of the Committee in order to guide decision making. The updates which have been incorporated are detailed in Table 9 alongside the impact each had on the ICER. ***[Table provided but not reproduced here]*** Results of the updated base case for AAP + ADT vs. docetaxel + ADT, applying the	

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			confidential CAA and list prices for downstream therapies which are known to have patient access schemes (PASs), are presented in Table 10. Results show that, under the confidential CAA, AAP + ADT is a cost-effective use of NHS resources in men with newly diagnosed high-risk mHSPC. Indeed, the majority of ICERs related to the sensitivity analysis of AAP + ADT vs. docetaxel + ADT alone fall within the cost-effective threshold for the NHS. These results recognise the value of treating men with newly diagnosed high-risk mHSPC with a novel agent as early as possible. As presented in Table 11, the series of scenario analyses which were conducted on the updated base case all consistently demonstrate that AAP + ADT remains a cost-effective use of NHS resources compared to docetaxel + ADT for the majority of scenarios tested. Of note, the LATITUDE only scenario (named "MSM" by the ERG) utilises LATITUDE survival data, and LATITUDE subsequent therapy market share data for AAP + ADT and ADT alone, to ensure consistency between the subsequent therapy costs that underpin the specific clinical outcomes. Janssen do not believe it is appropriate to adjust the subsequent therapy proportions without any adjustment to the LATITUDE curve and thus why it was presented as a trial-based scenario only. Janssen do acknowledge that the ERG and Committee were interested in this modelling approach and therefore we also conducted a threshold analysis on this scenario, as presented in Table 11. ***[Tables provided but not reproduced here]*** **Exploratory analysis of OS for AAP + ADT vs. docetaxel + ADT** In order to further address concerns raised by the Committee in the ACD, an additional exploratory analysis has been presented to test the robustness of the model outcomes to changes in assumptions around overall survival. This involved varying the HR for OS for the comparison of AAP + ADT vs. docetaxel over a range of values in increments of 0.01 to demonstrate the impact on the ICER when increasing the HR (and thus decreasing the predicted benefit). Results of the analysis are presented in Table 12, which shows the ICERs alongside the incremental difference in post-progression survival (PPS) between the AAP + ADT and docetaxel + ADT arms. This analysis has been presented for both the updated company model (named "MSM/TA387" by the ERG) and the LATITUDE only scenario (named "MSM" by the ERG).	

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			The analysis demonstrates that the ICER remains robust even as the HR increases, and PPS is increased in the docetaxel + ADT arm relative to the AAP + ADT arm.	
9	Consultee	Janssen	**Clarifying description of STAMPEDE patient population** Janssen wish to highlight the current description of the enrolled population of STAMPEDE in the ACD is misleading. The ACD states: *"STAMPEDE was a multi-arm multi-stage non-blinded adaptive trial of patients with newly diagnosed high-risk metastatic, node-positive or localised disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features."* Currently, this description implies that newly diagnosed high-risk metastatic patients (i.e. the licensed indication of abiraterone) were a pre-defined group of patients within study; however as discussed above, the identification and analysis of this group has not yet been completed. A more correct description would be that STAMPEDE is a multi-arm, multi-stage (MAMS) trial which studied men starting long-term hormone therapy for (a) metastatic or (b) high-risk non-metastatic prostate cancer.[14] *[References provided but not reproduced here]*	Comment noted. See section 3.4 of the FAD.
10	Consultee	Prostate Cancer UK	There are numerous sources which set out the clinical criteria to define people who are unable to receive docetaxel which should be considered. Paragraph 3.3 of the Clinical Commissioning Policy Statement for docetaxel in combination with ADT[i] includes: • severe prior hypersensitivity reaction to taxanes • poor overall performance status (WHO performance status 3-4, caution for those with performance status 2) • pre-existing significant peripheral neuropathy • poor bone marrow function due to extensive disease or other prior haematological problems • significant co-morbidity (e.g. cardio-vascular or respiratory disease) such that prostate cancer is not likely to be the life limiting illness for the patient Paragraph 4.31 of the FAD for TA412 for radium 223[ii] sets out criteria for defining the	Thank you for your comments. See section 3.2 of the FAD for the committee's considerations on this issue.

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			people for whom docetaxel is not suitable: • contraindications to docetaxel such as hypersensitivity to the active substance, a neutrophil count of less than 1.5x109/litre, or severe liver impairment • a platelet count of less than 100x109/litre • ongoing treatment with an immunosuppressant for any condition • an ECOG performance status of 3 or greater • comorbidities and an ECOG performance status of 2 or greater • comorbidities, including: ○ poor cognition or social support, which results in inability to understand treatment and provide consent	
11	Consultee	Prostate Cancer UK	While the impact on quality of life of adverse events during chemotherapy are well documented (more on this in our response to paragraph 3.13), the majority of patients quality of life will return to normal after stopping chemotherapy[iii]. There is no evidence that most patients suffer long-term consequences of chemotherapy treatment. A recently published study looked at the impact of ADT+docetaxel on prostate cancer patient quality of life at 3 months and 12 months. It found that quality of life is statistically worse than baseline at 3 months, but is then higher than for ADT alone at 12 months[iv]. (https://www.ncbi.nlm.nih.gov/pubmed/29522362) **On the long-term consequences of chemotherapy:** Chemotherapy can cause nerve damage that leads to neuropathic pain, however studies have suggested that this effect is more likely to occur in patients with pre-existing neuropathy[v]. (https://academic.oup.com/bjaed/article/16/4/115/2897725) Other chemotherapy treatments can increase the risk of heart disease, but this is generally not associated with taxanes like docetaxel. Further identified long-term consequences of chemotherapy are more strongly linked to higher doses of chemotherapy or longer treatment cycles than the six recommended for docetaxel. Patients can report problems with cognitive function or 'chemo brain' but there is no definitive evidence on the link between this and chemotherapy.	Thank you for your comments. The committee considered that a quality of life decrement for the period of time people take docetaxel was appropriate. See section 3.11 of the FAD.

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12	Consultee	Prostate Cancer UK	It is absurd to suggest that it is not plausible that quality of life would be worse while having docetaxel plus ADT. The paragraph goes on to highlight the impact of adverse events on quality of life. As we included in our original submission, several patients able to receive abiraterone were grateful to have avoided the side-effects associated with chemotherapy. We heard from one patient who was diagnosed before abiraterone was available but still refused chemotherapy due to the potential side-effects. *"He chose not to have chemotherapy after watching his mother suffer terribly from side effects when she was treated for breast cancer."* *"It was such a relief not to have to have chemo. The side effects of chemo would have made it much tougher for me to continue to work effectively which I needed to do in order to get my business in order and in a position where it can function effectively without me."* A recently published study looked at the impact of ADT+docetaxel on prostate cancer patient quality of life at 3 months and 12 months. It found that quality of life is statistically worse than baseline at 3 months, but is then higher than for ADT alone at 12 months[vi]. (https://www.ncbi.nlm.nih.gov/pubmed/29522362) Hopefully the EQ-5D data from the STAMPEDE trial will be made available and able to provide further insight on this.	Thank you for your comments. The committee considered that a quality of life decrement for the period of time people take docetaxel was appropriate. See section 3.11 of the FAD.

[i] https://www.england.nhs.uk/wp-content/uploads/2016/01/b15psa-docetaxel-policy-statement.pdf
[ii] https://www.nice.org.uk/guidance/ta412/resources/radium223-dichloride-for-treating-hormonerelapsed-prostate-cancer-with-bone-metastases-pdf-82604599866565
[iii] The Lancet Volume 387, Issue 10024, Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial Prof Nick James et al. March 2016
[iv] Journal of Clinical Oncology, Quality of Life During Treatment With Chemohormonal Therapy: Analysis of E3805 Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer, Morgans et al. April 2018
[v] BJA Education, Volume 16, Issue 4, Chemotherapy-induced peripheral neuropathic pain, Gupta et al. September 2015

[vi] Journal of Clinical Oncology, Quality of Life During Treatment With Chemohormonal Therapy: Analysis of E3805 Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer, Morgans et al. April 2018

The Department of Health and Social Care submitted a no comment response.

Janssen response to the Appraisal Consultation Document (ACD) for abiraterone in newly diagnosed high-risk metastatic prostate cancer

[ID945]

Overview

Janssen welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee detailed in the appraisal consultation document (ACD). We are extremely disappointed the Appraisal Committee's preliminary decision is that abiraterone acetate with prednisone/prednisolone is not recommended for patients with newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT). We are however committed to working with NICE to address the Committee's key concerns outlined in the ACD.

The key points covered in response to the ACD are as follows:

Issue 1: Clarifying the decision problem and place of abiraterone in the treatment pathway

Janssen wish to clarify that the use of abiraterone as first-line treatment for adults newly diagnosed with high-risk metastatic hormone sensitive prostate cancer (mHSPC) is not intended to replace use of abiraterone or enzalutamide for the treatment of adults with metastatic castrate resistant prostate cancer (mCRPC) post-ADT as previously recommended by NICE (TA387 and TA377). Janssen believe it is essential that the decision problem be further clarified because debate regarding whether men receive 'abiraterone now' (when mHSPC) or 'abiraterone later' (when mCRPC) is only relevant to the small cohort of this indication. The treatment pathway for the majority of men with metastatic prostate cancer in the UK remains unchanged.

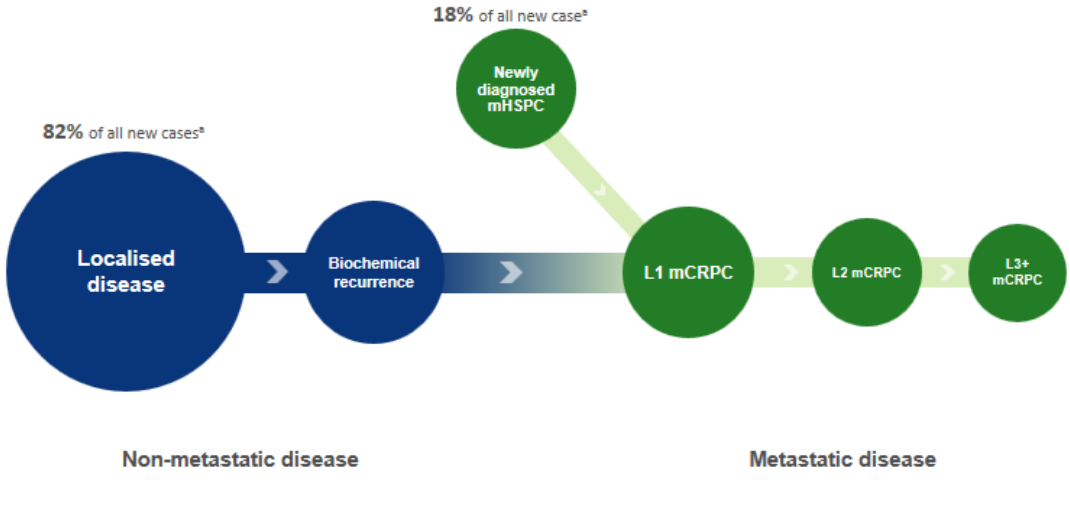
Prostate cancer can be diagnosed at localised or metastatic stage. Since most new cases of prostate cancer (82%) in the UK are for men with localised disease, the treatment pathway of that cohort will not change; those who eventually progress to mCRPC would still be entitled to abiraterone or enzalutamide as per NICE guidance (TA327 and TA377). As such, for the majority, 'abiraterone later' is always the answer.

Men newly diagnosed with high-risk mHSPC and relevant to this decision problem represent a small patient cohort accounting for approximately 8% of new prostate cancer cases (i.e. 3,500) each year in England. For these men, who have received the most severe type of diagnosis at first presentation of prostate cancer, 'abiraterone now or later' is a valid question. As highlighted by the Cancer Drugs Fund Lead (ACD Section 3.2, page 5), half of these men are unlikely to be fit for chemotherapy and thus 'abiraterone now' should always be the answer.

Consequently, when discussing the metastatic prostate cancer pathway, it is essential to recognise that this indication would not displace abiraterone or enzalutamide in mCRPC (TA327 and TA377) for most of the men with metastatic prostate cancer in the UK. This indication only moves the use of abiraterone earlier to benefit the small cohort who would be eligible when first diagnosed with high-risk metastatic disease. Please see pathway visualisation in Table 1 for further clarification.

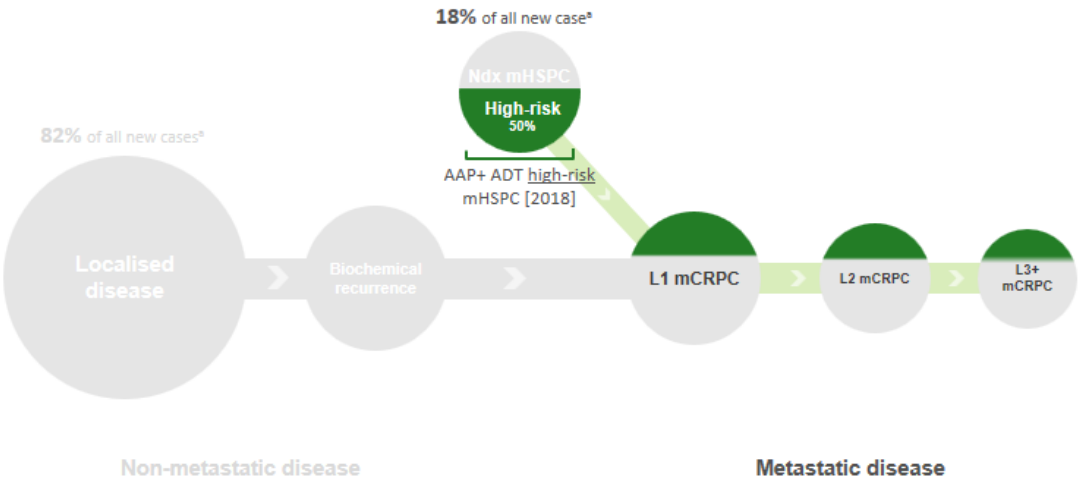
Table 1: Clarification on the impact of introducing abiraterone earlier in the pathway for men specifically newly diagnosed with high-risk mHSPC.

Recall the simplistic pathway presented in Figure 1; Form A, page 6 [ID945]

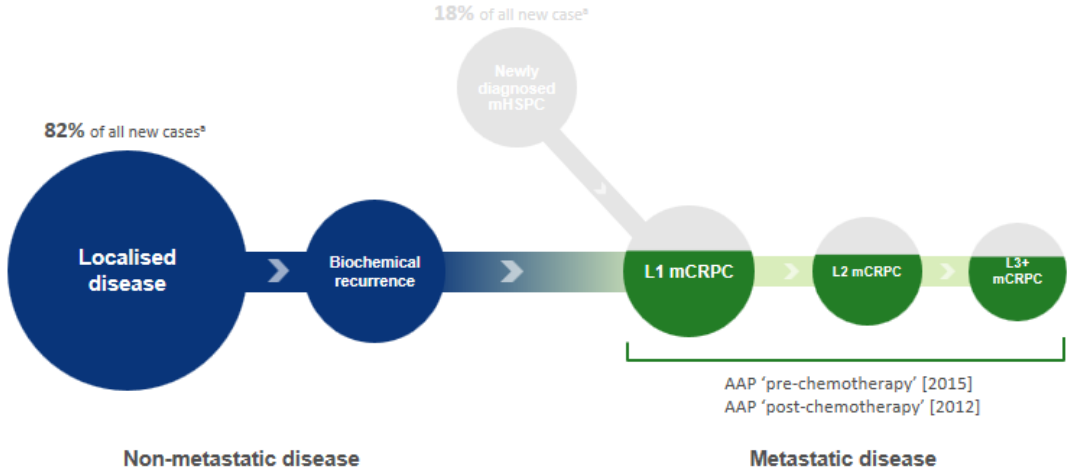


ACD Response: Abiraterone for treating newly diagnosed high-risk metastatic hormone sensitive prostate cancer [ID945]

The pathway for the specific cohort in consideration in this appraisal; men who receive AAP + ADT for newly diagnosed high-risk mHSPC:



This does not impact the treatment pathway for the majority of men with metastatic prostate cancer in the UK who were originally diagnosed with locaslised disease, since progressed to mCRPC and are eligble for abiraterone:



Of note: circles are not drawn/coloured to scale

[a] Cancer research UK: Prostate Cancer Statistics[1]

Key: AAP, abiraterone acetate prednisone/prednisolone; ADT, androgen deprivation therapy; mCRPC, metastatic castrate resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; NDx, newly diagnosed

Issue 2: Addressing the comparison of AAP + ADT vs. ADT alone

Janssen are concerned there has been very little consideration of the comparison of AAP + ADT vs. ADT alone in the Committee's preliminary decision, and we believe this is unreasonable in light of the evidence submitted to NICE. Both ADT alone and docetaxel + ADT are relevant comparators in this setting, yet significantly greater emphasis has been placed on the comparison with docetaxel + ADT, conveying an unbalanced assessment of the evidence.

The ACD recognises:

> *A patient expert explained that there is an unmet need for an alternative treatment option for people who cannot have docetaxel plus ADT. [Section 3.2]*

This statement signposts the high unmet need for an alternative life-extending therapy for men who cannot receive chemotherapy in the NHS. For these men, ADT alone is currently the only treatment option. Without AAP + ADT in mHSPC, men who cannot receive chemotherapy will remain sub-optimally treated, forcing them to wait for their cancer to progress before they can access a novel hormonal agent. Those men who do not wish to undertake chemotherapy will continue to face the difficult decision of whether to pursue docetaxel treatment regardless, adding to the psychological burden of this disease and its diagnosis.

The proportion of men with newly diagnosed high-risk mHSPC who cannot receive chemotherapy is substantial, as highlighted by the ACD:

> *The Cancer Drugs Fund's clinical lead noted that around 50% of people presenting with hormone-sensitive metastatic prostate cancer are not fit enough for docetaxel and have ADT alone. [Section 3.2]*

Real-world data on the usage of docetaxel + ADT indicates that, irrespective of its clinical benefit, only 40% of men actually receive chemotherapy for newly diagnosed mHSPC, indicating 60% remain on ADT alone[2]. Janssen also surveyed the broader clinical community to ascertain a balanced opinion on prescribing patterns in the NHS. Janssen conducted a survey with 27 clinical experts across the UK to better understand the current split between docetaxel + ADT and ADT alone in men newly diagnosed with high-risk mHSPC. Whilst the UK Clinical Survey (Appendix A) showed varied use of docetaxel + ADT across the UK, the most common response (n=12) was that 50% receive docetaxel + ADT and 50% remain on ADT alone. An average of 52.5% of patients receive docetaxel + ADT when accounting for all 27 responses. It must be recognised that estimates provided by respondents in this survey are likely to be based on the total number of patients referred to oncology, as all respondents were practising oncologists. Some patients, who are clearly not fit for chemotherapy, may not be referred to an oncologist for further treatment, and will instead continue to be managed by a urologist with ADT alone. This may result in an under-estimation of the true proportion of newly diagnosed mHSPC patients who do not receive docetaxel + ADT for their disease.

Whilst most men initially respond to ADT when given alone in mHSPC, the vast majority develop progressive disease within one to two years;[3] progression to mCRPC is associated with further deterioration in health-related quality of life (HRQL), increased healthcare costs and reduced survival. Compared to ADT alone, AAP + ADT has shown unequivocal benefits in significantly delaying disease progression, improving (and sustaining) HRQL and extending survival, in men with newly diagnosed high-risk mHSPC. The ACD recognises this, stating:

The clinical trial results show that, compared with ADT alone, AAP + ADT increases the time until disease progression and overall length of time people live. [Section 1.2]

And,

Abiraterone plus ADT statistically significantly improved both progression-free and overall survival compared with ADT alone in LATITUDE and in patients with metastatic disease in STAMPEDE, and the size of improvement was similar in the 2 trials. [Section 3.7]

Without question, the Committee have concluded that AAP + ADT improved both progression-free and overall survival compared with ADT alone, however, there is very little consideration given to the cost-effectiveness of AAP + ADT in this setting. Results presented below show AAP + ADT is highly cost-effective vs. ADT alone yet this preliminary decision means that men who cannot receive chemotherapy in England will remain sub-optimally treated in the NHS.

Issue 3: Addressing the economic modelling of AAP + ADT vs. ADT alone

Janssen acknowledge comments in the ERG Report and the ACD regarding the clinical data informing the comparison of AAP + ADT vs. ADT alone, as well as preference for certain model assumptions which were not incorporated into the original base case analysis. In this section, we wish to address:

1. Appropriateness of the clinical evidence base
2. Cost-effectiveness of AAP + ADT vs. ADT alone

1. Appropriateness of the clinical evidence base

LATITUDE is the pivotal Phase III randomised controlled trial (RCT) which was conducted in the license-indicated population to specifically investigate AAP + ADT vs. ADT alone in the newly diagnosed, high-risk mHSPC patient population. As such, LATITUDE should be used as the primary source of clinical data for informing the cost-effectiveness of AAP + ADT vs. ADT alone.

As highlighted in the submission [Section B.2.6], Janssen recognises that some subsequent therapies in LATITUDE would not have been permitted in the UK as only one novel hormonal agent in the metastatic pathway is currently funded by NHS England. The non-permitted sequences are presented in Table 2 and show the small number of patients who received a treatment sequence that may not be allowed in the NHS (n=[redacted] in the AAP + ADT arm and n=[redacted] in the ADT alone arm). In order to respond to the Committee's concerns, Janssen conducted an Inverse Probability of Censoring Weighted (IPCW) analysis which adjusted for these sequences to explore their impact on overall survival. These data were not presented in the submission and the caveat around uncertainty still applies; however, importantly, results showed an improved HR of [redacted] [95% CI: [redacted]].

Table 2: Sequences in LATITUDE not permitted in the UK

1st treatment (at randomisation)	2nd treatment (1st subsequent tx.)	3rd treatment (2nd subsequent tx.)	No. of patients
AAP+ADT	ENZ	n/a	[redacted]
AAP+ADT	AAP	ENZ	[redacted]
		Total	[redacted]

ADT alone	ENZ	AAP	[redacted]
ADT alone	AAP	ENZ	[redacted]
		Total	[redacted]

Janssen would like to address discussion within the ACD regarding the appropriateness of subsequent therapies in STAMPEDE:

> *STAMPEDE was a trial in patients from the UK and was unblinded. This meant that follow-on treatments in STAMPEDE reflected what people would have in clinical practice in the UK because the choice of next treatment depends on the first treatment had, unlike in the blinded LATITUDE trial. [Section 3.5]*

And,

> *The committee concluded that the estimates of survival from STAMPEDE after a patient needed a next treatment were likely to be more relevant to clinical practice in England than those from LATITUDE. [Section 3.5]*

Janssen are concerned that such statements do not recognise that STAMPEDE had a similar issue regarding subsequent therapies. Despite the study being unblinded and conducted in the UK, patients in STAMPEDE [Arm G] also received multiple novel agents in their pathway which would not be permitted by the NHS in normal practice. Whilst data on subsequent therapies specific to the metastatic cohort have not been published, of all those who had progressed in Arm G of STAMPEDE, 10% (25/248) received enzalutamide after AAP + ADT, and 3% (8/248) received abiraterone again.[4] In LATITUDE, these proportions were similarly 10% (30/314) and 3% (10/314), respectively.[5] Whilst the Committee suggest a preference for using data from STAMPEDE, specific data on subsequent therapies are not reported in sufficient detail to inform economic modelling; data (as currently reported) are not distinguished according to line of therapy in mCRPC,[4] or are only reported as time-to-event analysis for a sample few therapies.[6, 7]

In this context, Janssen wish to highlight that patterns of subsequent therapies are not dissimilar between LATITUDE[5] and STAMPEDE[4] (in fact, some proportions appear to be identical as presented above), and the results of overall survival for AAP+ADT vs. ADT alone were also very similar between the two trials (i.e. HR=0.62 [0.51-0.76] and HR=0.61 [0.49-0.75], respectively). This supports the generalisability of the LATITUDE survival estimates to the UK population and reaffirms the clinical benefit of AAP + ADT over ADT alone.

2. Cost-effectiveness of AAP + ADT vs. ADT alone

Janssen maintain the relevance of LATITUDE as the primary source of clinical data for informing the cost-effectiveness of AAP + ADT vs. ADT alone, given the similarities between LATITUDE and STAMPEDE. Janssen also recognise that the treatment of men with newly diagnosed high-risk mHSPC is a sequential pathway and thus appropriate to model this way. Given the limited evidence available to inform the sequence of therapies received after a patient has progressed to mCRPC after first-line mHSPC, Janssen held an advisory board with five practising UK clinicians in prostate cancer to ascertain the most probable sequences which could be captured in the model. These proportions were subsequently validated on two separate occasions and Janssen are concerned there has been no recognition of this advisory board as a valid data source in the ACD.

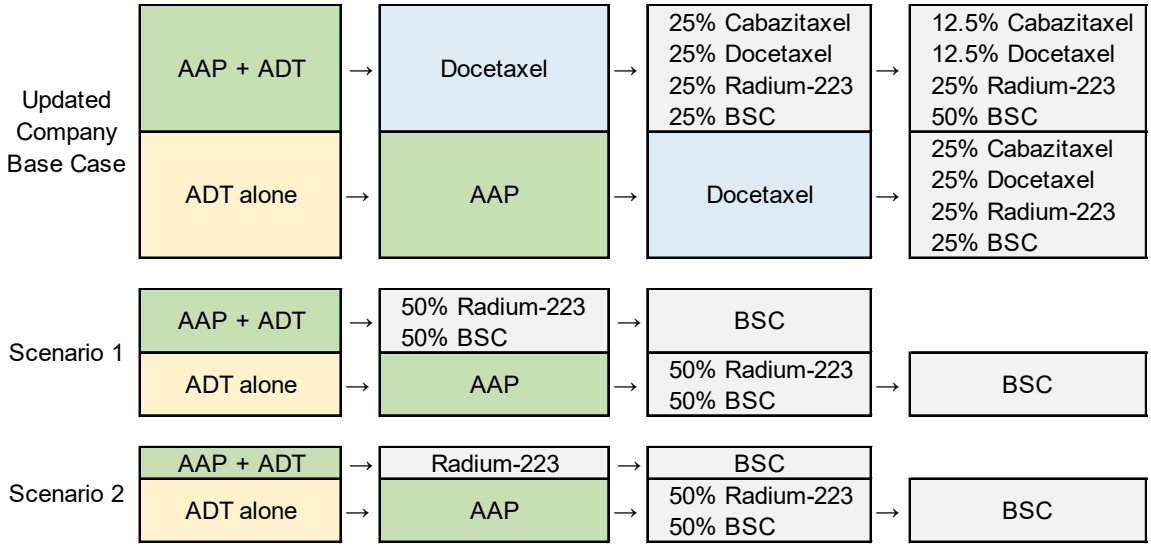
Nevertheless, Janssen do acknowledge the ERG and Committee's preference for certain model assumptions which were not incorporated into the original base case analysis. Although we maintain that the assumptions made in the original base case analysis were robust, several ERG and Committee preferences have now been incorporated into an updated base case to address some of the concerns raised and better reflect the views of the Committee in order to aid decision making.

To illustrate, the updated company base case has adopted the sequence shown in Figure 1, and two additional scenarios were also explored to capture the sequence of patients who would never receive a taxane chemotherapy. The key elements accounted for in the updated base case sequence for AAP + ADT and ADT alone and are detailed in Table 3.

Table 3: Key elements accounted for in the updated base case treatment sequences for AAP + ADT and ADT alone

AAP + ADT	ADT alone
Docetaxel is considered the most likely treatment option for 1L mCRPC after AAP + ADT in mHSPC.	Patients who receive ADT alone in mHSPC do so because they cannot receive, or do not want, chemotherapy. As such, a novel hormonal agent is the likely treatment option for 1L mCRPC following ADT alone.
No second novel hormonal agent is used.	Abiraterone and enzalutamide are assumed to be equivalent therefore enzalutamide is not explicitly modelled in the sequence.
Subsequent docetaxel, cabazitaxel, radium-223 and BSC are included as all could be received in NHS clinical practice. Therefore, an equal proportion of each was applied in 2L mCRPC.	Docetaxel is considered the most likely treatment option after AAP in 2L mCRPC
Subsequent docetaxel, cabazitaxel, radium-223 and BSC are included as all could be received in NHS clinical practice. Clinically plausible proportions of each were applied in 3L mCRPC.	Subsequent docetaxel, cabazitaxel, radium-223 and BSC are included as all could be received in NHS clinical practice. Therefore, equal proportions of each were applied in 3L mCRPC.
Assumptions maintain a clinically plausible sequence as permitted by NHS England.	Assumptions maintain a clinically plausible sequence as permitted by NHS England.

Figure 1: Additional treatment sequences explored: AAP + ADT vs. ADT alone



The model assumptions that have been amended for in the comparison of AAP + ADT vs. ADT alone are detailed in Table 4. The impact that each of these have on the ICER is also shown, as well as the cumulative impact of adopting these preferred assumptions.

Table 4: Updates to the CE model based on ERG/ACD feedback: AAP + ADT vs. ADT alone [with confidential CAA]

Assumption	Comments	AAP+ADT vs. ADT	
Original base case		**£17,418**	**Impact**
1L mCRPC Abiraterone CAA	Correcting the application of the CAA [redacted]. This is done by changing cell B101 on the ERG sheet to "TRUE". Full details of the model amendment are reported in the Proforma document sent by Janssen following the ERG report.	£18,233	£815
Tunnel state in mCRPC	Correcting the minor error identified in the mCRPC tunnel states in the sheets.	£17,212	-£206
Planned MRU for mCRPC	Correcting formulae for planned MRU costs for enzalutamide and radium-223 in mCRPC to reference correct model cell.	£17,310	-£108
Frequency of bone scans	The frequency of bone scans as scheduled MRU has been equalised in the model as per the ERG/Committee preference.	£17,244	-£174
Utilities from the full regression analysis of LATITUDE	The full set of utility coefficients for AE/SREs that were derived from the regression analysis of LATITUDE have now been used as per the ERG/Committee preference.	£17,393	-£25
	The utility regression model that produced a pooled SRE coefficient which was equal across treatment arms has now been used as per the ERG/Committee preference.	£17,012	-£406
BSC in mCRPC	The mCRPC treatment percentages have been amended so that the proportions receiving BSC are not differentiated between the arms as per the ERG/Committee preference.	£17,115	-£303
mCRPC cost calculations for fixed duration therapies	Concerns were raised regarding the estimation of treatment costs in the mCRPC phase of the model. There are limitations in the way that fixed duration treatment costs (docetaxel, radium-223 and cabazitaxel) can be calculated due to the cohort structure of the model, which limits the ability of the model to track individual patients over time and thus calculate treatment costs with complete precision. In attempt to address this concern, an alternative method for estimating these costs has been applied in the updated base case analysis. The way in which continuous therapies (i.e. abiraterone, enzalutamide, BSC) are costed remains unchanged, however the costs of fixed duration therapies are calculated in a different manner. Due to the difficulties in tracking patients over time, the costs of these therapies are applied as a one-off cost at the point at which patients are assumed to start receiving treatment in mCRPC. Whilst treatment costs are applied in a lump-sum rather than over time, this method addresses the ERGs concerns regarding the use of discontinuation curves to estimate the costs of fixed duration treatments. This change is implemented by changing cell B99 on the ERG sheet to "TRUE".	£14,513	-£2,905
Subsequent therapies	Subsequent therapies were set to proportions shown in Figure 1 to capture ERG/Committee feedback and preference whilst maintaining clinically plausible sequencing.	£14,078	-£3,340
Updated company base case		**£17,160**	-£258

Key: BSC, best supportive care; CAA, commercial access arrangement; mCRPC, metastatic castrate resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer MRU, medical resource use.
Of note, these ICERs include list prices for downstream therapies which are known to have patient access schemes (PASs).

Results of the updated base case for AAP + ADT vs. ADT alone, applying the confidential CAA and list prices for downstream therapies which are known to have patient access schemes (PASs), are presented in Table 5. Results show that, under the confidential CAA, AAP + ADT is a highly cost-effective use of NHS resources in men with newly diagnosed high-risk mHSPC. The incremental cost of using AAP (+ ADT) earlier in the treatment pathway is offset by its significant benefits in delaying disease progression, delaying chemotherapy, improving (and sustaining) HRQL and, ultimately, extending survival compared to ADT alone. Indeed, all ICERs related to the sensitivity analysis of AAP + ADT vs. ADT alone fall within the cost-effective threshold for the NHS. These results recognise the value of treating men with newly diagnosed high-risk mHSPC with a novel agent as early as possible.

Table 5: Updated base case: AAP + ADT vs. ADT alone

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	3.52	2.23	£18,146	1.52	1.06	£17,160
AAP + ADT	[redacted]	5.04	3.29				

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

The series of scenario analyses conducted on the updated base case all consistently demonstrate that AAP + ADT remains a highly cost-effective use of NHS resources compared to ADT alone, irrespective of the model assumptions varied.

Table 6: Updated scenario analyses: AAP + ADT vs. ADT alone

Model assumption	Scenario	ICER	Impact
Updated Base Case		**£17,160**	
Definition of progression	TTST used as an alternative definition of progression	£12,708	-£4,452
LATITUDE scenario	Survival estimates and subsequent therapy market shares estimated from LATITUDE	£22,245	£5,084
Time horizon	15 years	£17,334	£173
	10 years	£18,346	£1,186
	5 years	£28,740	£11,580
AA utility increment	Applied until death	£16,234	-£927
	No increment applied	£16,954	-£206
AE disutilities	Using literature values alone	£17,151	-£9
	Set to zero	£17,166	£6
mCRPC utilities	Assumed constant through mCRPC	£17,384	£224
AA increment in mCRPC	AA increment from TA387 removed during mCRPC	£16,907	-£253
Buchers NMA for subsequent therapy	Different HR are applied for each subsequent therapy based on Buchers NMA	£17,220	£60
Vial wastage	Set to zero	£17,114	-£46
Docetaxel cost source	MIMS price is assumed	£20,097	£2,937
Subsequent therapies	Original subsequent therapies assumptions	£15,075	-£2,085

Model assumption	Scenario	ICER	Impact
	Never receive Taxane chemotherapy - scenario 1	£20,558	£3,398
	Never receive Taxane chemotherapy - scenario 2	£25,148	£7,988

Key: mCRPC, metastatic castrate resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; MIMS, Monthly Index of Medical Specialities; MRU, medical resource use; NMA, network meta-analysis; TTST, time to subsequent treatment
Of note, these ICERs include list prices for downstream therapies which are known to have patient access schemes (PASs).

Issue 4: Clarifying the level of access Janssen have to STAMPEDE data

There are multiple statements within the ACD that convey the Committee's preference for receiving clinical and quality of life data from STAMPEDE to inform the comparison of AAP + ADT vs. docetaxel + ADT; however, Janssen do not currently have access to these data. Janssen are concerned these statements imply we have actively chosen not to utilise these data in our submission which is not the case. The ACD states:

> *The committee would have preferred data from patients with high-risk metastatic disease from STAMPEDE to have been included in the modelling. [Section 3.10]*

And,

> *The committee further noted that the company could have used trial-based EQ-5D results for docetaxel plus ADT in its model because STAMPEDE collected these for the trial arms assessing abiraterone plus ADT, docetaxel plus ADT and ADT alone. [Section 3.12]*

Janssen do not have access to the individual patient data (IPD), nor any other unpublished data, from STAMPEDE. Whilst Janssen supported the STAMPEDE trial with the provision of abiraterone acetate free-of-charge for the entire duration in which the compound has been investigated, and additionally financially contributed to sponsorship of the trial, Janssen do not own the STAMPEDE data. Furthermore, patients enrolled in the STAMPEDE trial have not given consent for the manufacturer (i.e. Janssen) to access their data which has also restricted Janssen access to IPD.

Finally, it is important to highlight that the key area of uncertainty lies with the comparative effectiveness of AAP + ADT [Arm G] and docetaxel + ADT [Arm C]. Since Janssen was not the manufacturer providing drug and additional financial support to Arm C, there are additional restrictions for Janssen to access the IPD related to patients who have received docetaxel + ADT and, to date, we have had to be reliant on published analyses.

As such, strict data governance does not permit Janssen access to IPD from STAMPEDE to conduct additional analyses which would address the Committee's request for the use of direct evidence for AAP + ADT vs. docetaxel + ADT, specifically in those with high-risk metastatic disease.

Of note, the identification and efficacy analysis of high-risk vs. low-risk (or similarly, high-volume vs. low-volume) patients from STAMPEDE has not yet been completed or published.

[redacted]

Issue 5: Addressing the comparison of AAP + ADT vs. docetaxel + ADT

Janssen wish to highlight that conclusive statements in the ACD regarding the generalisability of STAMPEDE data to the licensed population are currently unsubstantiated by evidence. The ACD also contains conflicting statements regarding the comparative effectiveness of AAP + ADT vs. docetaxel + ADT and Janssen do not believe the Committee's preliminary decision has accounted for the full evidence base. In this section we wish to address:

1. Generalisability of STAMPEDE data to the licensed indication
2. Appropriateness of utilising NMA

1. Generalisability of STAMPEDE data to the licensed indication

Janssen acknowledge there is a degree of uncertainty around the relative difference in overall survival for patients treated with AAP + ADT vs. docetaxel + ADT and therefore believe it is essential to consider all available evidence which is comparable to the licensed indication. Janssen do recognise the prominence of STAMPEDE, its unique design and relevance to the UK; however, we also wish to re-emphasise that the metastatic patient cohort in STAMPEDE is broader than the licensed indication for AAP + ADT. The ACD states:

> *The clinical experts explained that results for the licensed population (that is, the subgroup of patients with high-risk disease) had been collected, but not yet published. Two clinical experts, who were also investigators in STAMPEDE, explained that there was no reason to believe that there was any subgroup of people for whom abiraterone was more or less effective; abiraterone appeared similarly effective in localised, metastatic and high-risk hormone-sensitive prostate cancer. [Section 3.4]*

Therefore,

> *The committee agreed that, although STAMPEDE assessed treatments in a broader population than the population covered by the marketing authorisation for abiraterone, data from STAMPEDE are broadly generalisable to the population for whom abiraterone plus ADT is being appraised. [Section 3.4]*

To Janssen's knowledge, the identification and efficacy analysis of high-risk vs. low-risk (or similarly, high-volume vs. low-volume) patients of STAMPEDE [Arm G] has not yet been fully completed; [redacted].

Under these conditions, Janssen were unable to definitively state that the metastatic population from STAMPEDE is generalisable to the licensed indication for AAP + ADT in newly diagnosed high-risk mHSPC. For this reason, we chose to focus the clinical base case of AAP + ADT vs. docetaxel + ADT on the network meta-analysis (NMA) which utilised LATITUDE and the subgroups of patients with newly diagnosed high-volume disease from the CHAARTED and GETUG-AFU 15 studies as these were most similar to the LATITUDE population. The NMA utilised in the original base case derived a HR of 0.92 [0.69-1.23]; Bayesian probability in favour of AAP + ADT of 71.8%. Recognising the importance of STAMPEDE, these data were included in the NMA as a key scenario analysis and indeed results were very similar (HR=0.91 [0.76-1.09]; Bayesian probability 84.5% in favour of AAP + ADT).

2. Appropriateness of utilising NMA

In discussing the STAMPEDE data, the ACD states:

> *[The committee] preferred direct evidence from patients with high-risk metastatic disease from STAMPEDE for the comparison between abiraterone plus ADT with docetaxel plus ADT to indirect evidence from the company's network meta-analysis. [Section 3.4]*

This statement is misleading because this analysis was conducted in all metastatic patients, not specifically for the high-risk subgroup in which abiraterone is licensed; as mentioned above, the high-risk analysis has not yet been completed. Furthermore, Janssen do not believe it appropriate (nor consistent with NICE precedent) to solely focus on a single subgroup analysis of 342 metastatic patients from STAMPEDE which was not powered to detect any differences in overall survival between the two arms.

It should also be noted that the *post-hoc* subgroup analysis of AAP + ADT vs. docetaxel + ADT from STAMPEDE derived a HR of 1.13 (0.77-1.66) with a confidence interval indicating sizable uncertainty and lacking statistical significance (p=0.53). This result does not draw a consistent conclusion with the two larger cohort analyses of STAMPEDE that were powered to detect differences in overall survival. Indeed, the reported treatment effect on survival for AAP + ADT vs. ADT alone in metastatic patients from STAMPEDE (HR=0.61 [0.49-0.75])[4] was larger than the previously-reported treatment effect on survival for docetaxel + ADT vs. ADT alone in metastatic patients (HR=0.76 [0.62-0.92).[7] This suggests the direct analysis may not be reliable.

Given the uncertainty in the direct analysis of patients contemporaneously randomised in STAMPEDE to AAP + ADT or docetaxel + ADT, Janssen believe it is most appropriate to consider the wider evidence base to assess the comparative effectiveness of AAP + ADT vs. docetaxel + ADT. The ACD in fact concurs with Janssen in this regard as it subsequently states:

> *The committee concluded that the direct evidence could be further supported by a network meta-analysis including evidence from patients with high-risk metastatic disease from STAMPEDE, CHAARTED, GETUG-AFU 15 and LATITUDE. This would combine evidence from a larger number of people and potentially decrease the uncertainty about the relative effectiveness of abiraterone. [Section 3.6]*

Janssen wish to highlight that an NMA of this composition was presented in the submission and used in a scenario analysis although it has not been recognised in the ACD. The value of NMA is recognised by NICE DSU TSD 4, and of particular importance when inconsistency is detected in the clinical evidence base.[8]

Assuming the entire metastatic group from STAMPEDE is generalisable to the licensed indication, as previously inferred, and the Committee agrees that the direct analysis could be supported by an NMA, Janssen must emphasise the relevance of results already presented in the original submission and highlight these results is unlikely to change with additional data for high-risk patients. The result of the NMA which includes STAMPEDE are presented again in Table 2 and demonstrate a positive trend towards AAP + ADT being the better treatment compared to docetaxel + ADT in terms of overall survival, with a HR=0.91 (CrI: 0.76-1.09) and Bayesian probability of 84.5%.

In order to address the Committee's preference for STAMPEDE data, Janssen has also conducted another NMA using only STAMPEDE data from the three relevant published

analyses. The result of this analysis, also presented in Table 2, show a consistent HR=0.91 (CrI: 0.72-1.15) and thus derives the same conclusion in favour of AAP + ADT vs. docetaxel + ADT with a Bayesian probability of 79.2%.

These results could be explained by the size of the trial populations included in the network, and the power of each analysis. Since the comparison of AAP + ADT vs. ADT alone (HR=0.61 [0.49-0.75]) included 1,002 metastatic patients and the comparison of docetaxel + ADT vs. ADT alone (HR=0.76 [0.62-0.92] included 1,086 metastatic patients, these are given greater weight in the network than the unpowered analysis of AAP + ADT vs. docetaxel + ADT (HR=1.13 [0.77-1.66]) which only included 342 metastatic patients. Two alternative, independent NMAs have also been published investigating the relative effectiveness of ADT alone, AAP + ADT and docetaxel + ADT in this setting, both of which have drawn similar conclusions:

- The Systemic Treatment Options for Cancer of the Prostate (STOPCAP) NMA of aggregate data aimed to establish the optimal treatment from all available studies of ADT in combination with AAP, docetaxel or celecoxib.[9] The results showed that AAP + ADT was most likely to be the optimal treatment with regards to overall survival (94% probability), with docetaxel + ADT second best (35% probability).[9] In addition, the results showed that AAP + ADT was most likely to be optimal for failure-free survival (FFS) (100% probability), with docetaxel + ADT second best; however, results for FFS should be interpreted with caution due to variation in the definitions across included trials.[9]
- The NMA by Wallis et al. further supported these results, concluding that, while there was no statistically significant difference between AAP + ADT and docetaxel + ADT for overall survival based on Frequentist NMA, Bayesian analysis showed a high likelihood (89% probability) that AAP + ADT was the preferred approach for patients with newly diagnosed mHSPC.[10]

It is important to recognise that separate research groups have conducted independent analyses and reached similar conclusions regarding the difference in overall survival between AAP + ADT and docetaxel + ADT. Considering the trend in a series of published analyses adds greater weight to considering just one in isolation. It should also be noted that the authors of Sydes et al (2018)[6] signposted the importance of NMA and the necessary next step for taking all published data from STAMPEDE, alongside all other data from RCTs reported in metastatic prostate cancer, to derive an NMA which would enable an assessment of potential ranking of effective therapies.[6]

The NMA on “PFS-like” endpoints that Janssen have conducted is also presented in Table 2 for both the wider evidence base as well as an NMA based solely on STAMPEDE which utilises FFS only. These results show treatment with AAP + ADT is highly likely to be the better treatment compared to docetaxel + ADT in terms of delaying disease progression (HR=[redacted] [redacted] and HR=0.53 [0.44-0.93]), with Bayesian probability [redacted]% and 100%, respectively.

Table 7: Network-Meta Analysis

	AAP+ADT vs. ADT alone		ADT alone vs. dox+ADT			AAP+ADT vs. dox+ADT	NMA	
	LATITUDE	STAMPEDE	CHAARTED	GETUG-AFU 15	STAMPEDE	STAMPEDE	AAP + ADT vs. docetaxel + ADT	
	ITT	Metastatic subgroup	NDx HV subgroup	NDx HV subgroup	Metastatic subgroup	Metastatic subgroup	HR 95% CrI	P_{AA-Doc}
OS	0.62	0.61	0.63	0.78	0.76	1.13	0.91	84.5%
95% CI	0.51-0.76	0.49-0.75	0.49-0.81	0.54-1.12	0.62-0.92	0.77-1.66	0.76-1.09	
STAMPEDE only								
OS		0.61			0.76	1.13	0.91	79.2%
95% CI		0.49-0.75			0.62-0.92	0.77-1.66	0.72-1.15	
PFS-like[a] outcomes	0.47	0.31	0.58[b]	0.61[b]	0.61	0.56	[redacted]	[redacted]%
95% CI	0.39-0.55	0.26-0.37	0.47-0.71	0.44-0.83	0.53-0.71	0.42–0.75	[redacted]	
STAMPEDE only								
FFS		0.31			0.61	0.56	0.53	100%
95% CI		0.26-0.37			0.53-0.71	0.42–0.75	0.44-0.63	

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; dox, docetaxel; FFS, failure free survival; HR, hazard ratio; HV, high-volume; ITT, intent-to-treat; M1, metastatic disease; NDx, newly diagnosed; OS, overall survival; rPFS, radiographic progression-free survival; SA, sensitivity analysis.

Notes: $PA_{A>Doc}$, Bayesian pairwise probability for ADT+AAP being more effective compared with ADT+DOC; [a], LATITUDE + GETUG-AFU 15=rPFS, CHAARTED=Time to CRPC, STAMEPDE=FFS, [b] included prior treated

Issue 6: Addressing discussion around the subsequent therapies and post-progression survival

There are multiple statements in the ACD that suggest AAP + ADT and docetaxel + ADT have equal survival benefit, despite the progression-free survival benefit reported with AAP + ADT. Janssen are concerned the rationale for such claims are unsubstantiated by clinical evidence. In this section we wish to address:

1. Evidence for post-progression survival
2. Relevance of docetaxel re-challenge

1. Evidence for post-progression survival

As the Committee have focused on the unpowered analysis of AAP + ADT vs. docetaxel + ADT from STAMPEDE, the ACD suggests there is no difference in survival benefit between AAP + ADT and docetaxel + ADT, despite the progression-free survival benefit with AAP + ADT. On several occasions the ACD suggests that men treated with docetaxel + ADT in mHSPC have longer post-progression survival compared to those treated with AAP + ADT because of the number of treatment options available to them in mCRPC. The ACD states:

> *Two of the clinical experts explained that the reason for a progression-free survival benefit but lack of overall survival benefit with abiraterone plus ADT compared with docetaxel plus ADT in STAMPEDE was that patients may have had fewer treatment options after abiraterone plus ADT than after ADT alone or docetaxel plus ADT. The clinical experts involved in STAMPEDE explained that post-progression survival was reduced after abiraterone plus ADT compared with after ADT alone in this trial. [Section 3.9]*

And,

> *The committee concluded that the first-choice treatment option for hormone-sensitive metastatic prostate cancer affects the follow-on treatments a person may have, and that having abiraterone plus ADT results in fewer follow-on treatment options than having ADT alone or docetaxel plus ADT. [Section 3.3]*

Janssen are concerned these claims are unsubstantiated by clinical evidence. It should be noted that neither post-progression survival or 'PFS2' were included as pre-specified analyses within the STAMPEDE protocol. Furthermore, follow-up (FU) of patients in that study has been of insufficient length so far to make definitive statements around the sequence of treatment in mCRPC or the length of post-progression survival. The length of follow-up for patients who received docetaxel + ADT in STAMPEDE [Arm C] has been much longer (median FU=43 months) than for those who received AAP + ADT [Arm G] (median FU=40 months) as Arm C finished recruiting earlier. This could potentially result in additional bias in results.

2. Relevance of docetaxel re-challenge

The ACD states the reason the Committee believe patients have fewer treatment options after AAP + ADT is solely due to the use of docetaxel re-challenge after docetaxel + ADT. The ACD highlights:

The clinical experts explained that people who have previously had docetaxel as first-line treatment can be given docetaxel again (for up to 10 cycles) because the benefit of docetaxel is not exhausted when used with ADT for only 6 cycles. [Section 3.3]

To our knowledge, there is no robust clinical evidence to suggest that docetaxel re-challenge has significant clinical benefit or would be widely used in the NHS following docetaxel + ADT in mHSPC. This was also recognised by NICE TA101[11] which specially states that "repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy."

Whilst the ACD states that STAMPEDE could be more reflective of what subsequent therapies men in the UK receive in clinical practice, only 14% (i.e. 44/315) received docetaxel re-challenge in mCRPC after docetaxel + ADT in mHSPC as part of STAMPEDE [Arm C].[7] That said, Janssen do acknowledge that no longer term follow-up of STAMPEDE has been published to inform whether this percentage has subsequently changed.

A follow-up analysis of GETUG-AFU 15 has, however, been published in which the effectiveness of docetaxel re-challenge after docetaxel + ADT in mHSPC has been discussed.[12] To our knowledge, this is the only published evidence discussing the clinical benefit of docetaxel re-challenge in the relevant sequence and setting. Data in the publication showed that docetaxel re-challenge, following progression to mCRPC after upfront docetaxel + ADT in mHSPC was of limited clinical benefit and only active in a small number of patients (irrespective of being used first- or second-line mCRPC).[12]

The authors go on to suggest that taxane re-challenge with cabazitaxel, instead of docetaxel, could be the preferred strategy for patients with mCRPC who were treated with upfront docetaxel + ADT in mHSPC.[12] Indeed, this was also the opinion reflected at the advisory board that Janssen held in preparation for submission and, as a result, we included taxane re-challenge with cabazitaxel in the economic modelling. Janssen sought advice from five practising UK clinicians at this meeting to inform the most likely sequence/proportions of subsequent therapies after treatment in mHSPC and docetaxel re-challenge was not prominent in discussions.

Janssen have also surveyed 27 clinical experts across the UK to ascertain whether docetaxel re-challenge is common practice in the NHS. Whilst some experts (n=5) suggested there is not enough data/experience of this yet in the UK, most of the respondents agreed that docetaxel re-challenge is uncommon. The most frequent reason provided for not re-challenging was the availability of other treatments for mCRPC (including abiraterone/enzalutamide and cabazitaxel) that were considered more appropriate at this stage of disease progression. Where numbers were provided, the proportion of patients who would be re-challenged was estimated to be between zero and <25% (n=12). Respondents further advised that docetaxel re-challenge would only ever be in patients who have had a very good response on it previously, and most likely only after other agents have been given first. Cabazitaxel was identified as preferred option for re-challenge with a taxane due to the lower risk of neuropathy seen with it (n=2). The UK Clinical Survey report has been provided in Appendix A to this response.

It is important to also highlight that if docetaxel re-challenge is relevant after docetaxel + ADT then it could also be relevant downstream at third-line mCRPC after AAP + ADT. As such, an equal number of follow-on treatments would be available after AAP + ADT and docetaxel + ADT in mHSPC. There is however scarce evidence for the clinical benefit of docetaxel re-challenge irrespective of its position in the pathway. As a result, Janssen do not believe there is a valid, or evidence-based, rationale for concluding patients have a much

shorter post-progression survival after AAP + ADT which would ultimately result in equal overall survival benefit with docetaxel + ADT.

Issue 7: Discussing the interpretation of HRQL data for docetaxel + ADT

Janssen are concerned that the ACD contains conflicting statements regarding the health-related quality of life (HRQL) of patients treated with docetaxel + ADT and such statements are unsubstantiated by any evidence.

1. Evidence for patients' HRQL on docetaxel
2. Factual inaccuracy regarding model utility decrements

1. Evidence for patients' HRQL on docetaxel + ADT

To date, no EQ-5D utility data associated with docetaxel + ADT in mHSPC have been published, however, the ACD states:

> *The committee further noted that the company could have used trial-based EQ-5D results for docetaxel plus ADT in its model because STAMPEDE collected these for the trial arms assessing abiraterone plus ADT, docetaxel plus ADT and ADT alone. [Section 3.12]*

And,

> *[The committee] concluded that it was preferable to use EQ-5D data from the subgroup of people from STAMPEDE with metastatic and high-risk hormone-sensitive prostate cancer to assess quality of life because comparable data were available for abiraterone plus ADT, docetaxel plus ADT and ADT alone. [Section 3.12]*

As highlighted above, Janssen have not yet been able to access these data. We understand that HRQL analyses have been conducted on the EQ-5D data collected in STAMPEDE by the University of York, however, the results of these analyses have not yet been published and are not accessible to Janssen.

As a result, Janssen consulted the HRQL data published from the CHAARTED study which showed patients' HRQL over the course of treatment on and after docetaxel in mHSPC. These data assessed the change in patients' prostate cancer-specific functional status (measured by the FACT-P) as well as their level of pain (measured by the Bone Pain Index, BPI) over the course of a year.[13] Results showed that patients' HRQL was significantly impacted while on-treatment with docetaxel and that patients did take a long time to recover from treatment (i.e. 12 months).[13] These data validate the rationale for including a utility decrement on-treatment with docetaxel in the model, as well as a smaller decrement in the off-treatment phase to capture the fact that patients are still recovering. Janssen believe that the ACD considerably downplays the relevance of these data by suggesting the impact of docetaxel on patients' quality of life is small, transient, and without long-lasting effect:

> *The clinical expert noted that, in CHAARTED (a trial of docetaxel plus ADT compared with ADT), quality of life slightly declined on docetaxel in the first 3 months but then returned to normal. [Section 3.13]*

Janssen wish to highlight that, in the ACD, discussion of patients' quality of life are currently unsubstantiated by evidence and appear to contradict earlier statements made in the report. We believe this may be due to a misinterpretation of the evidence base which has translated into misleading statements regarding HRQL. The ACD states:

> *The clinical experts explained that they did not consider it plausible that quality of life would be worse while having docetaxel plus ADT because any treatment that improves prostate cancer symptoms would improve quality of life. [Section 3.13]*

And,

The clinical experts involved in STAMPEDE stated that quality of life was improved on docetaxel plus ADT in that trial. [Section 3.13]

These statements are confusing and contradict previous statements made earlier in the ACD regarding adverse events on docetaxel. The ACD had stated previously:

The committee heard that some people prefer having abiraterone first, rather than docetaxel, because it has fewer adverse effects and is better tolerated. However, it also heard that some people choose to have docetaxel first because of its shorter treatment. [Section 3.2]

Whilst we fully agree with this assertion as it emphasises the importance of patient preference in this setting, Janssen are concerned the inconsistent statements within the ACD regarding the impact docetaxel has on patients' HRQL do not portray an appropriate assessment of the evidence. Indeed, the patient voice within the NICE submission from Prostate Cancer UK clearly highlights how impactful the prospect of chemotherapy is to patient's lives:

"It was such a relief not to have to have chemo. The side effects of chemo would have made it much tougher for me to continue to work effectively which I needed to do in order to get my business in order and in a position where it can function effectively without me."
[Prostate Cancer UK submission to NICE]

2. Factual inaccuracy regarding model utility decrements

Janssen wish to highlight a factual inaccuracy in discussion around the relevance of including disutilities for AEs as the ACD states:

The committee noted that although adverse effects were worse during treatment with docetaxel plus ADT than with abiraterone plus ADT or ADT alone, the effect of adverse effects on quality of life had been accounted for separately in the company model thereby potentially double counting the utility loss from adverse events. [Section 3.13]

Due to the application of the utility decrements for on- and off-docetaxel, Janssen chose not to apply the AE utility decrements in the docetaxel + ADT arm in order to avoid double-counting the utility loss. The above statement is therefore factually incorrect.

Issue 8: Addressing the economic modelling of AAP + ADT vs. docetaxel + ADT

Janssen are concerned that the Committee's rationale for disagreeing with the validity of the economic model stem from a series of assumptions that have been addressed in above sections and as such, are not supported by robust evidence, given the ACD states:

> *The committee stated that, because the company's model structure did not reflect the treatment pathway for metastatic hormone-sensitive prostate and gave implausible survival estimates. [Section 3.16]*

In this section we wish to address:

1. Modelled treatment pathway
2. Modelled survival estimates
3. Cost-effectiveness of AAP + ADT vs. docetaxel + ADT
4. Exploratory analysis of OS for AAP + ADT vs. docetaxel + ADT

1. Modelled treatment pathway

Janssen wish to highlight that the current model does account for different sequences that may be received in the metastatic prostate cancer pathway, through the application of a matrix of subsequent therapies based on their market shares. These percentages depict the differing likelihoods of alternative treatments in each health state, given the distributions applied in the previous health state. This was considered the best way of capturing sequential treatments within the structure of a Markov model. We believe it is essential we clarify this to show that the current model is fit-for-purpose. The ACD however states:

> *The committee disagreed with the company's assumptions on follow-on treatments because: it did not model a second treatment course with docetaxel after docetaxel plus ADT; and it did not reflect that people having abiraterone plus ADT for hormone-sensitive prostate cancer have fewer treatment options available for hormone-refractory prostate cancer. [Section 3.11]*

And,

> *The committee would have preferred to have seen analyses on the effect of different sequences and numbers of follow-on treatments to understand the relationship between progression-free survival and overall survival in high-risk metastatic hormone-sensitive prostate cancer. [Section 3.9]*

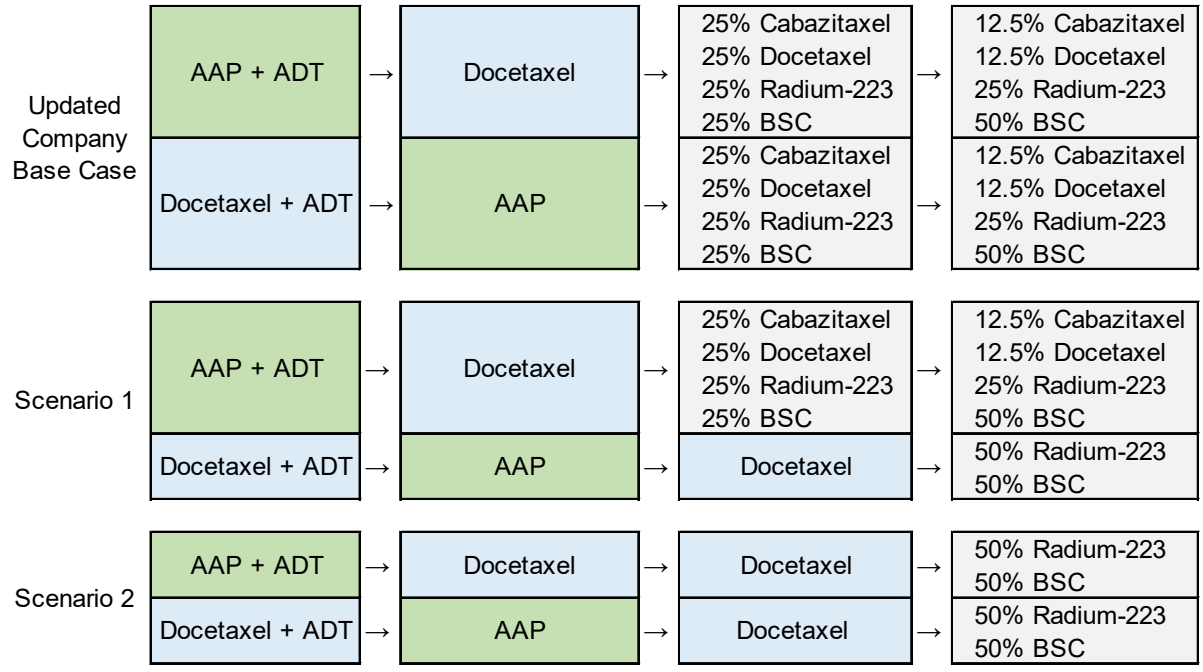
It is clear that the rationale for having fewer follow-on treatments after AAP + ADT is solely attributed to the use of docetaxel re-challenge after docetaxel + ADT. Given the expert clinical feedback attained from a sample of 27 practising clinical experts across the UK suggesting that docetaxel re-challenge is uncommon, Janssen maintain that the assumptions for subsequent therapies used in the original base case (i.e. utilising estimates attained from the advisory board and including cabazitaxel as a means of taxane re-challenge) were not inaccurate. Nevertheless, we acknowledge the Committee's preferences and, since the model is already suited to modelling different compositions of subsequent therapies, have presented scenario analyses in which a) docetaxel re-challenge is included after docetaxel + ADT and b) explicit sequences are explored. The sequence included as the updated company base case is illustrated in Figure 2 below, alongside two additional, clinically plausible scenario analyses that have been explored in Table 10. The key elements accounted for in the updated base case sequence for AAP + ADT and docetaxel + ADT are detailed in Table 8.

Of note, docetaxel re-challenge is now included following the Committee's preference but, as guided by the UK Clinical Survey, only after exposure to a novel agent and at a maximum of 25%. Cabazitaxel re-challenge is still included, as validated by the UK Clinical Survey with a maximum of 25%.

Table 8: Key elements accounted for in the updated base case treatment sequences for AAP + ADT and docetaxel + ADT

AAP + ADT	Docetaxel + ADT
Docetaxel is considered the most likely treatment option for 1L mCRPC after AAP + ADT in mHSPC.	A novel hormonal agent is the most likely treatment option for 1L mCRPC following ADT alone.
No second novel hormonal agent is used.	Abiraterone and enzalutamide are assumed to be equivalent therefore enzalutamide is not explicitly modelled in the sequence.
Subsequent docetaxel, cabazitaxel, radium-223 and BSC are included as all could be received in NHS clinical practice. Therefore, an equal proportion of each was applied in 2L mCRPC.	Subsequent docetaxel, cabazitaxel, radium-223 and BSC are included as all could be received in NHS clinical practice. Therefore, an equal proportion of each was applied in 2L mCRPC.
Subsequent docetaxel, cabazitaxel, radium-223 and BSC are included as all could be received in NHS clinical practice. Clinically plausible proportions of each were applied in 3L mCRPC.	Subsequent docetaxel, cabazitaxel, radium-223 and BSC are included as all could be received in NHS clinical practice. Clinically plausible proportions of each were applied in 3L mCRPC.
Assumptions maintain a clinically plausible sequence as permitted by NHS England.	Assumptions maintain a clinically plausible sequence as permitted by NHS England.

Figure 2: Additional treatment sequences explored: AAP + ADT vs. docetaxel + ADT



2. Modelled survival estimates

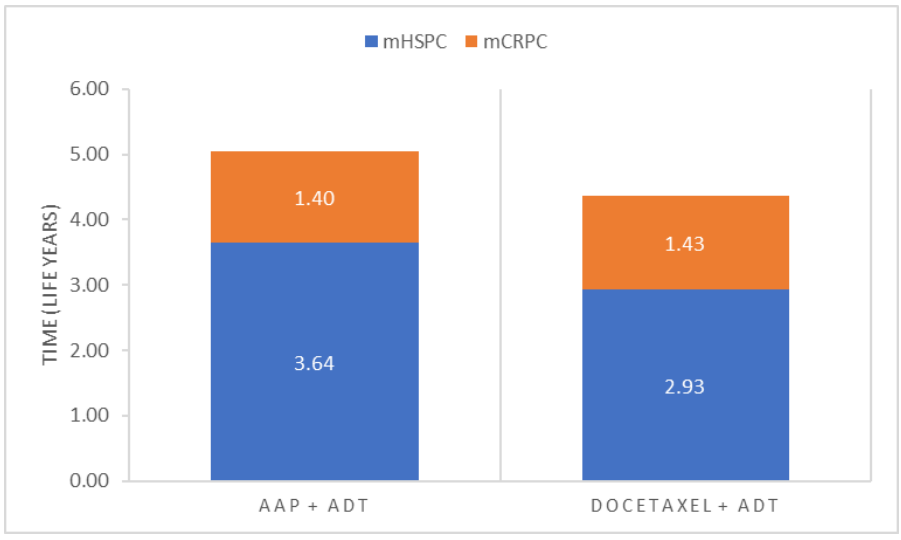
The ACD suggests the reason the Committee do not think the model derives plausible survival estimates is due to their focus on the single unpowered analysis from STAMPEDE. Janssen do not however believe the model derives implausible survival estimates because of the concordance in results from all three independent NMAs, which indicates that there is a very high probability of AAP + ADT being superior with regards to overall survival compared to docetaxel + ADT. The economic model also captures the progression-free survival benefit of AAP + ADT vs. docetaxel + ADT, which is a significant driver of cost and cost-effectiveness.

Furthermore, Janssen wish to highlight that the model still holds face validity with regards to the duration of time spent pre- and post-progression across treatment arms. The ACD highlights that:

> *The committee expected that, if the model reflected the treatment pathway, the benefits of abiraterone plus ADT in delaying progression might be balanced by the potential benefits of the availability of more treatment options after a person's prostate cancer has become hormone-relapsed after ADT alone or docetaxel plus ADT. [Section 3.16]*

Combined with discussion in the ACD which suggests the length of time a person lived after progressing on treatment for mHSPC was kept similar in the model regardless of treatment, Janssen are concerned these statements present an inaccurate summary of the model outcomes because the model did not assume equal post-progression survival between treatment arms. Modelled post-progression survival was dependent upon the subsequent therapies applied in mCRPC. As illustrated in Figure 3, post-progression survival for the docetaxel + ADT arm was indeed longer than AAP + ADT for the base case. Figure 3 shows that the model captured the longer time spent in mHSPC (i.e. pre-progression) with AAP + ADT compared to docetaxel + ADT (3.64 LYs vs. 2.93 LYs) whilst a shorter time in mCRPC (i.e. post-progression) with docetaxel + ADT compared to AAP + ADT (1.43 LYs vs. 1.40 LYs). It also shows that AAP + ADT derives an overall survival benefit because the longer time spent in mCRPC after docetaxel + ADT is not sufficient to offset the gains in mHSPC with AAP + ADT. The longer patients can remain hormone-sensitive, the longer they can retain a better quality of life which is of utmost importance to the patients themselves, their family, their carer and, ultimately, the NHS.

Figure 3: Comparison of time spent pre- and post-progression (life year gains): AAP + ADT vs. docetaxel + ADT



Note: Whilst Figure 3 illustrates updated base case, the same conclusion also applies for the original base case.

Nevertheless, Janssen recognise the Committee's concern over the uncertainty in the relative survival benefit of AAP + ADT vs. docetaxel + ADT and have thus conducted a threshold analysis to show that AAP + ADT remains a cost-effective use of resources whilst varying the HR against docetaxel + ADT. The results of this threshold analysis can be found in Table 12.

3. Cost-effectiveness of AAP + ADT vs. docetaxel + ADT alone

Janssen acknowledge the ERG and Committee's preference for certain model assumptions which were not incorporated within the original base case analysis. Although we maintain that the assumptions made in the original base case analysis were robust, several ERG and Committee preferences have now been incorporated into an updated base case to address some of their concerns and better reflect the views of the Committee in order to guide decision making. The updates which have been incorporated are detailed in Table 9 alongside the impact each had on the ICER.

Table 9: Updates to the CE model based on ERG/ACD feedback: AAP vs. docetaxel + ADT

Assumption	Comments	AAP+ADT vs. Dox + ADT	
Original base case		**£17,828**	**Impact**
1L mCRPC Abiraterone CAA	Correcting the application of the CAA [redacted]. This is done by changing cell B101 on the ERG sheet to "TRUE". Full details of the model amendment are reported in the Proforma document sent by Janssen following the ERG report.	£19,394	£1,566
Tunnel state in mCRPC	Correcting the minor error identified in the mCRPC tunnel states in the sheets.	£17,667	-£161
Planned MRU for mCRPC	Correcting formulae for planned MRU costs for enzalutamide and radium-223 in mCRPC to reference correct model cell.	£17,510	-£318
HR for docetaxel + ADT	As discussed in Issue 5:, Janssen maintain the relevance of NMA to inform AAP + ADT vs. docetaxel + ADT yet recognise the importance of including STAMPEDE data. As such, the HR of 0.91 (derived from the NMA utilising the entire evidence base, as per Table 7, has been applied.	£17,813	-£16
Frequency of bone scans	The frequency of bone scans as scheduled MRU has been equalised in the model as per the ERG/Committee preference.	£21,695	£3,867
Docetaxel compliance	Apply docetaxel compliance to administration, planned MRU and unplanned MRU as per ERG/Committee preference.	£18,039	£211
Utility after docetaxel before disease progression	The off-treatment utility decrement of [redacted] which aimed to capture the lasting impact of docetaxel on patients' HRQL (and applied instead of decrements for AE/SRE to prevent double counting) has been removed as per ERG/Committee preference. As these patients would still be receiving ADT, the AE/SRE utility decrement associated with ADT should be applied to reflect clinical practice. This is done by changing cell B95 on the ERG sheet to "TRUE".	£20,027	£2,199
Utilities from the full regression analysis of	The full set of utility coefficients for AE/SREs that were derived from the regression analysis of LATITUDE have now been used as per the ERG/Committee preference.	£21,199	£3,371
	The utility regression model that produced a pooled SRE	£16,965	-£864

ACD Response: Abiraterone for treating newly diagnosed high-risk metastatic hormone sensitive prostate cancer [ID945]

LATITUDE	coefficient which was equal across treatment arms has now been used as per the ERG/Committee preference.		
BSC in mCRPC	Amend the mCRPC treatment percentages so that the proportions receiving BSC are not differentiated between the arms as preferred by the ERG.	£17,271	-£557
mCRPC cost calculations for fixed duration therapies	Alternative method utilised for fixed duration therapies (see Table 4 for details).	£13,595	-£4,233
Subsequent therapies	Subsequent therapies were set to proportions shown in Figure 1 to capture ERG/Committee feedback and preference whilst maintaining clinically plausible sequencing.	£17,663	-£165
Updated Company base case		**£26,667**	£8,838

Key: ADT, androgen deprivation therapy; BSC, best supportive care; CAA, commercial access arrangement; mCRPC, metastatic castrate resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer MRU, medical resource use
Of note, these ICERs include list prices for downstream therapies which are known to have patient access schemes (PASs).

Results of the updated base case for AAP + ADT vs. docetaxel + ADT, applying the confidential CAA and list prices for downstream therapies which are known to have patient access schemes (PASs), are presented in Table 10. Results show that, under the confidential CAA, AAP + ADT is a cost-effective use of NHS resources in men with newly diagnosed high-risk mHSPC. Indeed, the majority of ICERs related to the sensitivity analysis of AAP + ADT vs. docetaxel + ADT alone fall within the cost-effective threshold for the NHS. These results recognise the value of treating men with newly diagnosed high-risk mHSPC with a novel agent as early as possible.

Table 10: Updated base case: AAP + ADT vs. docetaxel + ADT

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Docetaxel + ADT	[redacted]	4.36	2.75	£14,341	0.68	0.54	£26,667
AAP + ADT	[redacted]	5.04	3.29				

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

As presented in Table 11, the series of scenario analyses which were conducted on the updated base case all consistently demonstrate that AAP + ADT remains a cost-effective use of NHS resources compared to docetaxel + ADT for the majority of scenarios tested.

Table 11: Updates scenario analyses: AAP + ADT vs. docetaxel + ADT

Model assumption	Scenario	ICER	Impact
Updated Base Case		**£26,667**	
Definition of progression	TTST used as an alternative definition of progression	£19,394	-£7,273
LATITUDE scenario	Survival estimates and subsequent therapy market shares estimated from LATITUDE	£25,417	-£1,250
Time horizon	15 years	£27,283	£616
	10 years	£30,396	£3,729
	5 years	£53,781	£27,114
AA utility increment	Applied until death	£23,976	-£2,691
	No increment applied	£26,045	-£622
AE disutilities	Using literature values alone	£26,646	-£21
	Set to zero	£26,661	-£6
mCRPC utilities	Assumed constant through mCRPC	£27,017	£350
AA increment (mCRPC)	AA increment from TA387 removed during mCRPC	£25,970	-£697
Buchers NMA for subsequent therapy	Different HR are applied for each subsequent therapy based on Buchers NMA	£26,896	£229
Vial wastage	Set to zero	£26,802	£135
Docetaxel cost source	MIMS price is assumed	£23,616	-£3,051
Subsequent therapies	Original subsequent therapies assumptions	£20,770	-£5,897
	Alternative treatment sequence – scenario 1	£27,385	£718
	Alternative treatment sequence – scenario 2	£26,795	£128

Key: mCRPC, metastatic castrate resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer MRU, medical resource use; NMA, network meta-analysis; TTST, time to subsequent treatment
Of note, these ICERs include list prices for downstream therapies which are known to have patient access schemes (PASs).

Of note, the LATITUDE only scenario (named "MSM" by the ERG) utilises LATITUDE survival data, and LATITUDE subsequent therapy market share data for AAP + ADT and ADT alone, to ensure consistency between the subsequent therapy costs that underpin the specific clinical outcomes. Janssen do not believe it is appropriate to adjust the subsequent therapy proportions without any adjustment to the LATITUDE curve and thus why it was presented as a trial-based scenario only. Janssen do acknowledge that the ERG and Committee were interested in this modelling approach and therefore we also conducted a threshold analysis on this scenario, as presented in Table 11.

4. Exploratory analysis of OS for AAP + ADT vs. docetaxel + ADT

In order to further address concerns raised by the Committee in the ACD, an additional exploratory analysis has been presented to test the robustness of the model outcomes to changes in assumptions around overall survival. This involved varying the HR for OS for the comparison of AAP + ADT vs. docetaxel over a range of values in increments of 0.01 to demonstrate the impact on the ICER when increasing the HR (and thus decreasing the predicted benefit). Results of the analysis are presented in Table 12, which shows the ICERs alongside the incremental difference in post-progression survival (PPS) between the AAP + ADT and docetaxel + ADT arms.

This analysis has been presented for both the updated company model (named "MSM/TA387" by the ERG) and the LATITUDE only scenario (named "MSM" by the ERG).

The analysis demonstrates that the ICER remains robust even as the HR increases, and PPS is increased in the docetaxel + ADT arm relative to the AAP + ADT arm.

Table 12: Exploratory threshold analysis: AAP + ADT vs. docetaxel + ADT

	Update Base Case Model "MSM/TA387"		**LATITUDE only Trial Scenario** "MSM"	
OS Hazard ratio	**∆ PPS (LYs)**	**ICER**	**∆ PPS (LYs)**	**ICER**
Base case (HR = 0.91)	-0.032	£26,667	0.074	£25,417
0.92	-0.038	£26,877	0.056	£25,707
0.93	-0.044	£27,088	0.037	£26,006
0.94	-0.050	£27,302	0.018	£26,316
0.95	-0.056	£27,518	-0.001	£26,636
0.96	-0.061	£27,736	-0.019	£26,968
0.97	-0.067	£27,955	-0.038	£27,313
0.98	-0.072	£28,177	-0.057	£27,670
0.99	-0.078	£28,401	-0.076	£28,041
1.00	-0.083	£28,628	-0.094	£28,427
1.01	-0.088	£28,856	-0.113	£28,829
1.02	-0.093	£29,087	-0.132	£29,247
1.03	-0.098	£29,320	-0.151	£29,683
1.04	-0.103	£29,555	-0.169	£30,138
1.05	-0.108	£29,793	-0.188	£30,613

Key: ICER, incremental cost-effectiveness ratio; LYs, Life Years; OS, overall survival; PPS, post-progression survival

Issue 9: Clarifying description of STAMPEDE patient population

Janssen wish to highlight the current description of the enrolled population of STAMPEDE in the ACD is misleading. The ACD states:

"STAMPEDE was a multi-arm multi-stage non-blinded adaptive trial of patients with newly diagnosed high-risk metastatic, node-positive or localised disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features."

Currently, this description implies that newly diagnosed high-risk metastatic patients (i.e. the licensed indication of abiraterone) were a pre-defined group of patients within study; however as discussed above, the identification and analysis of this group has not yet been completed. A more correct description would be that STAMPEDE is a multi-arm, multi-stage (MAMS) trial which studied men starting long-term hormone therapy for (a) metastatic or (b) high-risk non-metastatic prostate cancer.[14]

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National Survey of UK Clinical Experts in Prostate Cancer

[June 2018]

Aim

This survey was conducted to better understand current clinical practice for men newly diagnosed with high-risk, metastatic hormone sensitive prostate cancer (mHSPC) in the UK, specifically in relation to the use of docetaxel in combination with ADT in the hormone sensitive setting and the rate of subsequent docetaxel re-challenge in the castrate resistant setting.

Methodology

Janssen approached a combination of leading specialists, practising in prostate cancer, in order to gather a sample representative of NHS clinical practice across the UK. Specialists approached are all highly specialised in the management of prostate cancer, and are also involved in clinical research, publications and academia, to varying degrees.

To account for regional variation in NHS practice, Janssen approached clinical experts from a variety of different centres across England, Scotland and Wales (Figure 1, overleaf).

Clinical experts were individually approached by the Janssen medical team (mostly via e-mail) and asked two key questions:

Question 1: What proportion of men newly diagnosed with mHSPC undertake treatment with ADT alone vs. docetaxel + ADT?

Question 2: In the NHS, how common is docetaxel re-challenge in mCRPC following treatment with docetaxel + ADT in mHSPC?

Each clinical expert was also asked whether they would consent to being acknowledged as contributing to the survey, provided the individual responses remain anonymised.

As each clinical expert was approached individually, each response reflects that individual's practice at their own institution, without bias or influence from other respondents.

Sample Overview

In total, 44 clinical experts were approached, of whom 28 have responded. Non-responders were categorised by no response, annual leave or self-declared conflict of interest. Only one respondent provided information yet declined to be included in this report.

Of the 27 respondents who agreed to be included in this report, 6 were Medical Oncologists, 19 were Clinical Oncologists, and 2 were Clinical Oncology Specialist Registrars.

Figure 1: Map of England showing the geographical location of each respondent (each hot spot represents one respondent)

Results

A tabulated summary of all 27 responses is provided in Table 1 overleaf.

Table 1: Clinical expert responses to questions relating to their docetaxel clinical practice for patients with metastatic prostate cancer

Expert	What proportion of men newly diagnosed with mHSPC undertake treatment with ADT alone vs. docetaxel + ADT?		In the NHS, how common is docetaxel re-challenge in mCRPC following treatment with docetaxel + ADT in mHSPC?	
	Summary	Additional comment	Summary	Additional comment
1	70-80% will receive docetaxel + ADT		No re-challenge	Patients will be treated with abiraterone/enzalutamide and cabazitaxel, or enrolled in trials.
2	30% will receive docetaxel + ADT		May re-challenge (10-15%)	This is new scenario to face in clinic. Does not think re-challenge will be common practice but if other options are limited it would be considered. Difficult to predict figures.
3	50% will receive docetaxel + ADT		Open to re-challenge	Open to re-challenge with docetaxel, but with so many available treatment options re-challenge might not happen.
4	70-80% will receive docetaxel + ADT	All newly diagnosed metastatic patients are offered docetaxel + ADT but clearly a proportion of patients are not fit for chemotherapy.	No re-challenge	
5	50% will receive docetaxel + ADT		May re-challenge	May re-challenge with docetaxel, but only after abiraterone/ enzalutamide and cabazitaxel.
6	50% will receive docetaxel + ADT	Docetaxel + ADT is considered for all mHSPC patients, however ~50% are not fit enough, or do not want chemotherapy.	No estimate provided	Not able to answer this yet as patients who have progressed on docetaxel in the mHSPC setting are still largely on abiraterone/enzalutamide. Tends to use cabazitaxel in patients who have previously had docetaxel (whether in the hormone sensitive or castrate resistant setting), as it causes less neuropathy in experience therefore feasible to give 10 cycles.
7	< 50% will receive docetaxel + ADT	Difficult to predict. The decision is largely based on fitness. There are a cohort who are clearly unfit and never get referred to an Oncologist, and a few who decline treatment.	<20%	Most patients will get abiraterone or enzalutamide first, then many will get cabazitaxel as their first chemotherapy in the CRPC. After that, there may be some re-challenge, but numbers are low.
8	50% will receive docetaxel + ADT		Not common	The first line choice in mCRPC would be abiraterone or enzalutamide.
9	70% will receive docetaxel + ADT	Most metastatic patients will be given chemotherapy, unless they are not fit at all.[a]	Approx. 20%	

10	>90% of eligible patients (based on stage, performance status, co-morbidities)	Now proposes docetaxel + ADT for most eligible (stage, performance status, co-morbidities) patients. It is up to the patient whether he chooses it or not.[a]	Not very common (<10%)	Some clinicians may still do a docetaxel re-challenge to complete a total of 10 cycles (6 in mHSPC and 4 in mCRPC) but advises the proportion would be <10%.
11	30% will receive docetaxel + ADT	70% will receive ADT and 30% are offered chemo-hormonal approach.[a]	Very low	Normally offer cabazitaxel as the next chemotherapy. However, docetaxel has not been used in the mHSPC long enough for patients to need a re-challenge yet.
12	50% will receive docetaxel + ADT	Estimate based on the internal database records of patients presenting with metastatic disease over the last year. A small proportion had received prior radical therapy. Half of patients received docetaxel (median age=69, mean ECOG 0.4 [median=0]) half received ADT alone (median age=75, mean ECOG 1.1 [median=1]).	No estimate provided	Difficult to estimate as numbers are quite low. Offer abiraterone or enzalutamide for chemotherapy failures initially. Advises cabazitaxel is offered next if their hormone sensitive phase was short or may consider docetaxel if the hormone sensitive phase is >18 months. No docetaxel re-challenge used as yet. Likely due to current patients being early failures. Advises that patients who fail docetaxel in the hormone sensitive setting early are less inclined to have more chemotherapy at all.
13	30-40% will receive docetaxel + ADT	Quite a large proportion get ADT alone, because they are ineligible for docetaxel, or do not wish to have it. Docetaxel cannot be given to all. Chemotherapy also has significant impact on clinical services (i.e. administration and potential significant side effects and admissions to hospital.)	None	
14	< 50% will receive docetaxel + ADT	For many men the potential toxicity of docetaxel precludes them from receiving it. Community of elderly population therefore, in experience, <50% will receive upfront docetaxel, leaving significant unmet need for those in whom docetaxel is unsuitable.	Not very common	When men relapse post upfront docetaxel, they almost invariably opt for an oral novel anti-androgen rather than face the challenges and toxicities of chemotherapy again. Advises men will accept re-challenge with docetaxel or cabazitaxel when there isn't an alternative. Department, capacity in chemotherapy unit is extremely limited, despite offering a 6-day service. Oral treatment that doesn't require

				physical chair space in their unit is very attractive.
15	Approx. 40% will receive docetaxel + ADT		20-25%	Docetaxel re-challenge is restricted to patients who progress more than a year post-docetaxel in mHSPC.
16	40% will receive docetaxel + ADT		Rare - approx. 10%	Re-challenge is currently rare, but will increase as there are more patients relapsing after docetaxel upfront.
17	60-70% will receive docetaxel + ADT	All patients who are fit with no contraindications to docetaxel will receive it.	Not very common	Not very common due to current line of treatments, especially with the approval of cabazitaxel.
18	50% will receive docetaxel + ADT		No estimate provided	If patients have relapsed early, will not re-challenge. Many of the patients still haven not relapsed so has not yet had to make a decision, but it is likely to consider retreatment.
19	50% will receive docetaxel + ADT		No estimate provided	Difficult to comment as most patients have not yet relapsed. If they have relapsed, it is likely they had very aggressive disease and would not be fit for chemotherapy anyway. Would consider re-treatment if the patient was fit enough.
20	40-50% will receive docetaxel + ADT	Of the whole mHSPC population, with no stratification of 'high' and 'low' volume disease.	Rare	
21	Approx. 60% will receive docetaxel + ADT	Difficult to be precise as the Urologists may manage men clearly not fit for chemotherapy and thus are not seen by Oncologist.	Very rare	A 'handful' of patients each year at present. May increase a little, as they are just seeing the mCRPC post-abiraterone, post-cabazitaxel patients failing now (of those who started on docetaxel following STAMPEDE data release).
22	Approx. 80% will receive docetaxel + ADT	All patients with new diagnosis of mHSPC receive docetaxel +ADT at present, if not contraindicated (i.e. 80%). Most likely if high volume of metastatic disease.[a]	Not very common	Patients failing on up front docetaxel will usually receive a new generation anti-androgen.
23	70% will receive docetaxel + ADT	Referrals received for men who want docetaxel, but cannot get it elsewhere.	None	Next line chemotherapy would be cabazitaxel as there is less peripheral neuropathy. If a patient fails cabazitaxel, docetaxel would not be given again as the patient is not responding to chemotherapy. Currently doing a survey to understand how to manage patients after upfront docetaxel.

24	Almost 75-80% will receive docetaxel + ADT	Of the patients referred to an Oncologist.	Not common (~5%)	After docetaxel, cabazitaxel, abiraterone/ enzalutamide and maybe radium-223, most of the patients are exhausted and they suffer from cumulative toxicities which makes them ineligible. Personal experience is not good with docetaxel re-challenge, and prefers cabazitaxel re-challenge as more convincing data is available.
25	Approx. 75% will receive docetaxel + ADT		<10%	
26	50% will receive docetaxel + ADT		No estimate provided.	Patients who have been treated with docetaxel upfront in mHSPC are only now coming through. The rate of docetaxel re-challenge solely in the mCRPC setting (i.e. after prior docetaxel in mCRPC) has been ~10% (which used to be higher as cabazitaxel was not previously funded in Wales).
27	Approx. 50% will receive docetaxel + ADT	Clinical practice heavily influenced by CHAARTED. Often avoids using docetaxel in oligo metastatic disease.	None (0%)	Very concerned about potential death on chemotherapy in an unlicensed indication.

[a] Further information provided upon request for clarification

Key: ADT, androgen deprivation therapy; mCRPC, metastatic castrate resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer

Summary and Interpretation of Results

Question 1: What proportion of men newly diagnosed with mHSPC undertake treatment with ADT alone vs. docetaxel + ADT?

Based on the above responses, between 30% and 90% of patients with a new diagnosis of metastatic hormone sensitive prostate cancer may receive upfront treatment with docetaxel + ADT. This estimate however includes some clear outliers, as the majority of respondents (n=19) provided estimates that fell between 40% and 70%. As many as 12 respondents stated that the proportion of patients treated with docetaxel + ADT was approximately 50% - this was by far the most common answer.

Possible explanations for the outliers who stated that the proportion of patients treated with docetaxel + ADT was >70% (n=6) include the following:

- One respondent (#10) was specifically referring to the proportion of eligible patients (based on stage, performance status, and co-morbidities) that would go on to receive docetaxel.
- One respondent (#23) stated that men who want to be treated with docetaxel, but cannot get it elsewhere, get referred to their clinic. This may result in this respondent seeing a disproportionate number of men who are both eligible and willing to have chemotherapy.

An additional confounding factor that should to be taken into account when interpreting these data is that the estimates provided by the respondents are likely to be based on the total number of patients referred to oncology. Some patients who are clearly not fit for chemotherapy may not get referred to oncology, and may instead continue to be managed by urology with ADT alone. This may result in an artificially inflated estimate of the true proportion of newly diagnosed mHSPC patients who receive docetaxel treatment for their disease. This was articulated by respondents #7, #21 and #24. Respondent 21 clearly stated that it was difficult to estimate the true figure as the urologists may manage men clearly not fit for chemotherapy, thus the oncologists never see those patients.

Question 2: In the NHS, how common is docetaxel re-challenge in mCRPC following treatment with docetaxel + ADT in mHSPC?

Based on the above responses, we conclude that docetaxel re-challenge in mCRPC following upfront docetaxel + ADT treatment in mHSPC is uncommon.

Most of the respondents agreed that this is a rare or uncommon event, and the most frequent reason provided for not re-challenging was the availability of other treatments for mCRPC, (including abiraterone/enzalutamide and cabazitaxel) that were considered more appropriate at this stage of disease progression. Where numbers were provided, the re-challenge was estimated to be between zero and <25% (n=14).

Cabazitaxel was identified as a relevant taxane to re-challenge with after docetaxel with respondents (n=2) suggesting this is due to its lower risk of peripheral neuropathy. Some respondents also commented that the true number of patients who are likely to be re-challenged with docetaxel is difficult to estimate at present as the patients who have received docetaxel in the upfront setting are still largely on their first line mCRPC treatment (abiraterone or

enzalutamide) (n=5). This does align with the overarching view that following progression on docetaxel + ADT the second line treatment at present is either abiraterone or enzalutamide.

There was general agreement among the respondents that, if the patient was to be re-challenged with docetaxel, this would only happen after the patient was treated with other available mCRPC treatments, and often only once all available treatments, including a second line of chemotherapy with cabazitaxel, were exhausted.

Clinical experts included in report:

[redacted]

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 27 June 2018 email: TACommB@nice.org.uk/NICE DOCS

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

Comment number	Comments

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 27 June 2018 email: TACommB@nice.org.uk/NICE DOCS

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Paragraph 3.2	There are numerous sources which set out the clinical criteria to define people who are unable to receive docetaxel which should be considered. Paragraph 3.3 of the Clinical Commissioning Policy Statement for docetaxel in combination with ADT[i] includes: • severe prior hypersensitivity reaction to taxanes • poor overall performance status (WHO performance status 3-4, caution for those with performance status 2) • pre-existing significant peripheral neuropathy • poor bone marrow function due to extensive disease or other prior haematological problems • significant co-morbidity (e.g. cardio-vascular or respiratory disease) such that prostate cancer is not likely to be the life limiting illness for the patient Paragraph 4.31 of the FAD for TA412 for radium 223[ii] sets out criteria for defining the people for whom docetaxel is not suitable: • contraindications to docetaxel such as hypersensitivity to the active substance, a neutrophil count of less than 1.5x109/litre, or severe liver impairment • a platelet count of less than 100x109/litre • ongoing treatment with an immunosuppressant for any condition • an ECOG performance status of 3 or greater • comorbidities and an ECOG performance status of 2 or greater • comorbidities, including: o poor cognition or social support, which results in inability to understand treatment and provide consent
Table 1	While the impact on quality of life of adverse events during chemotherapy are well documented (more on this in our response to paragraph 3.13), the majority of patients quality of life will return to normal after stopping chemotherapy[iii]. There is no evidence that most patients suffer long-term consequences of chemotherapy treatment. A recently published study looked at the impact of ADT+docetaxel on prostate cancer patient quality of life at 3 months and 12 months. It found that quality of life is statistically worse than baseline at 3 months, but is then higher than for ADT alone at 12 months[iv]. (https://www.ncbi.nlm.nih.gov/pubmed/29522362) **On the long-term consequences of chemotherapy:** Chemotherapy can cause nerve damage that leads to neuropathic pain, however studies have suggested that this effect is more likely to occur in patients with pre-existing neuropathy[v]. (https://academic.oup.com/bjaed/article/16/4/115/2897725) Other chemotherapy treatments can increase the risk of heart disease, but this is generally not associated with taxanes like docetaxel. Further identified long-term consequences of chemotherapy are more strongly linked to higher doses of chemotherapy or longer treatment cycles than the six recommended for docetaxel. Patients can report problems with cognitive function or 'chemo brain' but there is no definitive evidence on the link between this and chemotherapy.
Paragraph	It is absurd to suggest that it is not plausible that quality of life would be worse while having docetaxel

3.13	plus ADT. The paragraph goes on to highlight the impact of adverse events on quality of life. As we included in our original submission, several patients able to receive abiraterone were grateful to have avoided the side-effects associated with chemotherapy. We heard from one patient who was diagnosed before abiraterone was available but still refused chemotherapy due to the potential side-effects. *"He chose not to have chemotherapy after watching his mother suffer terribly from side effects when she was treated for breast cancer."* *"It was such a relief not to have to have chemo. The side effects of chemo would have made it much tougher for me to continue to work effectively which I needed to do in order to get my business in order and in a position where it can function effectively without me."* A recently published study looked at the impact of ADT+docetaxel on prostate cancer patient quality of life at 3 months and 12 months. It found that quality of life is statistically worse than baseline at 3 months, but is then higher than for ADT alone at 12 months[vi]. (https://www.ncbi.nlm.nih.gov/pubmed/29522362) Hopefully the EQ-5D data from the STAMPEDE trial will be made available and able to provide further insight on this.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or

not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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

[i] https://www.england.nhs.uk/wp-content/uploads/2016/01/b15psa-docetaxel-policy-statement.pdf

[ii] https://www.nice.org.uk/guidance/ta412/resources/radium223-dichloride-for-treating-hormonerelapsed-prostate-cancer-with-bone-metastases-pdf-82604599866565

[iii] The Lancet Volume 387, Issue 10024, Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial Prof Nick James et al. March 2016

[iv] Journal of Clinical Oncology, Quality of Life During Treatment With Chemohormonal Therapy: Analysis of E3805 Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer, Morgans et al. April 2018

[v] BJA Education, Volume 16, Issue 4, Chemotherapy-induced peripheral neuropathic pain, Gupta et al. September 2015

[vi] Journal of Clinical Oncology, Quality of Life During Treatment With Chemohormonal Therapy: Analysis of E3805 Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer, Morgans et al. April 2018

NHS England submission for the NICE appraisal of abiraterone for newly diagnosed high risk metastatic hormone sensitive prostate cancer (2nd meeting)

1. The current treatment pathway for newly diagnosed hormone sensitive prostate cancer (PC) consists of androgen deprivation therapy (hormone treatment) or the combination of docetaxel chemotherapy with androgen deprivation therapy. About two thirds of such patients receive ADT alone and about one third receive docetaxel plus ADT. This figure is in broad accordance with recently published Scottish data (Rulach et al). Higher figures may be observed in chemotherapy clinics because patient selection has already taken place for referral for consideration of chemotherapy. This two thirds/one third split of treatment choices depends on fitness for chemotherapy, visceral metastases (an adverse prognostic factor), high volume of metastatic load (another adverse prognostic factor) and patient choice. Most patients receiving chemotherapy plus ADT have adverse disease.
2. After ADT alone or ADT plus docetaxel (ie after the patient has developed castrate refractory PC), the main active treatment option is either abiraterone or enzalutamide, either used pre-chemotherapy or post chemotherapy.
3. NHS expects the over whelming majority of poor risk newly diagnosed metastatic patients to opt for abiraterone plus ADT as few will be unable to tolerate the combination and most will opt for abiraterone plus ADT rather than docetaxel plus ADT. The evidence bases for both options lie in similar types of patients.
4. NHS England notes the treatment pathway options assumed by Janssen in its revised base case, particularly after either abiraterone plus ADT or ADT alone. Whilst the options in themselves are reasonable, it is the percentage uptake within each line of therapy used in the economic model that NHS England cannot ascertain. Whilst it is reasonable to assume close to 100% use of 2nd line abiraterone/enzalutamide after 1st line ADT alone, only about 50% of patients will have docetaxel after failing 1st line abiraterone plus ADT or 2nd line abiraterone/enzalutamide. In addition there will be some use of radium-223 2nd line in the abiraterone plus ADT pathway and 3rd line in the ADT alone pathway. The mix of treatment options 3rd line and 4th line in the abiraterone plus ADT and ADT alone pathways respectively, are likely to have less use of chemotherapy (modest cabazitaxel, little docetaxel) and much more best supportive care. The Janssen scenarios 1 and 2 do not help to assist very much in exploring the uncertainty of subsequent treatment options in these pathways of care.
5. If NICE recommends abiraterone plus ADT as 1st line systemic therapy for newly diagnosed hormone sensitive PC, then for those patients who receive such upfront abiraterone treatment, there will be no further abiraterone or enzalutamide commissioned in the later stages of the treatment pathway (ie as pre-chemotherapy or post chemotherapy for castrate –refractory PC). This is because patients will have become resistant to abiraterone by then and there is only poor efficacy for the use

of enzalutamide after abiraterone. Thus NHS England will commission patients to receive one chance to receive abiraterone in the treatment pathway.

6. NHS England considers that the Janssen assumption of the cost of abiraterone drug in this appraisal is via Janssen's unilateral extension of the current commercial access agreement (CAA) between NHS England and Janssen. This CAA is in place for the CDF transition indication topic for abiraterone (pre-chemtherapy in castrate-refractory PC), appraised by NICE in 2016.
7. The DHSC has given NHS England the following remit regarding categories of medicines suitable for a CAA:

- Drugs with an indication that is entering the reformed Cancer Drugs Fund, for the duration that an indication is recommended by NICE for funding in the CDF
- A very limited number of indications and medicines which are/were being transitioned out of the legacy CDF arrangements (these were all in highly exceptional circumstances)
- Medicines being appraised through the Highly Specialised Technology (HST) route.
- Those medicines which are not subject to a NICE appraisal.

8. Janssen has been advised by both PASLU and NHS England that for the indication currently being appraised they need to offer a PAS as it is not possible to vary the current CAA to include a non-CDF, non-CDF transition topic. Such a PAS has not been agreed and hence the company's submission is not based on an approved method of varying the price of abiraterone from its list price.

Prof Peter Clark
NHS England Chemotherapy Lead and Clinical Lead for the Cancer Drugs Fund
July 2018

Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer

ADDENDUM to the ERG report

ERG's critique of the updated cost-effectiveness analyses sent by the company in response to the ACD

Produced by Aberdeen HTA Group

Date completed 4 July 2018

Contains CIC/AIC

This report provides the ERG's commentary and critique of revised evidence submitted by the company (Janssen) on 28/06/2018 as documents: "ID945 Janssen ACD Response_Abiraterone in mHSPC_270618 ACIC.docx" and "ID945 Janssen ACD Response_Appendix A_UK Clinical Survey_270618 [ACIC].docx". The evidence, revised model and results are discussed briefly in the following pages. This commentary should be read in conjunction with the company ACD response and associated appendices.

The company present a list of issues (1 to 9) as the key points of their response to the ACD. The ERG note that many of the issues are reiteration of previously submitted evidence that the appraisal committee has already seen. The ERG highlight below, in brief, where new pertinent evidence was presented. The ERG then go on to discuss in detail the economic considerations of the new evidence.

Issue 1: Clarifying the decision problem

No new evidence to critique.

Issue 2: Addressing the comparison of AAP+ADT vs ADT alone

No new evidence to critique.

Issue 3: Addressing the economic modelling of AAP+ADT vs ADT alone

1. Appropriateness of clinical base

   The company reported results of an IPCW analysis on overall survival to investigate the effect of treatment sequencing in the LATITUDE trial. The company states the uncertainty with the IPCW analysis though does not provide sufficient level of detail for the ERG to critique the analysis, and the ERG agrees that the analysis is likely to have high degree of uncertainty given the apparently small number of cases in Table 2 of the company response that would have been utilised in the IPCW approach.
2. Cost-effectiveness of AAP+ADT vs ADT alone

   The revised model is discussed in detail in economic section below.

Issue 4:Clarifying level of access to STAMPEDE data

No new evidence to critique.

Issue 5: Addressing the comparison of AAP+ADT vs docetaxel + ADT

1. Generalisability of STAMPEDE data

   No new evidence to critique.
2. Utilising NMA

   There was a new NMA conducted on a subset of published STAMPEDE data. The ERG have not had time to check the accuracy of this NMA, but the ERG note that the AC still had a preference for the STAMPEDE trial result in the first instance, albeit supplemented by NMS data.

Issue 6: Subsequent therapies and post-progression survival

1. Post progression survival
   No new evidence to critique.
2. Docetaxel rechallenge
   The results of a survey of 27 clinical experts was included. The results demonstrated a mix of opinion on the size and/or existence of a docetaxel rechallenge group.

Issues 7 (Interpretation of HRQL data for docetaxel+ADT and Issue 8 (the economic modelling of AAP+ADT vs docetaxel+ADT) are discussed in detail in the economics section below.

Issue 9: Description of STAMPEDE population
No new evidence to critique.

We now go on to discuss the ERG economic comments on the company response to the ACD.

Economics Summary
The ERG has had little time to review the company response to the ACD, and what follows is subject to error check by the company.

The company has revised the model by:

- Applying the 0.92 OS HR for AAP+ADT compared to DOC+ADT as derived from its NMA including STAMPEDE rather than the 0.91 OS HR derived from LATITUDE.
- Applying the full LATITUDE EQ-5D QoL regression, and basing this upon the ERG preferred regression that pools the SRE coefficient between the arms.
- Removing the ADT (post DOC+ADT) quality of life decrement of -0.03.
- Revising its assumption that the long term SAE/SRE profile of DOC+ADT would be akin to that of AAP+ADT to assuming it would be akin to ADT.
- Correcting the implementation of the DOC+ADT quality of life values.
- Revising the mCRPC treatment proportions.
- Correcting the implementation of the abiraterone CAA.
- Correcting the implementation of the mCRPC treatment costs.
- Equalising the frequency of bone scans between the arms.

- Applying docetaxel compliance to resource use other than just drug costs in the DOC+ADT arm.
- Correcting the minor error around tunnel states.

For the comparison of AAP+ADT with ADT the company estimates a net gain of 1.52 undiscounted life years, a net gain of 1.06 QALYs, a net cost of £18,146 and an ICER of £17,160 per QALY.

For the comparison of AAP+ADT with DOC+ADT the company estimates a net gain of 0.68 undiscounted life years, a net gain of 0.54 QALYs, a net cost of £14,341 and an ICER of £26,667 per QALY.

The model implementation of the comparison of AAP+ADT with DOC+ADT may exaggerate the overall survival gains. Applying an OS HR of 1.00 for AAP+ADT compared to DOC+ADT still results in the model estimating around a 13% gain in overall survival from AAP+ADT compared to DOC+ADT.

An OS HR input of 1.89 in the MSM/TA387 model equalises the overall survival between AAP+ADT and DOC+ADT and results in an ICER of £64,181 per QALY. An OS HR input of 1.24 in the MSM model equalises the overall survival between AAP+ADT and DOC+ADT and results in an ICER of £53,986 per QALY.

The company does not model mCRPC treatments having different clinical effects beyond the Bucher NMA as presented in the original submission, which has minimal effect upon the modelled mCRPC survival and the cost effectiveness estimates.

The MSM/TA387 model estimates a slightly superior mCRPC survival for AAP+ADT compared to DOC+ADT due to the application of the PFS HR and the OS HR for patients who have progressed but are yet to receive their 1st line mCRPC treatment and so enter the TA387 aspect of the model. There is a similar slightly superior mCRPC survival for AAP+ADT over ADT in the MSM/TA387 model, and this is retained in the MSM model. But the MSM model suggests that the mCRPC survival for DOC+ADT falls that little bit further behind that of AAP+ADT.

The company does not present any scenario analyses around the extrapolation of the duration of benefits.

The company notes that it does not yet have access to STAMPEDE EQ-5D data or analyses. It cites some FACT-P data as supporting its approach. The ERG views the FACT-P data it summarised in its original report as supporting a quality of life decrement for those receiving a course of docetaxel, but a quality of life increment for those who have completed a course of docetaxel. It can also be noted that the company still does not apply any quality of life decrement for docetaxel treatment of mCRPC, which would be to the detriment of the AAP+ADT arm.

The company proposes a number of revisions to the mCRPC treatment proportions. To all practical purposes, these only affect the costs that are modelled. For patients who are intolerant of docetaxel or strongly averse to docetaxel the comparator for AAP+ADT is ADT. The ERG is confused by the company proposing that in the AAP+ADT arm all these patients would receive docetaxel as their 1st line mCRPC treatment.

The ACD notes that AAP+ADT is well tolerated but accepts that time to treatment discontinuation data should be considered when costing AAP+ADT. The ERG remains of the opinion that given the abiraterone license it is improbable that only [redacted]. of patients remaining in mHSPC will receive abiraterone for their mHSPC at 40 months. [redacted].

As per the original ERG report the ERG presents two full sets of analyses, one for the MSM/TA387 model and one for the MSM model. These differ from the company analyses presented in response to the ACD in that they:

- Retain the original company assumption of SAEs and SREs quality of life effects for DOC+ADT and ADT (post DOC+ADT) being aligned with the AAP+ADT arm due its greater similarity in efficacy than with the ADT arm.
- [redacted].

- Apply the ERG preferred mCRPC treatment proportions of the original ERG report for the comparison of AAP+ADT with DOC+ADT.

For the ERG revised base case of the comparison of AAP+ADT with ADT, the MSM/TA387 model estimates a net gain of 1.53 life years, a net gain of 1.07 QALYs, a net cost of £18,223 and an ICER of £17,051. The MSM model estimates a net gain of 1.53 life years, a net gain of 1.08 QALYs, a net cost of £25,420 and an ICER of £23,459.

For the ERG revised base case of the comparison of AAP+ADT with DOC+ADT, the MSM/TA387 model estimates a net gain of 0.68 life years, a net gain of 0.54 QALYs, a net cost of £13,442 and an ICER of £25,027. The MSM model estimates a net gain of 0.79 life years, a net gain of 0.59 QALYs, a net cost of £21,966 and an ICER of £37,483.

Economics: Clinical effectiveness and modelling

OS HR threshold analyses and model reliability for the comparison with DOC+ADT
In the presentation of the threshold analyses around the OS HR the company only presents the difference in post progression survivals. For scenario analyses around the OS HR the ERG also presents the differences in overall survival below, coupled with an additional scenario analysis which applies the 1.13 OR HR for the M1 subgroup from STAMPEDE while recognising that this was not statistically significant with a CI of 0.77 to 1.66. The OS HRs that when inputted to the model result in the same overall survival estimate for AAP+ADT as for DOC+ADT are also presented. These sensitivity analyses apply the revised set of assumptions as preferred by the company in its response to the ACD

The company has introduced a new error in the implementation of the MSM modelling when coupled with the LATITUDE market share data. The LATITUDE market share data is applied in the AAP+ADT arm but is not applied in the DOC+ADT arm. Applying the LATITUDE market share data in the DOC+ADT arm worsens the ICER for this scenario from the company estimate of £25,417 per QALY to £29,804 per QALY. This error is corrected in the results of Table 1 below.

Table 1: Company revised base cases: OS HR sensitivity analyses

	MSM/TA387 model		MSM model	
OS HR	Δ OS (LYs)	ICER	Δ OS (LYs)	ICER
0.91 = Base case	**0.682**	**£26,667**	**0.789**	**£29,804**
0.92	0.670	£26,877	0.764	£30,141
0.93	0.657	£27,088	0.739	£30,489
0.94	0.645	£27,302	0.714	£30,848
0.95	0.634	£27,518	0.689	£31,218
0.96	0.622	£27,736	0.664	£31,602
0.97	0.610	£27,955	0.639	£31,998
0.98	0.599	£28,177	0.615	£32,409
0.99	0.588	£28,401	0.590	£32,834
1.00	**0.577**	**£28,628**	**0.566**	**£33,276**
1.01	0.566	£28,856	0.541	£33,735
1.02	0.556	£29,087	0.517	£34,211
1.03	0.545	£29,320	0.493	£34,707
1.04	0.535	£29,555	0.469	£35,224
1.05	0.525	£29,793	0.445	£35,763
1.13	**0.448**	**£31,781**	**0.255**	**£41,102**
1.24			0.000	£53,986
1.89	0.000	£64,181		

It might be anticipated that for an OS HR of 1.00 the model should estimate the same survival in the AAP+ADT arm as in the DOC+ADT arm. It does not do so, and OS gains are still anticipated from AAP+ADT compared to DOC+ADT.

For the MSM/TA387 model the estimated overall survival in the AAP+ADT arm is 5.04 undiscounted life years. When the OS HR is 1.00 the model still anticipated quite large OS gains from AAP+ADT over DOC+ADT. Even when the OS HR is in favour of DOC+ADT by around 10%, as per the 1.13 OS HR scenario analysis, the model still estimates an OS gain from AAP+ADT over DOC+ADT of around 10%. The OS HR has to be increased to 1.89 in favour of DOC+ADT for the model to estimate the same OS in both arms, at which point the ICER rises to £64,181 per QALY.

The situation is similar in the MSM modelling, though the OS HR has to be increased to 1.24 in favour of DOC+ADT for the model to estimate the same OS in both arms, at which point the ICER rises to £53,986 per QALY.

Reason for survival gains being different between treatment arms when the OS HR is assumed equal

As described in the original ERG report and reiterated here, the reason for the survival gains is a reflection of the modelling approach. The reason that this occurs is due to the application of the PFS HR and the OS HR to the AAP+ADT MSM TPMs, coupled with the probability of dying from PFS being much less than the probability of dying from post progression survival, PPS.

Table 2: AAP+ADT MSM monthly TPM

From \ To	PFS	PPS	Dead
PFS	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]
Dead	[redacted]	[redacted]	[redacted]

The base case 0.76 PFS HR can be applied to the [redacted].AAP+ADT monthly probability of progressing to yield a [redacted].DOC+ADT monthly probability of progressing. Similarly, for the sake of argument the STAMPEDE 1.13 OS HR can be applied to the above AAP+ADT probabilities of dying to yield probabilities of dying from PFS [redacted].and of dying from PPS of [redacted].for DOC+ADT. This gives the following DOC+ADT TPM.

Table 3: DOC+ADT monthly TPM

From \ To	PFS	PPS	Dead
PFS	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]
Dead	[redacted]	[redacted]	[redacted]

The DOC+ADT TPM has lower probabilities of dying than the AAP+ADT TPM. But these differences are dwarfed by the differences in the probability of dying from PFS compared to the probability of dying from PPS. Being in PPS has much larger probability of dying than being in PFS. The superior PFS HR of 0.76 for AAP+ADT means that patients spend longer in the PFS health state and so do not incur the PPS probability of dying as much as those in the DOC+ADT arm do. This results in a modelled overall survival gain for AAP+ADT even when the OS HR is in favour of DOC+ADT.

The treatment with the superior PFS HR is given an OS benefit that is larger than that implied by the OS HR. This may be seen as model bias in favour of AAP+ADT for the comparison with DOC+ADT. If so the bias seems to be quite serious.

Modelled treatment pathway

The company argues that sequences of mCRPC treatments are modelled. In the opinion of the ERG this does not address the concern of the AC.

Provided that the proportions receiving BSC as 1st line mCRPC treatment do not differ between the arms, varying the 1st line, 2nd line and 3rd line mCRPC treatment proportions has no impact upon the modelled survival or patient QALYs[1].

The scenario analysis that differentiates the treatment effectiveness of 1st line mCRPC treatments by the company Bucher NMA only affects the effectiveness of enzalutamide. The proportions receiving enzalutamide for 1st line mCRPC in the original company base case were such that this had only a small effect upon the modelled survival and cost effectiveness estimates.

Modelled post-progression survival estimates

The company argues that the MSM/TA387 model estimates a higher average amount of post progression survival (PPS) in the DOC+ADT compared to AAP+ADT: 1.43 years compared to 1.40 years. The company estimates appear to arise due to AAP+ADT patients spending longer in PFS and so a higher proportion of them dying directly from PFS without progressing through PPS. The ERG are not clear that this argument particularly addresses the concern of the AC.

The ERG understanding is that the main concern of the AC is that among those who have progressed the model simulates the same PPS survival in both arms. This can be explored by starting all patients in the PPS health state[2]. This results in survival estimates of 1.61 years in the AAP+ADT arm, 1.59 in the ADT arm and 1.58 years for DOC+ADT, despite 1st line

[1] There are some minimal adverse events effect differences but these can be ignored for the sake of the broader argument.

[2] Implemented in the markov worksheets by setting I11=0 and J12=1, this also requiring that the proportion of time the model applies the LATITUDE KM is zero to avoid patients in PFS subsequent to there being none in cycle zero.

mCRPC BSC rates being higher in the AAP+ADT arm in the original company base case. Equalising BSC rates between the arms marginally increases the estimate for the AAP+ADT arm to 1.62 years.

The slightly lower survival among those who have progressed in the DOC+ADT arm compared to the AAP+ADT arm is due to:

- Applying the PFS HR to the AAP+ADT PPS pre-1st line mCRPC treatment probability of moving on to receive 1st line mCRPC treatment, and so into the TA387 model aspect, to derive the corresponding probability for DOC+ADT.
- Applying the OS HR to the AAP+ADT PPS pre-1st line mCRPC treatment probability of dying to derive the corresponding probability for DOC+ADT.
-

If these probabilities are equalised between the arms the model estimates that the PPS survival among those who have progressed in the AAP+ADT arm is equal to that among those who have progressed in the DOC+ADT arm. But the base case estimates a marginally superior PPS survival among those who have progressed in the AAP+ADT arm compared to those in the DOC+ADT arm.

The slightly lower survival among those who have progressed in the ADT arm compared to the AAP+ADT arm is due to the differing MSM TPM probabilities. Their effect is similar to the discussion of the post progression, pre 1st mCRPC treatment probabilities for DOC+ADT as discussed above.

For the MSM model the differences between the AAP+ADT arm of 2.03 life years and the ADT arm of 2.00 life years are similar to those of the MSM/TA387 model. But the DOC+ADT arm is lower still with an estimate of 1.87 life years.

Duration of benefit

The company has not explored limiting the duration of benefit as per the NICE methods guide. Given the concerns around the application of the hazard ratios in the modelling of AAP+ADT compared to DOC+ADT coupled with time constraints the ERG has not further explored this. The ERG explores the impact of limiting the duration of benefits for the comparison of AAP+ADT with ADT. This is implemented by applying the ADT TPM

probabilities in the AAP+ADT arm from 40 months, 60 months and 80 months. For the TA387/MDM modelling these scenarios can be compared graphically as below.

Figure 1: Unlimited duration of benefits: MSM/TA387 model

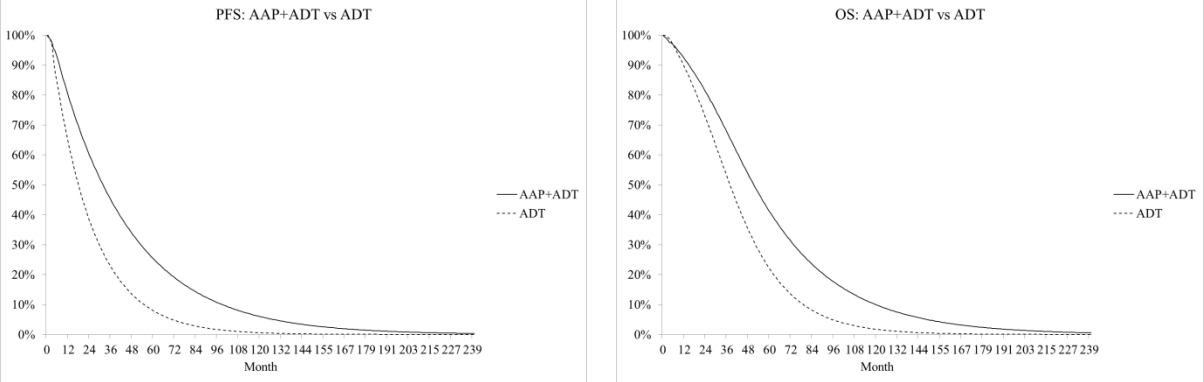


Figure 2: Duration of benefits limited to 40 months: MSM/TA387 model

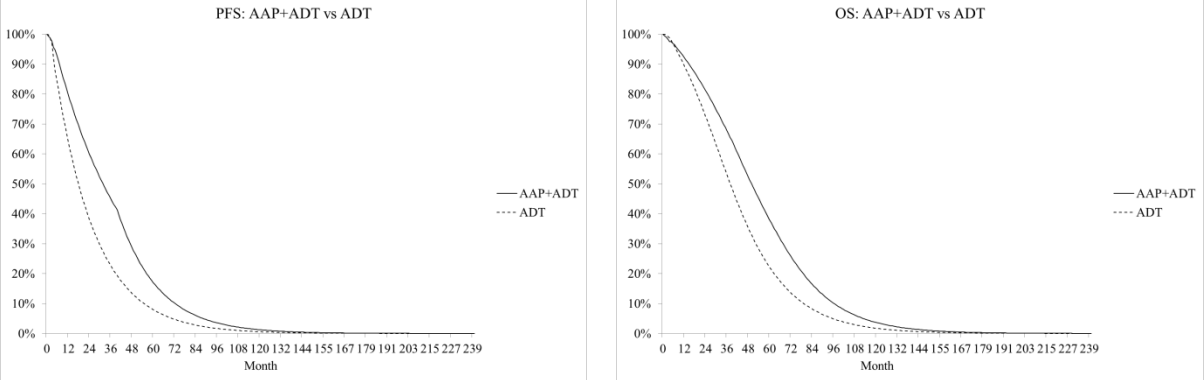


Figure 3: Duration of benefits limited to 60 months: MSM/TA387 model

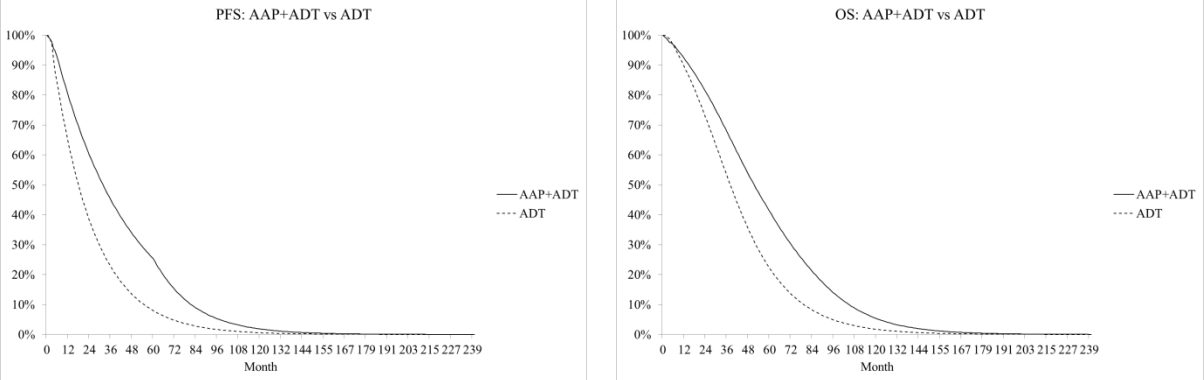
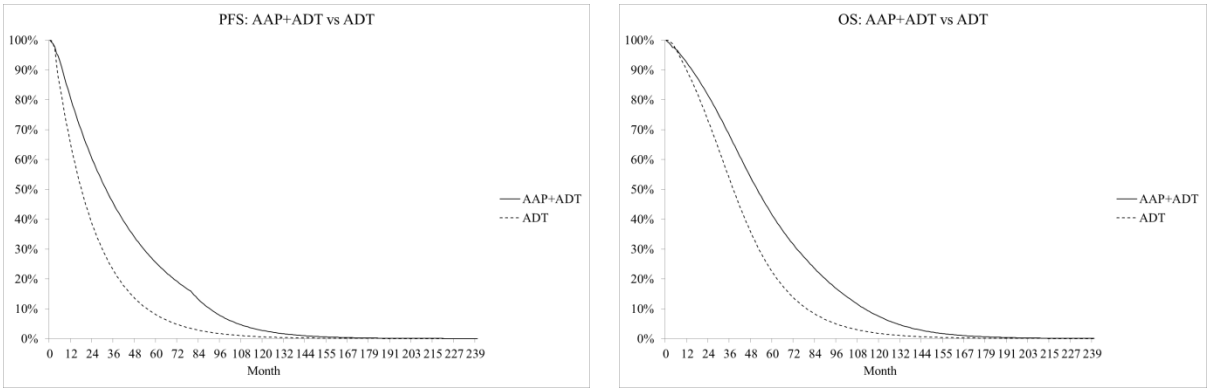


Figure 4: Duration of benefits limited to 80 months: MSM/TA387 model



Economics: Quality of life

Quality of life: AAP+ADT vs DOC+ADT

The company notes that it has not yet been able to access STAMPEDE EQ-5D data. The original ERG report noted that the company QoL literature review was deficient, the main points being reiterated below:

- The recent 2018 paper by Morgans et al analyse quality of life among an RCT of DOC+ADT (n=397) compared to ADT for mHSPC (n=393). Quality of life was assessed at baseline and 3 monthly to 12 months using FACT-P, FACT-Taxane, Functional Assessment of Chronic Illness Therapy-Fatigue and the Brief Pain Inventory with the data being analysed using a mixed effect model. FACT-P completion rates were high at 90%, 86%, 83%, 78% and 77% at the five timepoints, non-completions being roughly equally split between those not given the form by staff and for unknown reasons. DOC+ADT FACT-P scores were significantly lower at 3 months (-3.09, p=0.02) but significantly higher at 12 months compared to ADT (+2.85, p=0.04). But differences did not exceed the minimum clinically meaningful change at any time point, which was taken to be a change of 6 to 10 points. Both arms reported significantly poorer FACT-Taxane scores compered to baseline. Brief pain inventory scores were similar between the arms. The authors conclude that "*Although ADT+D was associated with statistically worse QOL at 3months, QOL was better at 12months for ADT+D patients than for ADT patients. Both arms reported a similar minimally changed QOL over time, suggesting that ADT+D is not associated with a greater long-term negative impact on QOL*".
- [redacted].The company do not reference

minimum clinically meaningful changes and conclude that "*Results of the ITC showed treatment with AAP+ADT was associated with notable benefits in HRQL compared to DOC+ADT. These benefits were observed from three months and sustained for at least one year after treatment*".

- A crude reading of the company ITC and the results of Morgans et al suggests that the 12 month FACT-P improvement from AAP+ADT compared to ADT is roughly double that of the improvement from DOC+ADT compared to ADT.
-

In the opinion of the ERG the above supports an assumption of a QoL decrement for DOC+ADT vs ADT while on docetaxel treatment, but a QoL increment for ADT (post DOC+ADT) vs ADT when docetaxel treatment has ceased.

It can also be noted that the company model still does not apply any quality of life decrement for DOC+ADT or for ADT (post DOC+ADT) in the mCRPC setting, to the benefit of AAP+ADT.

Economics: Cost inputs

Treatment sequences: AAP+ADT vs ADT

The company suggests some revised treatment proportions for the comparison of AAP+ADT, abbreviated to AAP in the following table due to reasons of space, with ADT.

Table 4: mCRPC treatment proportions: AAP+ADT vs ADT

			Company proportions							
	ERG		Original		ACD response		ACD Scenario 1		ACD Scenario 2	
	AAP	ADT	AAP	ADT	AAP	ADT	AAP	ADT	AAP	ADT
1st line										
ABIR	..	35%	..	35%	..	100%	..	100%	..	100%
ENZA	..	35%	..	35%	..	..	..	..	..	..
DOC	65%	15%	60%	15%	100%	..	..	..	..	..
CABA	..	..	..	..	..	..	..	..	..	..
R223	30%	10%	30%	10%	..	..	50%	..	100%	..
BSC	5%	5%	10%	5%	..	..	50%	..	..	..
2nd line										
ABIR	..	10%	..	10%	..	..	..	..	..	..
ENZA	..	10%	..	10%	..	..	..	..	..	..
DOC	..	10%	..	10%	25%	100%	..	..	..	..
CABA	15%	5%	15%	5%	25%	..	..	..	..	..
R223	25%	20%	20%	20%	25%	..	..	50%	..	50%
BSC	60%	45%	65%	45%	25%	..	100%	50%	100%	50%
3rd line										
DOC	..	..	..	..	13%	25%	..	..	..	..
CABA	2%	1%	2%	1%	13%	25%	..	..	..	..
R223	3%	9%	8%	9%	25%	25%	..	..	..	..
BSC	95%	90%	90%	90%	50%	25%	100%	100%	100%	100%

ABIR: abiraterone, ENZA: enzalutamide, DOC: docetaxel, CABA: cabazitaxel, R223: radium-223

1st line mCRPC active treatments are all assumed to have exactly the same effectiveness in the model. Varying their proportions simply varies the costs. There is no impact upon patient benefits. These are only slightly affected if differing proportions of patients are assumed to receive BSC for 1st line mCRPC. The ERG revised base case of the original ERG report did not differentiate the proportions receiving BSC at 1st line mCRPC, and neither do the above company ACD response sequences. Consequently, the above revisions mainly only really affect costs. Immediately obvious is that the original company base case AAP+ADT proportion who are anticipated to receive 1st line mCRPC radium-223 has been revised to receive the somewhat cheaper docetaxel treatment.

Varying the proportions of 2nd line and 3rd line mCRPC treatments, including BSC, does not affect patient benefits and only affects costs. As a consequence, more patients in the

AAP+ADT arm receiving BSC than in the ADT arm tends to improve the cost profile and benefit the cost effectiveness estimate. This is particularly notable in the two scenarios, but also applies to some extent in the company ACD response revised base case.

The ERG is confused by the revised company base case assuming that for the comparison with ADT, all AAP+ADT patients will receive docetaxel as 1st line mCRPC treatment. For the comparison with ADT the company argument appears to be that there is "*a high unmet need for an alternative life-extending therapy for men who cannot receive chemotherapy in the NHS*". This seems to suggest that those who currently only receive ADT for mHSPC may either not be suitable for docetaxel or may be strongly averse to receiving it.

In the light of this the ERG revised base case will retain the ERG preferred treatment proportions. Illustrative scenario analyses will be conducted that halves the proportion of AAP+ADT patients who receive 1st line mCRPC docetaxel and assumes that these patients receive cabazitaxel, with the company ACD revised base case proportions and scenario analyses also being presented.

Treatment sequences: AAP+ADT vs DOC+ADT

The company suggests some revised treatment proportions for the comparison of AAP+ADT, with DOC+ADT, abbreviated to AAP and DOC respectively in the following table due to reasons of space.

Table 5: mCRPC treatment proportions: AAP+ADT vs DOC+ADT

			Company proportions							
	ERG		Original		ACD response		ACD Scenario 1		ACD Scenario 2	
	AAP	DOC	AAP	DOC	AAP	DOC	AAP	DOC	AAP	DOC
1st line										
ABIR	..	39%	..	39%	..	100%	..	100%	..	100%
ENZA	..	39%	..	39%	..	..	..	..	..	..
DOC	65%	..	60%	..	100%	..	100%	..	100%	..
CABA	..	12%	..	12%	..	..	..	..	..	..
R223	30%	5%	30%	5%	..	..	..	..	..	..
BSC	5%	5%	10%	5%	..	..	..	..	..	..
2nd line										
ABIR	..	5%	..	5%	..	..	..	..	..	..
ENZA	..	5%	..	5%	..	..	..	..	..	..
DOC	..	..	..	..	25%	25%	25%	100%	100%	100%
CABA	15%	5%	15%	5%	25%	25%	25%	..	..	..
R223	25%	25%	20%	25%	25%	25%	25%	..	..	..
BSC	60%	60%	65%	60%	25%	25%	25%	..	..	..
3rd line										
DOC	..	..	..	..	13%	13%	13%	..	..	..
CABA	2%	1%	2%	1%	13%	13%	13%	..	..	..
R223	3%	4%	8%	4%	25%	25%	25%	50%	50%	50%
BSC	95%	95%	90%	95%	50%	50%	50%	50%	50%	50%

ABIR: abiraterone, ENZA: enzalutamide, DOC: docetaxel, CABA: cabazitaxel, R223: radium-223

Similar arguments hold for this comparison as for the comparison of AAP+ADT with ADT. The ERG will retain its previously preferred treatment sequences, and apply the others as scenario analyses.

Treatment sequences: AAP+ADT vs DOC+ADT: MSM modelling

The company retains the argument that since the MSM model extrapolates LATITUDE data the LATITUDE mCRPC treatment proportions should be retained as well. The ERG disagrees with this as discussed in greater detail in the original ERG report. In essence, revising the mCRPC treatment proportions to reflect UK clinical practice has negligible effects upon the modelled patient outcomes, so there is no modelling downside to their adoption. The upside is that their adoption causes the model to more accurately estimate UK relevant costs.

Time on AAP treatment: TTD to PFS ratio

Section 3.15 of the ACD states that expert opinion was that AAP+ADT is well tolerated and that few would discontinue treatment. But for costing purposes the AC thought it appropriate to consider time to discontinuation data.

As per figure 9 of the ERG report, and replicated below, after month 20 the TTD curve falls somewhat below the PFS curve. This separation causes the ratio between the TTD curve and the PFs curve to fall to [redacted].by month 40, and causes the ratio of the areas under the curves to be [redacted].. The company model qualifies the abiraterone costs by this [redacted]..

Figure 5: AAP+ADT TTD and PFS curves

[redacted]

As discussed in more detail in the original ERG report, the ERG finds it implausible that by month 40 only [redacted].of patients who remain in PFS will remain on AAP+ADT treatment. This seems at odds with the expert opinion given during the 1st AC. The low ratios towards the tails of the curves are what drag the qualifying percentage down to [redacted]..

[redacted]

ERG revised modelling

As per the original ERG report the ERG presents two full sets of analyses, one for the MSM/TA387 model and one for the MSM model. These differ from the company analyses presented in response to the ACD in that they:

- Retain the original company assumption of SAEs and SREs quality of life effects for DOC+ADT and ADT (post DOC+ADT) being aligned with the AAP+ADT arm due its greater similarity in efficacy than with the ADT arm.
- [redacted]
- Apply the ERG preferred mCRPC treatment proportions of the original ERG report for the comparison of AAP+ADT with DOC+ADT.

The ERG also conducts the following sensitivity analyses:

- SA01: Applying the M1 1.13 OS HR and 0.69 PFS HR of STAMPEDE for AAP+ADT compared to DOC+ADT
- SA02: Limiting the treatment benefits of AAP+ADT over ADT to 40 months, 60 months and 80 months, by applying the ADT MSM TPM probabilities from month 40, month 60 and month 80 in the ADT arm[3].
- SA03: Applying a quality of life increment for ADT (post DOC+ADT) compared to ADT of half that of AAP+ADT compared to ADT.
- SA04: Applying the [redacted]. TTD:RFS ratio for costing that the company derives from the 40 month LATITUDE trial data.
- SA05: For the comparison of AAP+ADT with ADT, halving the proportion of AAP+ADT patients who receive docetaxel as 1st line treatment for mCRPC with these patients instead receiving cabazitaxel.
- SA06: Applying the mCRPC treatment proportions of the original company submission, that the company prefers in its ACD response, and those of the two company scenarios of the ACD response.
- SA07: Applying the LATITUDE treatment proportions in the MSM modelling.

Table 6: ERG revised base case: MSM/TA387 model

	LYs	QALYs	Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	5.030	3.281	[redacted]				
ADT	3.505	2.213	[redacted]	1.525	1.069	£18,223	£17,051

[3] The cohort flow construction is quite convoluted and adapting the model for this scenario analysis is complex. The ERG has had little time to implement this and none to cross check it. The company is urged to cross check the implementation of this prior to the 2nd AC.

DOCE	4.347	2.744	[redacted]	0.683	0.537	£13,442	£25,027

Table 7: ERG revised base case: MSM model

	LYs	QALYs	Costs	Δ LYs	Δ QALYs	Δ Costs	ICER
AAP+ADT	5.129	3.242	[redacted]				
ADT	3.597	2.158	[redacted]	1.532	1.084	£25,420	£23,459
DOCE	4.340	2.656	[redacted]	0.789	0.586	£21,966	£37,483

Table 8: ERG scenario analyses: MSM/TA387 model

	AAP+ADT vs ADT			AAP+ADT vs DOC+ADT		
	ΔQALYs	ΔCosts	ICER	ΔQALYs	ΔCosts	ICER
Base case	1.069	£18,223	£17,051	0.537	£13,442	£25,027
01: STAMPEDE HRs	..	[redacted]	..	0.533	[redacted]	£21,968
02a: 40 mths benefit	0.711	[redacted]	£23,291	..	[redacted]	..
02b: 60 mths benefit	0.863	[redacted]	£19,990	..	[redacted]	..
02c: 80 mths benefit	0.949	[redacted]	£18,625	..	[redacted]	..
03: DOC+ADT QoL inc.	..	[redacted]	..	0.489	[redacted]	£27,481
04: Co. TTD:RFS	1.069	[redacted]	£15,110	0.537	[redacted]	£21,164
05: Less DOC 1st mCRPC Tx	1.068	[redacted]	£19,151	..	[redacted]	..
06a: Co. Original mCRPC Tx	1.062	[redacted]	£17,029	0.530	[redacted]	£25,089
06b: Co.ACD mCRPC Tx	1.057	[redacted]	£19,122	0.527	[redacted]	£31,122
06c: Co. Scen1 mCRPC Tx	0.994	[redacted]	£22,645	0.527	[redacted]	£31,857
06d: Co. Scen2 mCRPC Tx	1.059	[redacted]	£27,107	0.527	[redacted]	£31,254

Table 9: ERG scenario analyses: MSM model

	AAP+ADT vs ADT			AAP+ADT vs DOC+ADT		
	ΔQALYs	ΔCosts	ICER	ΔQALYs	ΔCosts	ICER
Base case	1.084	£25,420	£23,459	0.586	£21,966	£37,483
01: STAMPEDE HRs	..	[redacted]	..	0.461	[redacted]	£40,633
02a: 40 mths benefit	0.724	[redacted]	£33,010	..	[redacted]	..
02b: 60 mths benefit	0.878	[redacted]	£28,002	..	[redacted]	..
02c: 80 mths benefit	0.964	[redacted]	£25,889	..	[redacted]	..
03: DOC+ADT QoL inc.	..	[redacted]	..	0.538	[redacted]	£40,825
04: Co. TTD:RFS	1.084	[redacted]	£21,544	0.586	[redacted]	£33,943
05: Less DOC 1st mCRPC Tx	1.083	[redacted]	£25,523	..	[redacted]	..
06a: Co. Original mCRPC Tx	1.084	[redacted]	£23,356	0.586	[redacted]	£37,291
06b: Co.ACD mCRPC Tx	1.081	[redacted]	£25,076	0.583	[redacted]	£37,749
06c: Co. Scen1 mCRPC Tx	1.081	[redacted]	£23,933	0.583	[redacted]	£40,937
06d: Co. Scen2 mCRPC Tx	1.081	[redacted]	£29,037	0.583	[redacted]	£37,972
07: LATITUDE mCRPC Tx	1.086	[redacted]	£24,155	0.586	[redacted]	£33,864

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Abiraterone for untreated high-risk hormone-sensitive metastatic prostate cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using abiraterone in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: TBC 2018

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using abiraterone in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: TBC

Third appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5.

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1 Recommendations

1.1 Abiraterone with prednisone or prednisolone plus androgen deprivation therapy (ADT) is not recommended, within its marketing authorisation, for untreated high-risk hormone-sensitive metastatic prostate cancer in adults.

1.2 This recommendation is not intended to affect treatment with abiraterone plus ADT that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for untreated high-risk hormone-sensitive metastatic prostate cancer includes 2 treatment regimens: ADT alone and docetaxel plus ADT. Clinical trial results show that, compared with ADT alone, abiraterone plus oral prednisone or prednisolone plus ADT increase the time until the disease progresses and the overall length of time people live. The results of trials also show that, compared with docetaxel plus ADT, abiraterone plus ADT increases the time until the disease progresses but not the overall length of time people live.

The company's economic model does not accurately reflect the differences in the effectiveness and the number of treatments available to people with high-risk hormone-sensitive metastatic prostate cancer in NHS clinical practice. Also, the model estimates longer survival for people having abiraterone plus ADT compared with docetaxel plus ADT, which was not supported by the clinical evidence. This means that no plausible estimates of the cost-effectiveness of abiraterone plus ADT can be established. So, there is no basis on which to recommend abiraterone

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plus ADT for untreated high-risk hormone-sensitive metastatic prostate cancer in adults.

2 Information about abiraterone

Marketing authorisation	Abiraterone (Zytiga; Janssen) with prednisone or prednisolone has a UK marketing authorisation for treating 'newly diagnosed high risk metastatic hormone-sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT)'. In the LATITUDE clinical trial, high-risk prognosis was defined as having at least 2 of the following 3 risk factors: a Gleason score of 8 or more; 3 or more lesions on bone scan; and measurable visceral metastasis (excluding lymph node disease).
Dosage in the marketing authorisation	1,000 mg as a single daily dose. It is administered orally.
Price	

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Janssen and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical management

Androgen deprivation therapy (ADT) with and without docetaxel are the first-line treatment options for metastatic hormone-sensitive prostate cancer

3.1 The clinical experts explained that people with newly diagnosed hormone-sensitive (that is, hormone-naive) metastatic prostate cancer have ADT or docetaxel plus ADT in clinical practice. NICE's guideline for prostate cancer recommends ADT, specifically continuous luteinising hormone-releasing hormone agonists, bilateral orchidectomy (removal of the testicles), or bicalutamide monotherapy. The clinical experts explained that orchidectomy and bicalutamide monotherapy are rarely used in this way in the NHS. The committee agreed that ADT alone or with docetaxel

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or abiraterone would include luteinising hormone-releasing hormone agonists. It understood that, although docetaxel is not licensed for use with ADT for hormone-sensitive metastatic prostate cancer, NHS England commissions 6 cycles of docetaxel with ADT based on evidence from 3 trials assessing docetaxel plus ADT vs ADT alone (CHAARTED, GETUG-AFU 15 and STAMPEDE). The committee concluded that ADT and docetaxel plus ADT were appropriate comparators.

It is not appropriate to consider separately the clinical and cost effectiveness of abiraterone in people who currently have ADT alone

3.2 The committee were aware of the company proposal for abiraterone as an alternative for patients who would currently have ADT alone, rather than those who would have docetaxel plus ADT. The Cancer Drugs Fund's clinical lead noted that half of people presenting with hormone-sensitive metastatic prostate cancer in England have ADT alone. While some people are not fit enough for docetaxel, most choose not to have it because of the adverse events associated with chemotherapy. The Committee recognised therefore that there were 2 distinct populations and considered each in turn.

- **People who are not fit enough for docetaxel.** A patient expert explained that there is an unmet need for an alternative treatment option for people who cannot have docetaxel plus ADT. NHS England's commissioning policy indicates that someone may not be fit enough for docetaxel if they have: a poor overall performance status (WHO performance 3 to 4), poor bone marrow function, or a 'life limiting illness'. The policy also states that there are "few absolute contraindications for docetaxel therapy". The committee was aware that LATITUDE and STAMPEDE, the key clinical trials of abiraterone with oral prednisone or prednisolone plus ADT (see section 3.4) included only people with adequate haematological function, an Eastern Cooperative Oncology Group (ECOG) status 0, 1 or 2 and without any condition that would interfere with participation. The committee was

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aware that NICE recommends radium-223 as an option for treating hormone-relapsed prostate cancer with bone metastases in adults only if they already had docetaxel or if docetaxel is contraindicated or not suitable. However, this guidance notes that people for whom docetaxel is contraindicated or not suitable are difficult to define. The committee was aware that it had not been presented with evidence of abiraterone's effectiveness in people who cannot take docetaxel, because these people were excluded from LATITUDE and STAMPEDE.

- **People who chose not to have docetaxel.** The committee recognised that the majority of people who currently have ADT alone rather than docetaxel plus ADT do so because of patient choice. This is mainly because they wish to avoid the adverse events associated with docetaxel. The clinical experts explained that there are no clear clinical criteria to differentiate between people for whom abiraterone plus ADT, ADT alone or docetaxel plus ADT is the most appropriate treatment option. The committee recognised that patient choice was important. It also agreed that people who currently chose to have docetaxel may be as likely to choose to have abiraterone if it were available, as those who currently choose to have ADT alone. The committee agreed therefore that abiraterone should be considered as an alternative for all patients, not just those who currently choose ADT alone.

The committee agreed that there are no clear-cut clinical criteria to define who could have abiraterone, but not docetaxel, or any supporting evidence of the effectiveness of abiraterone for those for whom docetaxel is contraindicated. In addition it would be inappropriate to only consider abiraterone for those who choose to have ADT and not those who chose to have docetaxel. Therefore, it concluded that it could not consider separately the clinical and cost effectiveness of abiraterone in people who cannot have docetaxel, or only consider ADT alone as a comparator.

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The first treatment for metastatic hormone-sensitive prostate cancer affects the number of follow-on treatments a person might have

3.3 The clinical experts explained that people who have previously had docetaxel as first-line treatment can be given docetaxel again (for up to 10 cycles) because the benefit of docetaxel is not exhausted when used (with ADT) for only 6 cycles. The Cancer Drugs Fund clinical lead explained that abiraterone and enzalutamide are commissioned by NHS England only once in the treatment pathway because there is as yet no evidence of clinical benefit for enzalutamide after abiraterone and vice versa. The committee understood that people who have abiraterone plus ADT for hormone-sensitive prostate cancer have fewer options for active follow-on treatments available because they will not be able to have abiraterone (or enzalutamide) later in the treatment pathway. It noted that the sequence of follow-on treatments may vary from person to person and possible follow-on treatments include:

- After ADT alone:
  - abiraterone or enzalutamide (before or after docetaxel)
  - docetaxel
  - other active treatments such as cabazitaxel or radium-223.
- After docetaxel plus ADT:
  - abiraterone or enzalutamide (before or after docetaxel)
  - docetaxel again
  - other active treatments such as cabazitaxel or radium-223.
- After abiraterone plus ADT:
  - docetaxel
  - other active treatments such as cabazitaxel or radium-223.

In response to consultation the company submitted evidence from a survey they carried out with 27 clinicians. Most respondents reported that less than 25% of people have docetaxel again. The committee interpreted this as evidence that some people have docetaxel again in the NHS, so it is relevant to consider docetaxel as a subsequent treatment option. The

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committee concluded that the first-choice treatment for hormone-sensitive metastatic prostate cancer affects the follow-on treatments a person may have, and that having abiraterone plus ADT limits the follow-on treatment options compared with having ADT alone or docetaxel plus ADT.

Clinical evidence

LATITUDE and STAMPEDE are both relevant for assessing the clinical effectiveness of abiraterone plus ADT

3.4 Two randomised controlled trials have investigated the clinical effectiveness of abiraterone plus ADT, LATITUDE and STAMPEDE:

- LATITUDE was a double-blind trial including 1,199 patients with newly diagnosed high-risk hormone-sensitive metastatic prostate cancer. Patients were randomised to either abiraterone plus prednisone plus ADT or ADT alone.
- STAMPEDE was a multi-arm multi-stage non-blinded adaptive trial of patients with newly diagnosed high-risk metastatic, node-positive or localised disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features. Randomised trial arms included abiraterone plus ADT, ADT alone and docetaxel plus ADT. The abiraterone plus ADT compared with ADT alone comparison was pre-specified in the trial protocol and compared patients in these arms recruited at the same time. Data were available for 502 patients with metastatic prostate cancer in the ADT alone arm, 500 in the abiraterone plus ADT arm and 115 in the docetaxel plus ADT arm.

The company considered LATITUDE to be the most relevant trial for appraising the clinical effectiveness of abiraterone plus ADT. It considered STAMPEDE to be less relevant because it included patients with locally advanced (as well as patients with metastatic) prostate cancer, which was broader than the licensed population for abiraterone. The results from STAMPEDE for docetaxel plus ADT compared with abiraterone plus ADT

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in hormone-sensitive metastatic prostate cancer have been published. However, the clinical experts explained that results for the licensed population (that is, the subgroup of patients with high-risk disease) had been collected, but not yet published. Two clinical experts, who were also investigators in STAMPEDE, explained that there was no reason to believe that there was any subgroup of people for whom abiraterone was more or less effective; that is, effect modification by risk level was unlikely as abiraterone appeared similarly effective in localised, metastatic and high-risk hormone-sensitive prostate cancer. The committee agreed that, although STAMPEDE assessed treatments in a broader population than the population covered by the marketing authorisation for abiraterone, data from STAMPEDE are broadly generalisable to the population for whom abiraterone plus ADT is being appraised. It concluded that LATITUDE and STAMPEDE were both relevant for assessing the clinical effectiveness of abiraterone plus ADT for high-risk metastatic hormone-sensitive prostate cancer.

Follow-on treatments in STAMPEDE reflect clinical practice in England more than those in LATITUDE

3.5 STAMPEDE was a trial in patients from the UK and was unblinded. This meant that follow-on treatments in STAMPEDE reflected what people would have in clinical practice in the UK because the choice of next treatment depends on knowing the first treatment, unlike in the blinded LATITUDE trial. The company noted that a limitation of LATITUDE was that the follow-on treatments did not reflect those used in the UK but highlighted that patients in the abiraterone arm of STAMPEDE also had treatments that did not reflect UK clinical practice. 10% of patients had enzalutamide after abiraterone and 3% had abiraterone again - similar to the proportions in LATITUDE. However, because it was carried out in the UK and reflected NHS practice, the committee concluded that the estimates of survival from STAMPEDE after a patient needed a next treatment were likely more relevant to clinical practice in England than those from LATITUDE.

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STAMPEDE provides direct evidence when comparing abiraterone plus ADT with docetaxel plus ADT

3.6 STAMPEDE directly compared abiraterone plus ADT with docetaxel plus ADT. However, the company preferred to use a network meta-analysis to compare abiraterone plus ADT with docetaxel plus ADT because of its concerns about the generalisability of the STAMPEDE population to people with high-risk hormone-sensitive metastatic prostate cancer (see section 3.4). The clinical experts explained that the trials of docetaxel plus ADT compared with ADT alone in the company's network meta-analysis (that is, CHAARTED and GETUG-AFU 15) had different populations from LATITUDE. This was because they included both patients who were or were not newly diagnosed, and only a subgroup of patients with high-volume disease (which is similar to high-risk disease). The company also provided a scenario analysis that included the data from the STAMPEDE direct comparison in the network meta-analysis. The committee considered the estimated effect measures from STAMPEDE to be less biased than those from the network meta-analysis because STAMPEDE collected randomised data directly comparing abiraterone plus ADT with docetaxel plus ADT that were generalisable to the UK population (see section 3.4). The committee recalled hearing from clinical experts in the first meeting that the effect of abiraterone is unlikely to be modified by risk, but considered that the trials in the network may differ in other ways which influence the effect estimate (section 3.4). In response to consultation the company provided the results of an indirect comparison of abiraterone plus ADT compared with docetaxel plus ADT using the 3 arms of the STAMPEDE trial only (the abiraterone compared with ADT arm, the docetaxel compared with ADT arm and the abiraterone compared with docetaxel arm). The committee considered that it preferred direct evidence from STAMPEDE for the comparison between abiraterone plus ADT with docetaxel plus ADT but was aware that STAMPEDE was not statistically powered to detect a difference in survival in the metastatic subgroup because it was a post-hoc analysis. The committee

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acknowledged that both direct and indirect evidence contributes to the total body of evidence, so it concluded that it would also consider the indirect evidence from the company's network meta-analyses in its decision-making.

Abiraterone plus ADT extends survival compared with ADT alone

3.7 Abiraterone plus ADT statistically significantly improved both progression-free and overall survival compared with ADT alone in LATITUDE and in patients with metastatic disease in STAMPEDE, and the size of improvement was similar in the 2 trials. In LATITUDE, median progression-free survival was 14.8 months with ADT alone and 33.0 months with abiraterone plus ADT (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.39 to 0.55), and median overall survival with ADT alone was 34.7 months and was not reached with abiraterone plus ADT (HR 0.62, 95% CI 0.51 to 0.76). In STAMPEDE, the hazard ratio for progression-free survival was 0.43 (95% CI 0.36 to 0.52), and for overall survival was 0.61 (95% CI 0.49 to 0.75). The committee concluded that abiraterone plus ADT improved both progression-free and overall survival compared with ADT alone.

Compared with docetaxel plus ADT, the effects of abiraterone plus ADT on disease progression and overall survival vary

3.8 In patients with metastatic disease in STAMPEDE, abiraterone plus ADT improved progression-free survival compared with docetaxel plus ADT (HR 0.69, 95% CI 0.50 to 0.95), but overall survival was similar (HR 1.13, 95% CI 0.77 to 1.66) with the point estimate favouring docetaxel. In the company's updated base case, it used the results of the network meta-analysis that included data from LATITUDE, CHAARTED, GETUG-AFU 15 and STAMPEDE. This showed that abiraterone plus ADT improved progression-free survival compared with docetaxel plus ADT (HR 0.64, 95% Credible Interval [CrI] 0.54 to 0.76), and the point estimate for overall survival favoured abiraterone (HR 0.91, 95% CrI 0.77 to 1.09). The network meta-analysis using data from 3 arms of the STAMPEDE

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trial showed similar results; abiraterone improved progression-free survival compared with docetaxel plus ADT and while the point estimate for overall survival favoured abiraterone, the credible interval included 1 (i.e. was not statistically significant). Two of the clinical experts explained that a possible reason for a progression-free survival benefit but lack of overall survival benefit with abiraterone plus ADT compared with docetaxel plus ADT in STAMPEDE related to the treatments that people could receive later in the treatment pathway. People who had docetaxel plus ADT or ADT alone could still go on to receive abiraterone and docetaxel, whereas people who had already had abiraterone could only go on to have docetaxel. The clinical experts involved in STAMPEDE confirmed that that post-progression survival was shorter after abiraterone plus ADT than after ADT alone in this trial. Taking into account the direct and indirect comparisons, the committee concluded that abiraterone plus ADT improves progression-free survival. However, none of the estimates from the direct comparisons or indirect comparisons showed statistically significant differences in mortality between abiraterone and docetaxel. The committee therefore concluded that there is currently no evidence that abiraterone plus ADT improves overall survival compared with docetaxel plus ADT.

The company's economic model

The company's model does not produce plausible estimates of post-progression or overall survival

3.9 The company assessed cost effectiveness of abiraterone using a multi-state Markov model. The model was split into 2 phases:

- In the **hormone-sensitive** phase, the company modelled probabilities of progressing and dying while on abiraterone plus ADT and ADT alone using data from LATITUDE. For abiraterone plus ADT compared with docetaxel plus ADT, the company applied hazard ratios from its revised network meta-analysis (including STAMPEDE) to the LATITUDE data.

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- In the **hormone-relapsed** phase, the company based overall survival on the survival curves from TA387 abiraterone for treating metastatic hormone-relapsed prostate cancer before docetaxel is indicated. For all active treatments, the company used the abiraterone overall survival curve. This is because an indirect comparison of treatments for hormone-relapsed disease suggested no differences in efficacy. The ERG explained that this meant that although different proportions of subsequent treatments were modelled for each arm, this affected only the costs, and post-progression survival was similar in each arm. Further, it explained that a 'calibration factor' was applied to the TA387 curve so that the results were in line with the data from LATITUDE.

The committee considered that the model did not reflect the differences in survival that might arise from having abiraterone later in the treatment pathway or having a second course of docetaxel (see section 3.12). Moreover, modelled overall survival was much longer with abiraterone than docetaxel than even when using the overall survival hazard ratio of 1.13 from the STAMPEDE direct comparison. This is because the probability of dying in the progression-free survival state is much lower than the probability of dying in the post-progression state, and patients having abiraterone remain progression-free for longer than patients who receive other treatments. As such, even when the model incorporates an overall survival hazard ratio of 1 (implying that people taking abiraterone are no more likely to die than people taking docetaxel), the model continues to predict that patients on abiraterone live longer. The ERG explained that this is because of the way that the company models transitions to death from the progression-free and post-progression health states. The committee considered that appropriate transition probabilities that produce outcomes reflecting the clinical data should be used. The committee noted that a company scenario analysis using the transition probabilities derived from LATITUDE data alone did not address these issues. The committee further considered that the survival curves from TA387 may not be the most appropriate to use, because they had to be

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'calibrated' to fit the LATITUDE data. The committee considered that data from STAMPEDE could be used to validate the outputs of the company's model and the ERG explained that the STAMPEDE data could be used as the primary source for modelling treatments during hormone-relapsed disease. The committee concluded that the company's approach to modelling does not provide plausible estimates of post-progression survival or overall survival and therefore does not generate valid estimates of cost effectiveness.

Utility values in the model

The utility estimates for being on abiraterone plus ADT, docetaxel plus ADT and ADT alone should be based on the same measure of quality of life

3.10 The company took into account separately the effects on quality of life of adverse effects and of being on treatment. The sources of these data are in table 1.

Table 1 Data sources for the utility value estimates in the model

Treatment	Quality of life relating to treatment	Quality of life relating to adverse events
ADT alone	Based on EQ-5D data from LATITUDE.	Published utility values for adverse effects and skeletal-related events.
Abiraterone plus ADT	Based on EQ-5D data from LATITUDE. There was a utility increase for being on abiraterone compared with ADT alone.	
Docetaxel plus ADT	Based on a company survey. There was a utility decrement when treated with docetaxel.	
Abbreviation: ADT, androgen deprivation therapy.		

The committee was aware that the company used different approaches to estimate the effect on quality of life of having abiraterone plus ADT or ADT than to estimate the effect with docetaxel plus ADT. The utility values for being on abiraterone plus ADT were based on EQ-5D results from LATITUDE, and for being on docetaxel plus ADT were based on a

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separate survey of the general public carried out by the company. The committee was aware that the NICE methods guide states that EQ-5D is the preferred measure of health-related quality of life. The committee further noted that the company could have used trial-based EQ-5D results for docetaxel plus ADT in its model because STAMPEDE collected these for a UK population randomised to abiraterone plus ADT, to docetaxel plus ADT and to ADT alone. The committee stated that although it considered the effectiveness data from the metastatic subgroup from STAMPEDE to be generalisable to the population under appraisal (see section 3.4), it was plausible that level of risk affects quality of life. It concluded that it was preferable to use EQ-5D data from the subgroup of people from STAMPEDE with metastatic and high-risk hormone-sensitive prostate cancer to assess quality of life because comparable data were available for abiraterone plus ADT, docetaxel plus ADT and ADT alone.

The risk of serious and skeletal-related adverse events after docetaxel should be based on direct evidence

3.11 The committee was aware that after patients reach the 6 cycle maximum for docetaxel but remain progression-free, they take ADT alone. The company assumed that the risk of serious adverse events and skeletal-related adverse events (associated with disease progression) for these patients equalled that for patients who started therapy with ADT alone. The ERG explained that because docetaxel is more similar in effectiveness to abiraterone than ADT alone, it might be more appropriate to assume that the risk of these events was the same as in the abiraterone arm. The committee considered that the company should provide direct evidence rather than applying evidence for other treatments to docetaxel. In this absence of direct evidence, the committee agreed that it was more appropriate to assume that the risk of serious adverse events and skeletal-related adverse events in the docetaxel plus ADT arm was the same as the abiraterone plus ADT arm in line with the ERG's approach.

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Costs used in the company's model

The company's model does not reflect the treatment pathway in the NHS

3.12 In its consultation response, the company revised the treatment pathways in the hormone-relapsed state. It:

- Increased the proportion of people that receive docetaxel after abiraterone to 100% (previously 60%)
- Increased the proportion of people receiving abiraterone after ADT and docetaxel plus ADT to 100%
- Included docetaxel retreatment in up to 25% of patients in line with its survey of clinicians (section 3.3)
- Excluded having abiraterone or enzalutamide twice, or after each other.

The CDF clinical lead explained that the updated treatment sequence was not plausible because everyone would not receive docetaxel after abiraterone and the proportions of people receiving subsequent therapies was more accurately reflected in the company's original base case model. The committee recalled that the company's model addressed differences in costs for subsequent therapies, but not in effectiveness of treatments for hormone-relapsed disease (see section 3.9). As such, the company's changes in the distribution of treatments presented at the committee's second meeting did not address the model's implausible results for overall survival by treatment (section 3.9). The committee recognised the importance of accurately reflecting NHS costs but concluded that the company's model does not reflect the treatment pathway as it does not reflect the effectiveness of subsequent treatments.

Few people will stop treatment with abiraterone plus ADT before progression

3.13 The ERG was concerned about how the company had adjusted the costs of abiraterone in the progression-free hormone-sensitive health states for people who had stopped having abiraterone before disease progression. The company modelled time on treatment in the health state using the

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time people continued to take abiraterone relative to the time to disease progression in LATITUDE. The ERG estimated this based on the proportion of tablets taken in the safety population of LATITUDE, which was larger than the company's estimate of the proportion of people who would continue having abiraterone before disease progression. The clinical experts explained that they expected few people would stop having abiraterone plus ADT before disease progression because it is generally well tolerated. The committee concluded that it was appropriate to consider time on treatment data when modelling the cost of abiraterone plus ADT in line with the ERG's approach.

Cost-effectiveness results

It is not possible to determine a plausible cost-effectiveness estimate

3.14 The committee stated that, because the company's model structure did not reflect the treatment pathway for metastatic hormone-sensitive prostate cancer and gave implausible survival estimates that did not reflect the clinical data (see section 3.11), it was unable to determine a plausible incremental cost-effectiveness ratio (ICER) for abiraterone plus ADT compared with ADT alone or with docetaxel plus ADT. It noted that the company did not provide probabilistic ICERs and the committee would prefer to see these in addition to the deterministic ICERs. Further, none of the sensitivity analyses provided by the company or the ERG allowed it to assess the effect of different numbers of follow-on treatments on post-progression survival. The committee expected that, if the model reflected the treatment pathway, the benefits of abiraterone plus ADT in delaying progression might be balanced by the potential benefits of the availability of more treatment options after a person's prostate cancer has become hormone-relapsed after ADT alone or docetaxel plus ADT. It concluded that it was not possible to determine a plausible ICER for abiraterone plus ADT compared with ADT or with docetaxel plus ADT, and that without a plausible ICER it could not recommend abiraterone as a cost-effective use of NHS resources.

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The committee would like to see cost-effectiveness estimates from analyses that include its preferences

3.15 The committee agreed that its preferred approach to modelling would reflect:

- no survival benefit of abiraterone compared with docetaxel plus ADT therapy (section 3.9)
- sensitivity analyses around the abiraterone compared with docetaxel plus ADT overall survival hazard ratio (see sections 3.9)
- treatment pathways for hormone-relapsed prostate cancer that reflect NHS clinical practice (see section 3.9 and 3.12)
- differences in effectiveness of treatments for hormone-relapsed prostate cancer (see sections 3.9 and 3.12)
- quality of life data from STAMPEDE for docetaxel treatment (see section 3.12)
- fully incremental, probabilistic cost effectiveness analyses (section 3.14).

Equality issues

The recommendations apply to all people with prostate cancer

3.16 The committee noted that, as in previous appraisals for technologies for treating prostate cancer, its recommendations should apply to people with prostate cancer because men and transgender women have a prostate. No other equality issues were raised during the scoping process or in the submissions for this appraisal.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based

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on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
XXX 2018

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Jessica Cronshaw and Mary Hughes

Technical Leads

Ross Dent and Jasdeep Hayre
Technical Advisers

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Jeremy Powell

Project Manager

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Submission Addendum

[July 2019]

File name	Version	Contains confidential information	Date
ID945_Abiraterone mHSPC_Final Analysis Addendum_120719 [ACIC]	1.0	Yes	July 2019

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B.1. Introduction

B.1.1. ID945 appraisal context

Appraisal ID945 was originally submitted in February 2018 and underwent subsequent assessment by the Evidence Review Group (ERG) and NICE Committee. After the 2nd Appraisal Committee Meeting in July 2018, ID945 was suspended. At the time of suspension, the Committee highlighted their preferred assumptions to be accounted for when the appraisal was re-initiated and, where feasible, Janssen have endeavoured to address these within this addendum.

Primarily, the Committee wished to see an alternative model structure for assessing cost-effectiveness enabling more extensive sensitivity analyses around survival projections; Janssen have presented a new model herein which allows for this. The Committee also debated the representativeness of treatment pathways simulated within the model; Janssen have sought expert clinical opinion to revise and re-validate model assumptions to ensure these are reflective of current practice within the NHS. Janssen also recognise the Committee's interest in attaining health-related

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quality of life (HRQL) data from the STAMPEDE trial; however, these remain unpublished to date.

Finally, Janssen wish to emphasise the acute unmet need within this setting: men with high-risk metastatic hormone-sensitive prostate cancer (mHSPC), who are chemo-ineligible at diagnosis, have very poor prognoses and urgently need access to a life-extending treatment option within the NHS. As re-affirmed within this addendum, abiraterone has been consistently shown to be a highly cost-effective use of NHS resources within this cohort of patients.

B.1.2. Indication

Abiraterone acetate (AA) plus prednisolone (AAP) for the treatment of adult men with newly diagnosed high-risk mHSPC in combination with androgen deprivation therapy (ADT).[1]

The NICE Committee have concluded that LATITUDE and STAMPEDE trials are both relevant for assessing the clinical effectiveness of AAP + ADT for high-risk mHSPC:

- LATITUDE is the pivotal registration trial and primary source of evidence for the use of AAP + ADT vs ADT alone in patients with newly diagnosed high-risk mHSPC.[2 3]
- STAMPEDE is a primarily UK-based trial investigating the use of AAP + ADT in early prostate cancer within the NHS; however, the enrolled population of STAMPEDE is much broader than the licensed indication for AAP + ADT.[4]

Since this appraisal (ID945) was suspended in July 2018, the final analysis of LATITUDE has been conducted,[3] and *post-hoc* analyses of STAMPEDE have been published which specifically look at AAP + ADT vs ADT alone in the subgroup of patients with metastatic high-risk prostate cancer whom are comparable to those in LATITUDE.[5]

B.1.3. Disease background

In 2016, 40,489 men were diagnosed with prostate cancer in England, of whom 18% will have presented with metastases.[6] This means curative treatment is no longer

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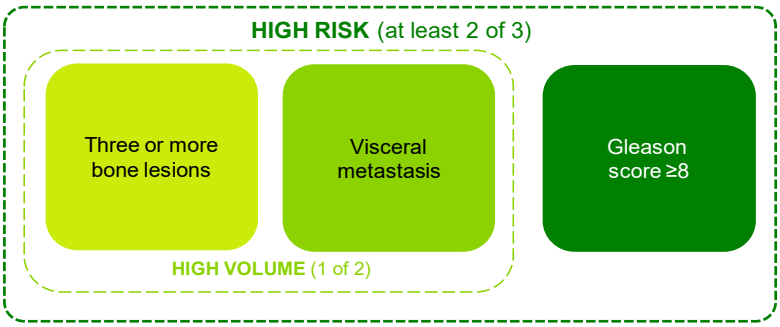
feasible as the cancer has already spread beyond the prostate.[6] Approximately 50% of men newly diagnosed with mHSPC are likely to be further classified as 'high-risk',[7] meaning they have two of the following three poor prognostic factors: a Gleason score of ≥8 (describing the aggressiveness of the tumour), the presence of ≥3 lesions on a bone scan, or the presence of visceral metastases (both describing the extent of tumour spread).[2] As illustrated by Figure 1, high-volume criteria (used elsewhere in mHSPC research) and high-risk significantly overlap, and published literature has shown these definitions to be closely comparable.[7]

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



Key: mHSPC, metastatic hormone-sensitive prostate cancer

Patients with newly diagnosed high-risk mHSPC often have debilitating symptoms that significantly impact quality of life, such as bone pain, urinary problems, tiredness, or unexpected weight loss;[8] [9] the psychological burden of receiving a diagnosis of metastatic prostate cancer is hard to quantify.

It is estimated that 3,700 men are diagnosed with high-risk mHSPC in England each year, equating to <7 patients per 100,000 population (see Appendix A), thus emphasising the small size of this patient cohort.

B.1.4. Current treatment

Docetaxel + ADT is unlicensed in this setting; however, following recent trials such as CHAARTED, GETUG-AFU 15 and STAMPEDE, this chemotherapy regimen is now commissioned by NHS England for patients who are fit enough and willing to receive it. According to real-world data, off-label docetaxel + ADT is only used in 40% of patients with newly diagnosed mHSPC, and feedback from a Clinical Survey

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emphasises how practice varies nationally in the NHS.[10 11] These data highlight that many men are unfit for chemotherapy, or are unwilling to receive cytotoxic docetaxel so early in their treatment pathway, because of its known side effects.[12]

Alternatively, ADT alone is the only licensed treatment available for patients with newly diagnosed high-risk mHSPC in England. Real-world data have also shown 60% of men are still treated with ADT alone in the UK, despite the availability of unlicensed but funded chemotherapy.[10 11] Of these men currently on ADT alone, 20% are likely to be clinically unsuitable for chemotherapy (herein referred to as 'chemo-ineligible'),[13] and others are simply unable to receive it. For example, a patient's emotional and physical ability to endure the expected toxicities of chemotherapy need to be considered as well as other socio-economic factors, such as presence of a carer and proximity/ accessibility of health services. In clinical practice, the overarching decision to undertake early chemotherapy lies between a patient and their clinician.

These data signpost the significant unmet need for an efficacious yet tolerable treatment option, particularly for those patients who are chemo-ineligible, because ADT alone ultimately always fails. Most patients progress on ADT alone within one to two years as they develop metastatic castration-resistant prostate cancer (mCRPC).[14] ADT alone is poor at delaying disease progression, ineffective at delaying the deterioration of HRQL and unable to prolong survival,[15] yet it is the only currently available treatment option for men who are chemo-ineligible at diagnosis.

B.1.5. Survival prospects

Men with newly diagnosed high-risk mHSPC have the worst prognosis of all metastatic prostate cancer patients, and those still treated with ADT alone die within three years.[5 16-18] Only 30% of men diagnosed with stage IV (i.e. metastatic) prostate cancer are likely to survive for five years.[19] Prognosis is even poorer for those with high-risk (or similarly high-volume) prognostic factors at diagnosis because their cancer is likely to spread quicker.[20-22] The control arms from four clinical trials in high-risk/high-volume mHSPC patients demonstrate that life expectancy for men deemed chemo-ineligible at diagnosis is three years or less (median overall survival

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[OS]: LATITUDE=36.5 mo;[3] STAMPEDE, <35 mo;[5] CHAARTED, 33.1 mo;[18] GETUG-AFU 15, 34.0 mo[17]).

At time of the LATITUDE final analysis (median follow-up 51.8 months), median OS was 53.3 months for patients treated with AAP + ADT, compared to only 36.5 months for those treated with ADT alone (hazard ratio [HR]=0.66 [95% Confidence Interval [CI]: 0.56, 0.78]; p<0.0001).[3] Indeed, AAP + ADT prolonged OS by 16.8 months, which equates to a 46% increase in median survival relative to the current life expectancy of chemo-ineligible patients. The robustness of this result is further validated by the significant benefit of even greater magnitude (HR=0.54 [95% CI: 0.41-0.70]; p<0.001) observed in *post-hoc* analysis of the high-risk mHSPC subgroup of the STAMPEDE trial.[5] STAMPEDE is considered most representative of UK clinical practice by the Committee.

These results show that a patient's total life expectancy when treated with ADT alone (median OS=36.5 months) is of similar length to the time a patient spends progression-free when treated with AAP + ADT (median radiographic progression free survival [rPFS]=33.0 months),[3] thereby emphasising the substantial value of AAP + ADT to patients deemed chemo-ineligible at diagnosis. Importantly, clinicians have suggested there is no clinical or biological reason why the treatment effect of AAP + ADT, as seen in LATITUDE, would differ based on suitability for chemotherapy.[13]

B.1.6. Clinical experience and tolerability

AAP has an established safety and tolerability profile, with seven years of clinical experience in the NHS. Patients receiving AAP + ADT in LATITUDE experienced significant improvements in their HRQL. Compared to ADT alone, treatment with AAP + ADT significantly reduced the worsening of pain and fatigue by 28% and 35%, respectively, contributing to a significantly better general quality of life.[23] This enables patients to go about their daily lives with more energy and in more comfort.[2] [23] These significant benefits were sustained for the entire treatment period. Furthermore, utility analysis of LATITUDE EQ-5D data derived an on-treatment utility increment of [redacted] for AAP + ADT further substantiating the patient benefit.

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While no direct HRQL data are available to compare AAP + ADT with docetaxel + ADT as it has not been published by the STAMPEDE group, it is widely known that docetaxel is a cytotoxic chemotherapy which is often associated with severe side effects; these may include neutropenia, diarrhoea, nausea, vomiting and hair loss.[12] Indeed, evidence has shown how patients and their carers can be substantially affected by experience with docetaxel.[24] Results from a Bayesian network meta-analysis (NMA) have also shown that treatment with AAP + ADT was associated with notable benefits in reducing pain and improving HRQL compared to docetaxel + ADT.[16] Collectively, these data confirm that AAP + ADT provides substantial improvements in patients' quality of life irrespective of whether they are currently treated with ADT alone or docetaxel + ADT.

B.1.7. Value for money

Men with high-risk mHSPC deemed chemo-ineligible at diagnosis have similar life expectancy to those with mCRPC assessed in TA387, yet AAP elicits greater relative gains in survival when used earlier in the treatment pathway. Indeed, when used in mCRPC (TA387), AAP increases survival vs 'best supportive care' (i.e. ADT alone) by 4.4 months (median follow-up: 49.2 months)[25] compared to 16.8 months when used in newly diagnosed high-risk mHSPC (median follow-up: 51.8 months).[3] The fact that AAP elicits an approximately four times greater relative survival gain when used in mHSPC versus mCRPC emphasises the value of treating those patients eligible for AAP + ADT as early as possible.

Following the suspension of this appraisal (ID945) in July 2018, a revised *de novo* economic model has assessed the cost-effectiveness of AAP + ADT vs ADT alone in newly diagnosed high-risk mHSPC. Results have shown AAP + ADT is a highly cost-effective use of NHS resources for those deemed chemo-ineligible at diagnosis, yielding an incremental cost-effectiveness ratio (ICER) between [redacted] and [redacted] per quality adjusted life year (QALY) gained vs ADT alone, under the confidential commercial access arrangement (CAA). Importantly, the ICER was largely insensitive to variation in parameters/assumptions tested in scenario analyses and one-way sensitivity analysis (OWSA) demonstrating certainty in the model outcomes. Of note, at the time this appraisal was suspended, the ICER for AAP + ADT vs ADT alone using the previous model structure was [redacted] (ID945

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Company appraisal consultation document [ACD] Response).[26] These robust results across two different model structures provide irrefutable evidence that AAP + ADT is cost-effective in men who are chemo-ineligible at diagnosis within the NHS.

In addition to this and at the request of NICE, the revised model has assessed the cost-effectiveness of AAP + ADT vs docetaxel + ADT in newly diagnosed high-risk mHSPC. The ICER for AAP + ADT vs docetaxel + ADT is inevitably associated with greater uncertainty, given the lack of head-to-head evidence in a trial powered to detect a difference in OS vs docetaxel. The Committee has previously concluded there is evidence to suggest AAP + ADT delays disease progression compared to docetaxel + ADT, however there is uncertainty in the OS benefit. This uncertainty translates into the cost-effectiveness analysis because the ICER for AAP + ADT vs docetaxel + ADT is sensitive to variation in model assumptions. The base case ICER likely resides between [redacted] and [redacted] per QALY gained, under the confidential CAA. It is important to highlight the significant challenge in demonstrating cost-effectiveness against an inexpensive generic regimen which has demonstrated benefit in those fit enough to receive it. Indeed, Janssen considers the optimal use for AAP + ADT is in patients unable to receive chemotherapy, where the unmet need is the greatest. Nevertheless, results for this comparison are still presented herein at the request of NICE.

In summary, Janssen requests reimbursement without further delay for the highly cost-effective use AAP + ADT in those who are chemo-ineligible at diagnosis, as these men have the greatest unmet need with no alternative life-extending options.

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B.1.8. Chemo-ineligibility

Approximately 750 patients are diagnosed with high-risk mHSPC and deemed chemo-ineligible each year in England (Appendix A).

As previously noted by the Committee, agreeing criteria for chemo-ineligibility may be challenging, but recognising these patients are a distinct cohort within the NHS is imperative to fulfilling this acute unmet need. Indeed, there is precedent for NICE to recommend treatments within subgroups of cancer patients who are chemo-ineligible in mCRPC (TA412) and, most recently, thalidomide-ineligible in multiple myeloma (TA587).

Clinical experts at a UK advisory board agreed men would be unfit for docetaxel if they had severe liver impairment, neuropathy or thrombocytopenia/ neutropenia, had poor Eastern Cooperative Oncology Group (ECOG) performance status or were very frail. This indicates that these patients are identifiable at diagnosis based upon expert experience and clinical judgement. Important precedent can be sought from TA587 in which the Committee reviewed a comparable issue of thalidomide-ineligibility, as this cohort represented the key area of unmet need. As with chemo-ineligibility in mHSPC, definition of thalidomide ineligibility in multiple myeloma varies in clinical practice. Importantly the final appraisal determination (FAD) for TA587 states that:

"The committee agreed that it could not define this population any further because there are no strict criteria used in clinical practice to determine who can or cannot take thalidomide. However, it expected that clinicians would exercise their judgement when deciding whether someone can take thalidomide, taking into account the contraindications in the summary of product characteristics, the person's medical history and pre-existing conditions, and the effect of toxicity on overall treatment benefit." [Section 3.2]

TA587 provides clear precedent for the Committee recognising the importance of exercising clinical judgement in making treatment decisions regarding patients' eligibility to existing treatments associated with toxicity. Furthermore, the FAD for TA587 also states that:

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"The clinical experts explained that being unable to take thalidomide would not be expected to change the rates of disease progression or death on lenalidomide seen in the trial. Therefore, they considered the results would be generalisable to the group who cannot have thalidomide." [Section 3.6]

Again, this is highly-relevant precedent for the Committee accepting the generalisability of clinical trial outcomes to a subgroup based upon expert clinical opinion. Indeed, eligibility to chemotherapy was not a pre-defined criterion in LATITUDE and clinicians could not determine what proportion of the trial population may be chemo-ineligible in practice when reviewing patient's baseline characteristics; however, clinical experts at a UK advisory board agreed that there was no clinical or biological reason why the treatment effect of AAP + ADT, as seen in LATITUDE, would differ based on suitability for docetaxel. This notion is substantiated within the ACD which states:

"Two clinical experts, who were also investigators in STAMPEDE, explained that there was no reason to believe that there was any subgroup of people for whom abiraterone was more or less effective." [Section 3.4]

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B.2. Clinical Effectiveness

Key efficacy data from the pre-planned final analysis of the LATITUDE trial are presented herein as these data have been released since this appraisal (ID945) was suspended in July 2018. The objective of this final analysis was to obtain results for updated OS) and other secondary endpoints. These data are based on a clinical cut-off date of 15th August 2018, at which point median follow-up was 51.8 months.[3] Of note, the final analysis of rPFS was planned after 565 events, which was reached at the first interim analysis (IA1). Final analysis of rPFS and all HRQL endpoints have been presented previously and as such are not recapitulated within this addendum. Comparison of OS and other secondary endpoints results between IA1, IA2 and final analysis are presented in Appendix B.

Clinical Summary

- The pivotal Phase III LATITUDE study is the primary source of evidence for the use of AAP + ADT vs ADT alone in men with newly diagnosed, high-risk mHSPC.
- The ongoing multi-arm, multi-stage STAMPEDE study provides strong supportive data for AAP + ADT vs ADT alone in a *post-hoc* high-risk subgroup.
- Treatment with AAP + ADT significantly delayed disease progression for patients with high-risk mHSPC in both LATITUDE (rPFS HR=0.47; p<0.0001)[2] and STAMPEDE (progression free survival [PFS] HR=0.46; p<0.001).[5]
- Treatment with AAP + ADT also significantly extended survival for patients with high-risk mHSPC in both LATITUDE (HR=0.66; p<0.0001)[3] and STAMPEDE (HR=0.54; p<0.001).[5]
- At time of final analysis, 72 out of 602 patients (12%) in the ADT alone group had crossed over to receive open-label treatment with AAP + ADT.
- Results from LATITUDE indicate that a patient's median life expectancy when treated with ADT alone (36.5 months)[3] is comparable to median time spent progression-free when treated with AAP + ADT (33 months).[2]
- Treatment with AAP + ADT was also consistently superior to ADT alone in all pre-defined secondary endpoints in LATITUDE.[3]
- Considering all of the relevant evidence available, a series of Bayesian NMAs have shown AAP + ADT has the highest probability of being the superior treatment option vs docetaxel + ADT for patients with mHSPC.
- Treatment with AAP + ADT is associated with significant improvements in HRQL, with results from LATITUDE showing statistically significant reductions in pain and fatigue, with patients having more energy, and generally better quality of life when compared with ADT alone.[23]
- Bayesian NMA indicated that AAP + ADT is also highly likely to be superior to docetaxel + ADT in HRQL domains such as reductions in pain and fatigue.[16]
- AAP already has an established efficacy and safety profile in mCRPC, and no new safety signals were flagged in either LATITUDE or STAMPEDE.[2 4] AAP + ADT was well tolerated in both trials, with a comparable incidence of treatment-emergent adverse events (TEAEs) to ADT alone.

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- In line with the known safety profile of AAP, the most frequently reported grade 3 or 4 TEAEs were mineralocorticoid-associated adverse events (AEs); the EMA accepted that all events were medically manageable, only rarely requiring treatment discontinuation and seldom leading to serious consequences.[28]

B.2.1. Patient disposition

A total of 597 patients in the AAP + ADT group and 602 patients in the ADT alone group were included in both the intention-to-treat (ITT) and safety populations. At the time of final analysis, treatment was ongoing for 157 (26.3%) patients in the AAP + ADT group whilst all patients had discontinued from the ADT alone group. The most common reasons for discontinuation remained progressive disease, reported for 42.5% and 64.5% of patients in the AAP + ADT and ADT alone groups, respectively.

B.2.2. Treatment exposure

The median total treatment duration was 25.8 months for patients in the AAP + ADT group and 14.4 months for the ADT group, with a total of [redacted]% patients in the AAP + ADT group and [redacted] % of patients in the ADT alone group having received ≥36 cycles of treatment. Crossover was permitted after the trial was unblinded at IA1 and, as of 15th August 2018, 72 of 602 (12%) patients in the ADT alone group had crossed over to receive AAP + ADT, with a median duration of exposure to subsequent AAP + ADT of 11.9 months; as such, this could have introduced some degree of bias against AAP + ADT at final analysis.

B.2.3. Overall survival

At the time of final analysis, 618 deaths were observed; 275 (46.1%) in the AAP + ADT group and 343 (57.0%) in the ADT alone group. As shown in Figure 2, median OS was 53.3 months in the AAP + ADT group (95% confidence interval [CI]: 48.2-not reached [NR]) and was 36.5 months (95% CI: 33.5-40.0) in the ADT alone group. Treatment with AAP + ADT resulted in a 34% reduction in the risk of death compared with ADT alone (HR=0.66 [95%CI: 0.56–0.78]; p<0.0001), despite permitted crossover after the trial was unblinded. At the time of final analysis, the majority ([redacted] %) of patients in the AAP + ADT group were still alive, compared to [redacted]% of

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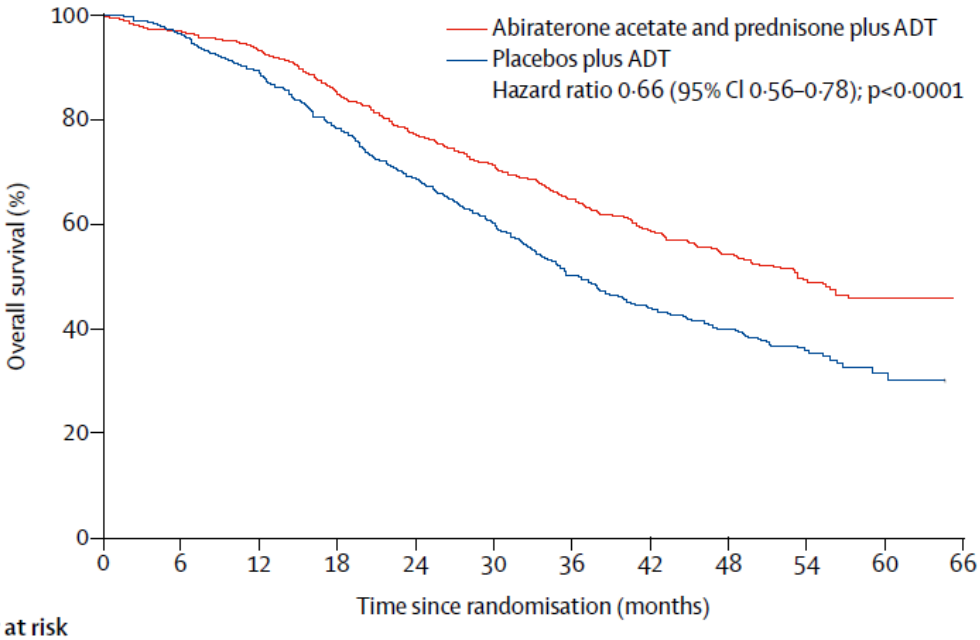
patients in the ADT alone group, reaffirming the sustained survival benefit of AAP + ADT.

Figure 2: KM plot for OS [LATITUDE, ITT population]



Number at risk (number censored)												
Abiraterone acetate and prednisone plus ADT	597	565 (14)	529 (28)	479 (34)	425 (42)	389 (46)	351 (50)	311 (57)	240 (106)	124 (205)	40 (282)	0 (322)
Placebos plus ADT	602	564 (17)	505 (34)	432 (47)	368 (58)	315 (37)	256 (74)	220 (79)	165 (114)	69 (197)	23 (237)	0 (259)

Key: ADT, androgen deprivation therapy; ITT, intention-to-treat; KM, Kaplan–Meier; OS, overall survival.
Source: Fizazi et al. 2019[3]

Subgroup analysis

Consistent with the results for IA1 and IA2, the point estimates for the treatment effect of AAP + ADT vs ADT alone on OS were favourable for nearly all subgroups in the final analysis (HRs ranging from 0.44 to 0.81).[29] All were consistent with the overall study results, except for the subgroup of patients with an ECOG performance status score of 2 (HR=1.42). For this subgroup, eight additional death events were reported; however, the small sample size (n=40) precludes drawing any meaningful conclusion. Forest plots of these analyses are presented in Figure 3

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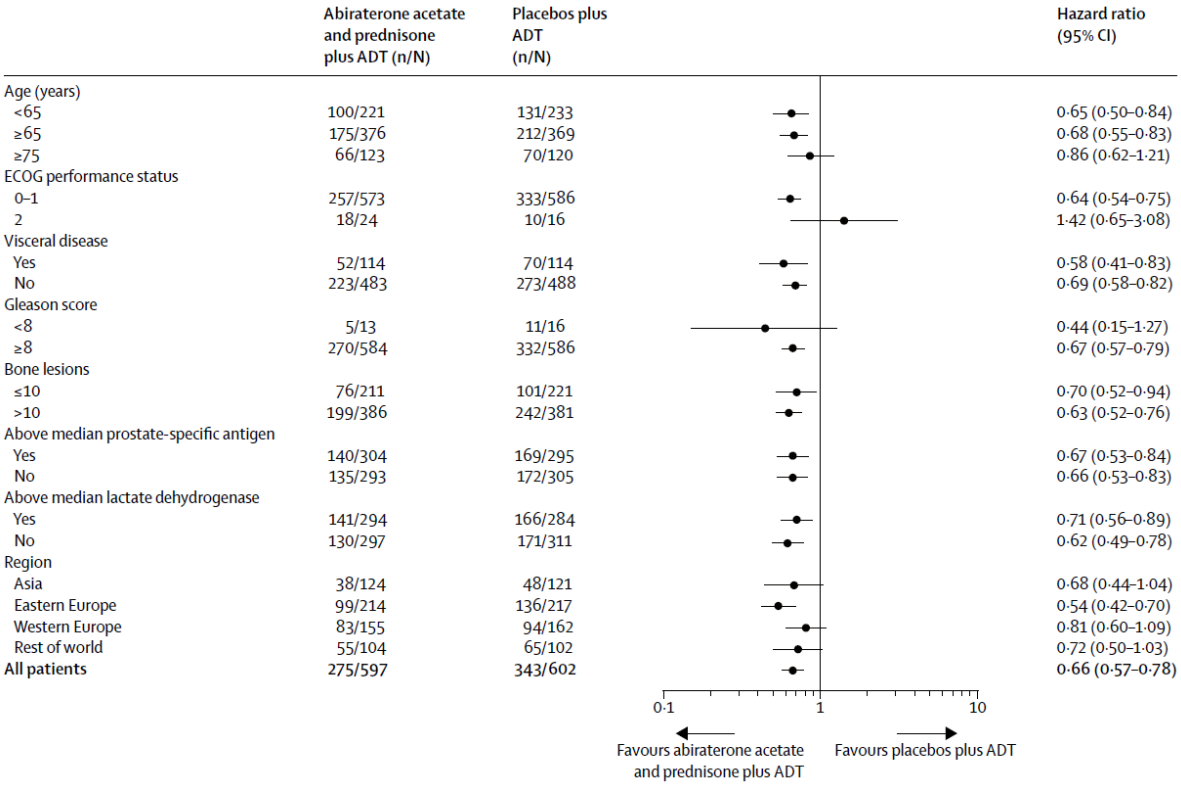
Figure 3: Subgroup analyses of OS [LATITUDE, ITT population]



Key: ADT, androgen deprivation therapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat.
Source: Fizazi et al. 2019[3]

STAMPEDE

The statistically significant improvement in OS associated with AAP + ADT has been reaffirmed by the most recent data released from STAMPEDE, in which *post-hoc* analyses of a high-risk mHSPC subgroup were presented. Of note, 95% of this subgroup were newly diagnosed and therefore considered comparable to the licensed indication for AAP + ADT.[5] Results showed 52.5% of metastatic patients met the high-risk criteria of LATITUDE and in this subgroup, AAP + ADT was also associated **46% reduction in the risk of death compared to ADT alone** (HR=0.54 [0.41-0.70]; p<0.001).[5] Of note, median OS values were not reported for either arm.

This is an exceedingly important observation given this was a *post-hoc* analysis, underpowered to detect differences between treatment arms. The fact it has still derived a statistically significant difference in OS means the treatment effect is large enough to derive a difference despite having an underpowered sample size.

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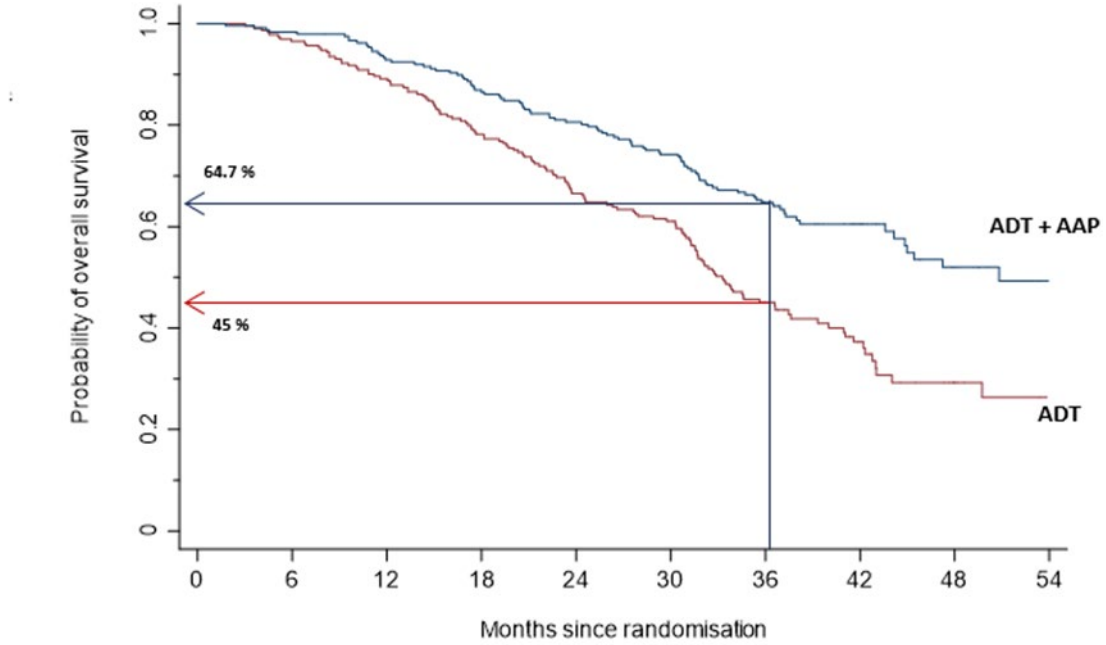
Figure 4: KM plot for OS [STAMPEDE, *post-hoc* high-risk mHSPC subgroup]



No. of patients (Events)

AAP	241	(17)	220	(29)	190	(35)	106	(12)	28
ADT alone	232	(25)	204	(51)	148	(44)	71	(15)	13

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; KM, Kaplan–Meier; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival.
Source: Hoyle et al. 2018[5]

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B.2.4. Secondary endpoints

A summary of all pre-specified secondary endpoints at time of final analysis is presented in Table 1, with further details provided in Appendix C. Treatment with AAP + ADT was consistently superior to ADT alone for all secondary efficacy endpoints.[29] Results from the final analysis were consistent with those seen in IA1 and IA2, as presented in Appendix B.

Table 1: Summary of secondary endpoints [LATITUDE, ITT population, final analysis]

	AAP + ADT (n=597)	ADT alone (n=602)
Time to pain progression		
Events, n (%)	245 (41.0)	292 (48.5)
Median months (95% CI)	47.4 (33.2-NE)	16.6 (11.1-24.0)
HR (95% CI) [p-value]	0.72 (0.61-0.86) [p=0.0002]	
Time to subsequent prostate cancer therapy		
Events, n (%)	248 (42.0)	355 (59.0)
Median months (95% CI)	54.9 (45.4-NE)	21.2 (18.6-23.5)
HR (95% CI) [p-value]	0.45 (0.38-0.53) [<0.0001]	
Time to life-extending subsequent therapy for prostate cancer		
Events, n (%)	[redacted]	[redacted]
Median months (95% CI)	[redacted]	[redacted]
HR (95% CI) [p-value]	[redacted]	
Time to initiation of chemotherapy		
Events, n (%)	150 (25.1)	218 (36.2)
Median months (95% CI)	NE (62.6-NE)	57.6 (38.2-NE)
HR (95% CI) [p-value]	0.51 (0.41, 0.63) [p<0.0001]	
Time to PSA progression		
Events, n (%)	273 (45.7)	448 (74.4)
Median months (95% CI)	33.3 (29.4-46.1)	7.4 (7.2-9.2)
HR (95% CI) [p-value]	0.31 (0.27-0.63) [p<0.0001]	
Time to next SRE		
Events, n (%)	132 (22.3)	150 (24.9)
Median months (95% CI)	NE (NE-NE)	NE (NE-NE)
HR (95% CI) [p-value]	0.75 (0.60-0.95) [0.0181]	

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; PSA, prostate-specific antigen; SRE, skeletal-related event.
Source: Fizazi et al. 2019[3]; LATITUDE final clinical study report, 2018.[29]

Where available, relevant secondary endpoints from the high-risk mHSPC subgroup from STAMPEDE are presented in Appendix D.

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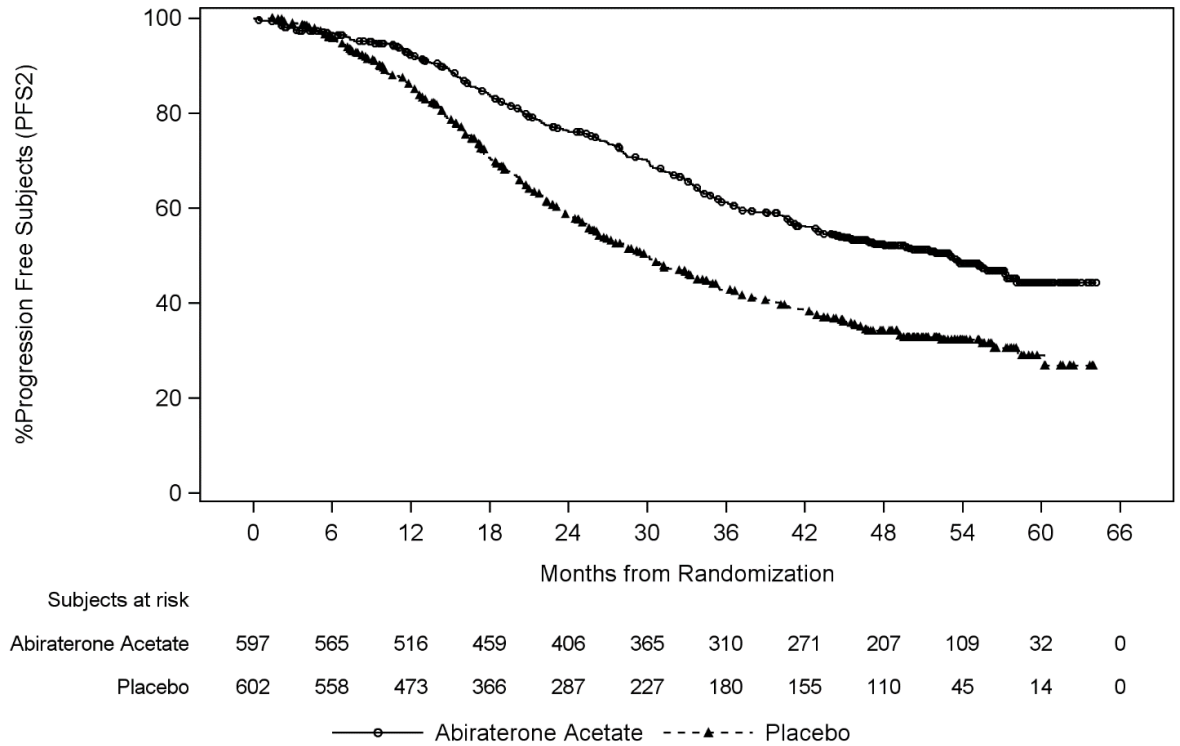
B.2.5. Exploratory endpoints

Progression-free survival following subsequent therapy

Progression-free survival following subsequent therapy (defined as PFS2) was based on investigator-assessed progression (clinical/radiographic/PSA progression), after first subsequent therapy, and this progression was not based on a protocol-defined criterion definition. At time of final analysis, [redacted]% of patients from the AAP + ADT group and [redacted]% of patients from the ADT alone group had experienced a PFS2 event. As shown in Figure 5, treatment with AAP + ADT statistically significantly extended PFS2 by 42% compared with ADT alone (HR=0.58 [95% CI:0.49-0.68]; p<0.0001). The median time to PFS2 was 53.3 months in the AAP + ADT group compared with 30.1 months in the ADT alone group; this means patients who received ADT alone in mHSPC will have progressed twice in their treatment pathway before patients who received AAP + ADT will have experienced any progression.

Figure 5: KM plot for PFS2 [LATITUDE, ITT population]



Key: ITT, intention-to-treat; KM, Kaplan–Meier; PFS2, progression free survival following subsequent therapy.
Source: Fizazi et al. 2019[3]

B.2.6. Safety endpoints

A summary of safety data at time of final analysis is presented in Table 2. Of note, patients originally randomised to ADT alone have since crossed over to receive AAP + ADT

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treatment and, as a result, the median duration of treatment for the AAP + ADT group is 80% longer than that for ADT alone; as such, a direct comparison of the safety profile for AAP + ADT vs ADT alone is of limited value. Results for the AAP + ADT group were similar to those reported at IA1, with slight increases in incidence of each category of TEAEs, corresponding with prolonged exposure.

At the final analysis, AEs were broadly comparable, although patients treated with AAP + ADT had more drug-related TEAEs and grade 3–4 TEAEs.[29] The incidence of TEAEs leading to deaths that were considered drug-related were comparably low with only [redacted]% in both arms.

Table 2: Summary of adverse reactions [LATITUDE, safety population, final analysis]

	IA1[2 28]		Final analysis[3]	
	AAP + ADT (n=597)	**ADT alone (n=602)**	**AAP + ADT (n=597)**	**ADT alone (n=602)**
Any TEAE, n (%)	558 (93.5)	557 (92.5)	569 (95.3)	561 (93.2)
Drug-related	336 (56.3)	269 (44.7)	[redacted]	[redacted]
Any serious TEAE, n (%)	165 (27.6)	146 (24.3)	192 (32.2)	151 (25.1)
Drug-related	29 (4.9)	12 (2.0)	[redacted]	[redacted]
Grade 3–4 TEAE, n (%)	374 (62.6)	287 (47.7)	403 (67.5)	299 (49.7)
Drug-related	162 (27.1)	67 (11.1)	[redacted]	[redacted]
Discontinuation due to TEAE, n (%)	73 (12.0)	61 (10.1)	93 (15.7)	63 (10.5)
Drug-related	21 (3.5)	11 (1.8)	[redacted]	[redacted]
Death due to TEAE, n (%)	28 (4.7)	24 (4.0)	38 (6.4)	27 (4.5)
Drug-related	3 (0.5)	3 (0.5)	[redacted]	[redacted]

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; TEAE, treatment-emergent adverse event.

At the final analysis, grade 3 or 4 AEs were reported in 68% of patients in the AAP + ADT arm compared to 50% of patients in the ADT alone arm, as presented in Table 24 in Appendix B.[3] This was consistent with results at IA1, where 63% of patients receiving AAP + ADT reported a grade ≥3 TEAE. The most commonly reported grade 3 and 4 TEAEs at the final analysis were [redacted] ([redacted]% for patients receiving AAP + ADT and [redacted]% in patients receiving ADT alone), followed by [redacted] ([redacted]% and [redacted]% respectively).[29]

In summary, AA has a well-established safety profile, and clinicians have seven years of experience with it in the NHS. As highlighted in the European public assessment report, AA's safety profile is 'well-characterised' and 'no new unexpected events have been

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reported'.[28] Indeed, AAP demonstrates a favourable risk–benefit profile when added to ADT for the treatment of newly diagnosed, high-risk mHSPC patients. This is of considerable benefit to those who wish to avoid chemotherapy due to toxicity concerns and is of utmost importance for those who are chemo-ineligible at diagnosis.

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B.3. Comparative effectiveness

B.3.1. AAP + ADT vs ADT alone

As highlighted in Section B.1.4, ADT alone is the only licensed treatment available for patients with high-risk mHSPC deemed chemo-ineligible at diagnosis. The LATITUDE trial provides randomised, robust head-to-head evidence of the superiority of AAP + ADT vs. ADT alone and therefore (as the registrational study in the relevant licensed population) forms the basis of this comparison in the economic modelling. To validate the representativeness of LATITUDE results, a meta-analysis was conducted which combined data reported from STAMPEDE for patients specifically with high-risk mHSPC.[5] The results presented in Table 3 reaffirm the robustness of LATITUDE results, their representativeness to UK clinical practice and thus the appropriateness of using the LATITUDE ITT analysis in economic modelling.

Table 3: Comparative evidence for AAP + ADT vs. ADT alone

	LATITUDE AAP + ADT vs. ADT	**STAMPEDE AAP + ADT vs. ADT**	**Meta-analysis**
	HR [95% CI]		
PFS	0.47 [0.39, 0.55]; p<0.001	0.46 [0.36, 0.59]; p<0.001	[redacted]
OS	0.66 [0.57-0.78]; p<0.001	0.54 [0.41-0.70]; p<0.001	[redacted]
Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.			

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B.3.2. AAP + ADT vs docetaxel + ADT

Docetaxel + ADT is unlicensed in this setting but used off-label in patients who are fit enough and willing to receive it. The Committee have concluded there is evidence to suggest AAP + ADT delays disease progression vs docetaxel + ADT, but question whether there is improved OS.

The only existing direct evidence of AAP + ADT vs. docetaxel + ADT is in the form of a *post-hoc* subgroup analysis of 342 metastatic patients from STAMPEDE which was significantly underpowered to detect any differences in survival. This analysis is associated with sizable uncertainty as indicated by the wide confidence interval around the point estimate (0.77-1.66).

Not only was this analysis significantly underpowered, it was also subject to a noticeable mis-match in censoring between treatment arms. Figure 6 shows a comparison of the number of progression events, death events and censors that occurred over time in the STAMPEDE analysis. These graphics indicate a significantly greater proportion of patients in the docetaxel + ADT arm were censored compared to the AAP + ADT arm. Given the known toxicities of chemotherapy, this may be a consequence of more patients in the docetaxel + ADT arm withdrawing from follow-up. This greater extent of censoring is more likely to exclude higher risk patients who are associated with worse outcomes, and thus bias the results in favour of docetaxel + ADT.

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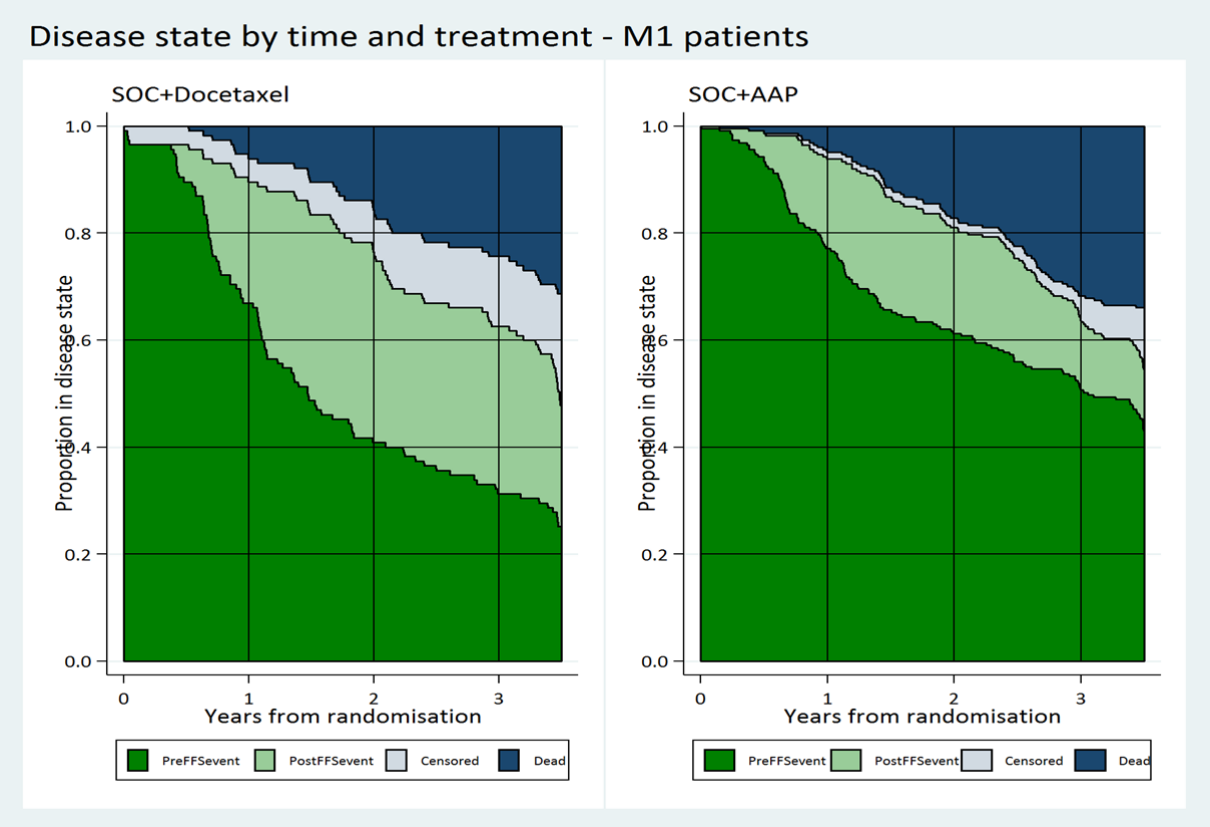
Figure 6: Comparison of events/censoring in STAMPEDE analysis of AAP + ADT vs. docetaxel + ADT



Key: AAP, Abiraterone acetate (AA) plus prednisolone; ADT, androgen deprivation therapy; FFS, failure-free survival; M1, metastatic; SOC, standard of care.
Source: Sydes et al. (2018)[30] [Supplementary Materials]

Furthermore, Figure 7 compares the OS Kaplan-Meier (KM) curves from LATITUDE with the digitized OS KM curves from STAMPEDE for the high-risk mHSPC subgroup which the Committee considers most representative of NHS clinical practice. These plots show that over time the treatment effect of AAP + ADT is highly consistent between LATITUDE and STAMPEDE, despite the differences in subsequent therapies between trials. Furthermore, OS KM curves from the STAMPEDE mHSPC subgroups shown in Figure 8 indicate there is a survival benefit for AAP + ADT vs docetaxel + ADT. This evidence contradicts previous statements made in the ACD which suggest the reason the analysis of AAP + ADT vs. docetaxel + ADT did not show a difference in OS was because post-progression survival is shorter after AAP + ADT than after ADT alone or docetaxel + ADT. As there is no indication these curves converge at any point over time, there is no evidence to support the notion that post-progression survival would be shorter after AAP + ADT in mHSPC. Instead, the most likely reason the analysis of AAP + ADT vs. docetaxel

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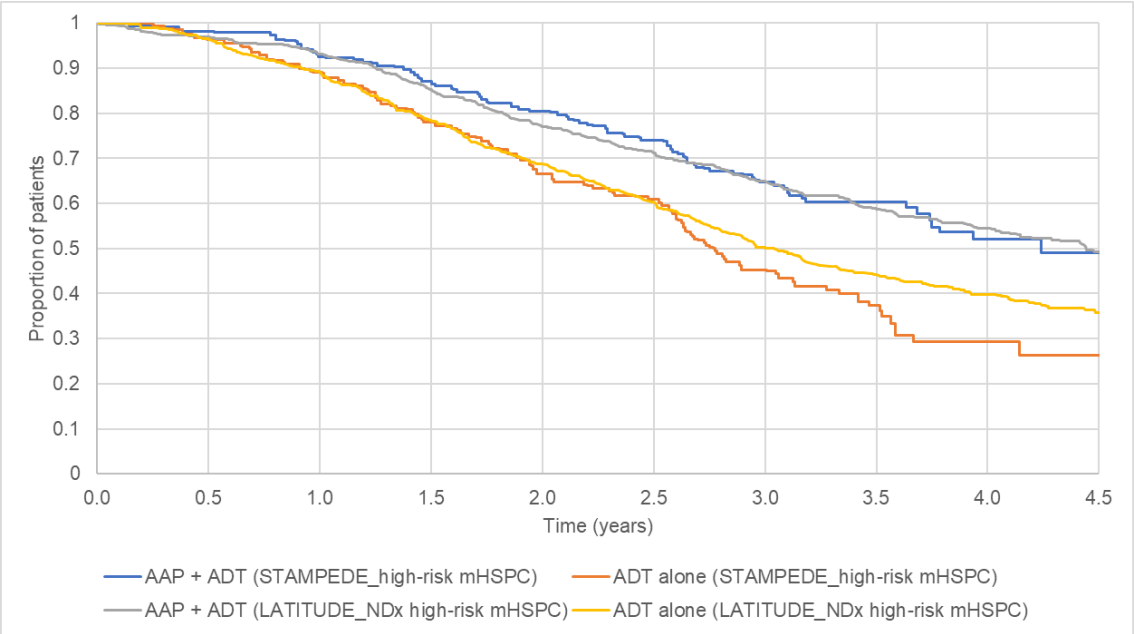
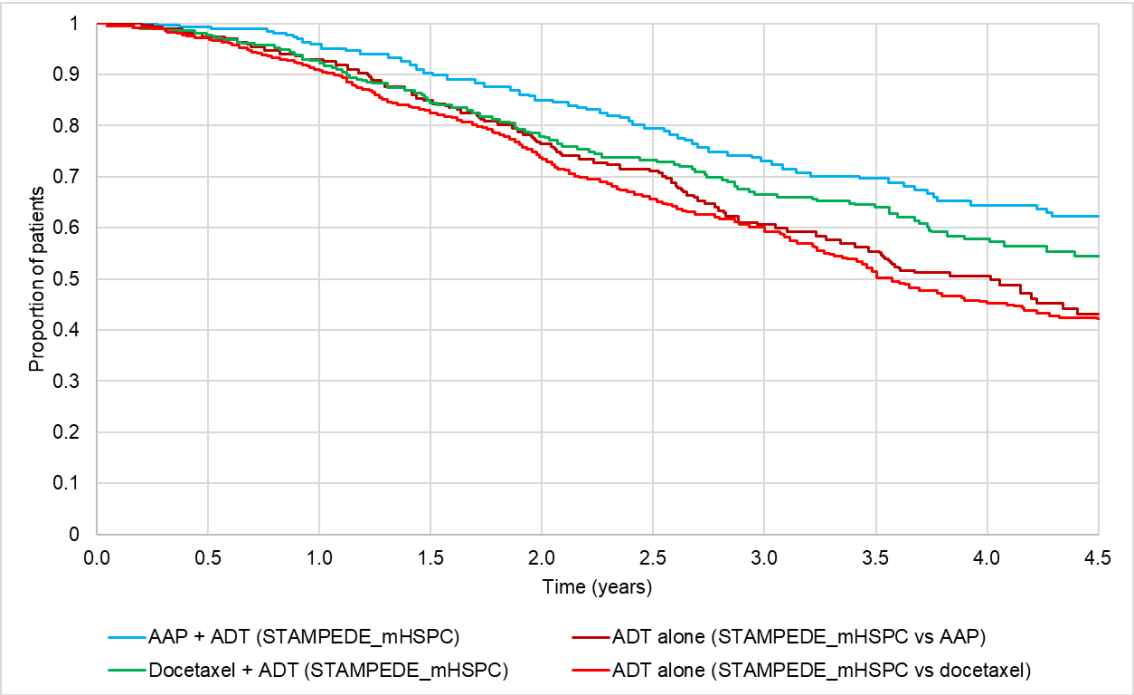
+ ADT could not show a difference in OS are because of statistical underpowering and a mismatch in censoring.

Figure 7: Comparison of OS curves from LATITUDE [ITT population] vs STAMPEDE [high risk mHSPC subgroup]



Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; ITT, intention to treat; mHSPC, metastatic hormone-sensitive prostate cancer; NDx, newly diagnosed; OS, overall survival.

Figure 8: Comparison of OS curves from STAMPEDE [mHSPC subgroup] for AAP + ADT vs ADT alone and docetaxel + ADT vs ADT alone



Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival.

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Whilst Janssen recognise the Committee's interest in the STAMPEDE comparison of AAP + ADT vs docetaxel + ADT, we wish to reiterate the highly uncertain nature of the analysis, with its considerable limitations, and refer to the ACD, which states:

"The Committee concluded that the direct evidence could be further supported by a network meta-analysis including evidence from patients with high-risk metastatic disease from STAMPEDE, CHAARTED, GETUG-AFU 15 and LATITUDE. This would combine evidence from a larger number of people and potentially decrease the uncertainty about the relative effectiveness of abiraterone." [Section 3.6]

Of note, the authors of Sydes et al. (2018) from STAMPEDE also signposted the importance of NMA in taking account of these available data from all relevant trials.[30] Janssen have actioned the Committee's conclusion with the ACD and presented Bayesian NMA for both PFS and OS which incorporate the most relevant evidence available from each of the named trials, to reduce the uncertainty associated with outcomes. As presented in Table 4 and Table 5, NMA results show AAP + ADT has a [redacted]% probability of being the superior treatment in terms of delaying disease progression (mean HR=[redacted]), and an [redacted]% probability of being the superior treatment in terms of extending OS (mean HR=[redacted]), when compared with docetaxel + ADT. Of note, the OS HR from IA1 is not confounded by crossover and when this is maintained within the NMA AAP + ADT has an [redacted]% probability of being the superior treatment in terms of extending OS (mean HR=[redacted]).

As previously mentioned in the appraisal process, two alternative, independent NMAs have been published investigating the relative effectiveness of ADT alone, AAP + ADT and docetaxel + ADT in this setting, and both have drawn similar conclusions. [31] [32] Indeed, considering the trend in a series of published analyses adds greater weight to conclusions on comparative effectiveness than considering just one underpowered analysis in isolation.

Janssen maintain the appropriateness of NMA, with most of the evidence concluding AAP + ADT is highly likely to improve OS vs docetaxel + ADT. We have however, recognised the Committee's request for an analysis assuming an OS HR of 1 and have provided this as a scenario analysis.

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Table 4: Network-meta analysis of PFS for AAP + ADT vs. docetaxel + ADT

	Direct evidence, HR [95% CI]						NMA results	
	AAP+ADT vs. ADT		D+ADT vs. ADT			AAP+ADT vs. D+ADT	AAP+ADT vs. D+ADT	
Trial	**LATITUDE**	**STAMPEDE**	**CHAARTED**	**GETUG-AFU 15**	**STAMPEDE**	**STAMPEDE**	**HR [95% CrI]**	**Probability HR<1**
Population	**NDx HRD**	**HRD**	**NDx HVD**	**NDx HVD**	**M1**	**M1**		
Updated PFS NMA With STAMPEDE	0.47 [0.39, 0.55]	0.46 [0.36, 0.59]	PFS not reported	0.61 [0.44, 0.83]	PFS not reported	0.69 [0.50, 0.95]		
Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; CrI, credible interval; D, docetaxel; HR, hazard ratio; HRD, high-risk disease; HVD, high-volume disease; M1, metastatic; NDx, newly diagnosed; NMA, network meta-analysis; PFS, progression-free survival.								

Table 5: Network-meta analysis of OS for AAP + ADT vs. docetaxel + ADT

	Direct evidence, HR [95% CI]					NMA results	
	AAP+ADT vs. ADT		D+ADT vs. ADT			AAP+ADT vs. D+ADT	AAP+ADT vs. D+ADT	
Trial	**LATITUDE**	**STAMPEDE**	**CHAARTED**	**GETUG-AFU 15**	**STAMPEDE**	**STAMPEDE**	**HR [95% CrI]**	**Probability HR<1**
Population	**NDx HRD**	**HRD**	**NDx HVD**	**NDx HVD**	**M1**	**M1**		
Updated OS NMA with STAMPEDE	0.62 [0.51, 0.76]	0.54 [0.41, 0.70]	0.63 [0.49, 0.81]	0.78 [0.54, 1.12]	0.76 [0.62, 0.92]	1.13 [0.77, 1.66]		
Updated OS NMA LATITUDE FA - with STAMPEDE	0.66 [0.57; 0.78]	0.54 [0.41, 0.70]	0.63 [0.49, 0.81]	0.78 [0.54, 1.12]	0.76 [0.62, 0.92]	1.13 [0.77, 1.66]		
Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; CrI, credible interval; D, docetaxel; FA, final analysis; HR, hazard ratio; HRD, high-risk disease; HVD, high-volume disease; M1, metastatic; NDx, newly diagnosed; NMA, network meta-analysis; OS, overall survival.								

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B.4. Cost Effectiveness

This appraisal (ID945) was suspended in July 2018, after the 2nd Appraisal Committee Meeting. At the time of suspension, the Committee highlighted their requests for when the process was to be re-initiated. Table 6 notes each request and how this has been considered/ accounted for in this addendum to the appraisal.

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Table 6: Janssen response to Committee requests at suspension

The Committee preferred model assumptions	Janssen response
No survival benefit of AAP + ADT compared with docetaxel + ADT	As noted in Section B.3.2, Janssen maintain the appropriateness of NMA accounting for all relevant evidence when there is considerable uncertainty associated with the single direct analysis. A scenario analysis has been tested in which no survival benefit is assumed between AAP + ADT and docetaxel + ADT, despite benefit in delaying disease progression.
Sensitivity analyses around the OS HR for AAP + ADT vs docetaxel plus ADT	The revised model structure allows for this.
Treatment pathways for hormone-relapsed cancer that reflect NHS clinical practice	Simulated treatment pathways within the revised model structure are aligned with current NHS clinical practice, and usage of subsequent therapies is informed by expert clinical opinion. These data reflect, in general, that patients who receive AAP + ADT in mHSPC are likely to receive fewer subsequent therapies than patients who receive docetaxel + ADT or ADT alone.
Differences in effectiveness of treatments for hormone-relapsed prostate cancer	There are no robust data to determine the relative effectiveness of subsequent therapies in mCRPC, specifically after active treatment in mHSPC. The revised model structure allows OS to be tested independently to PFS which consequentially assesses differences in post-progression survival after treatment in mHSPC.
Quality of life data from STAMPEDE for docetaxel treatment	No HRQL data has been published from STAMPEDE for docetaxel treatment.
Fully incremental, probabilistic cost effectiveness analyses	Janssen maintain that the comparisons of AAP + ADT with ADT alone and with docetaxel + ADT are relevant for different patient populations. That is, the comparison of AAP + ADT versus ADT alone is relevant for the chemo-ineligible population and the comparison of AAP + ADT versus docetaxel + ADT is relevant for the chemo-eligible population. Therefore, pairwise rather than fully incremental analyses have been presented within this addendum.

Key: AAP, abiraterone acetate with prednisone; ADT, androgen deprivation therapy; HR, hazard ratio; HRQL, health-related quality of life; mCRPC, metastatic castrate resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

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Cost-effectiveness Summary

- A revised *de novo* economic model was constructed using robust evidence from the LATITUDE trial to inform the cost effectiveness of AAP + ADT vs ADT alone or docetaxel + ADT in men with newly diagnosed high-risk mHSPC.

<u>AAP + ADT vs ADT alone in a chemo-ineligible cohort</u>

- When compared to ADT alone, AAP + ADT was associated with an incremental gain of 1.5-2.2 life years equating to 1.0-1.4 QALYs per patient, at an incremental cost of [redacted]. This resulted in an ICER vs ADT alone between [redacted] per QALY gained under the confidential CAA.
- The results demonstrate that treatment with AAP + ADT is a highly cost-effective use of NHS England resources for patients with newly diagnosed high-risk mHSPC who are chemo-ineligible and have no alternative life-extending treatment option.
- The ICER vs ADT alone was largely insensitive to the parameters and assumptions tested in both the OWSA and scenario analysis. Key sensitivities of the model identified include:
  - The QALY discount rate
  - The AA on-treatment utility increment
  - Baseline utility value

<u>AAP + ADT vs docetaxel + ADT alone in a chemo-eligible cohort</u>

- When compared to off-label docetaxel + ADT, AAP + ADT was associated with an incremental gain of 0.3-0.6 life years equating to 0.4-0.6 QALYs per patient, at an incremental cost of [redacted]. This resulted in an ICER vs docetaxel + ADT alone between [redacted] per QALY gained under the confidential CAA.
- OWSA and scenario analysis indicate greater uncertainty in the ICER for AAP + ADT vs docetaxel + ADT due to the nature of the clinical evidence base and absence of head-to-head data powered to detect difference between treatment arms. Key sensitivities of the model identified include:
  - The PFS and OS HRs for AAP + ADT vs docetaxel + ADT
  - The AA on-treatment utility increment
  - QALY discount rate
- Whilst recognising the challenge in determining cost-effectiveness against generic chemotherapy, results for [redacted] of the scenario analyses range between £20,000-£33,000 per QALY gained demonstrating the significant value being offered to the NHS through the confidential CAA.
- AAP + ADT should be recommended to address the clear unmet need for a tolerable, life-extending treatment which can delay disease progression while improving quality of life for patients with newly diagnosed high-risk mHSPC.

B.4.1. Partitioned survival analysis

Taking account of feedback from the Appraisal Committee and the ERG, a partitioned survival analysis (PartSA) has now been explored as an alternative modelling approach to address potential limitations in the originally-submitted Markov model. This approach has allowed for the data for rPFS from IA1 to be applied alongside OS data from the final analysis of LATITUDE because these data

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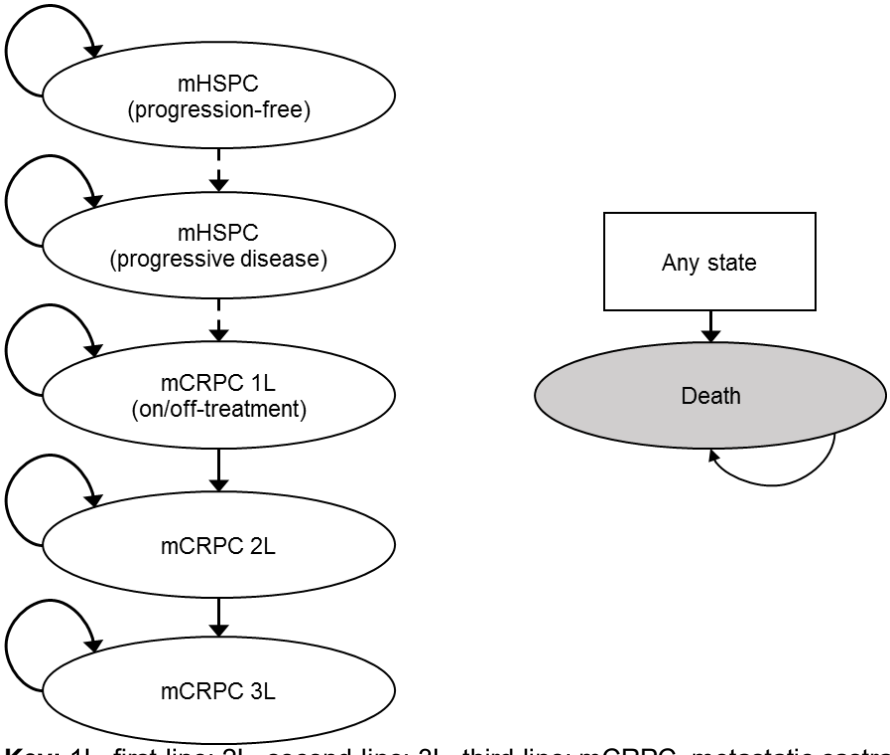
are applied independently in the model. Whilst Janssen maintain that an observed benefit in PFS translates to a benefit in OS in metastatic prostate cancer, this modelling approach also allows the OS HRs to be varied whilst holding a beneficial PFS HR (i.e. to test differences in post-progression survival, irrespective of benefits in pre-progression survival). As such, this revised functionality addresses several of the Committee's concerns simultaneously, as explained in Table 6.

As shown in Figure 9, the PartSA has maintained the same health states as previously as these are still deemed to be the clinically and economically relevant stages of disease progression.

Figure 9: Model structure



Key: 1L, first-line; 2L, second-line; 3L, third-line; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer.

All patients started in the mHSPC phase of the model, initiating treatment with either AAP + ADT or a comparator therapy. Patients either remained progression-free or experienced disease progression, in which case they transitioned to subsequent lines of therapy. Subsequent therapy was initiated when patients entered the mCRPC phase of the model, reflecting NHS clinical practice. From each of the health states, patients could transition to death.

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The model estimated the proportion of the modelled cohort in each health state, for each model cycle, based on the difference in parametric survival distributions fitted to the rPFS and OS data from LATITUDE. The rPFS data were used to define the time in the mHSPC health state, with the time in mCRPC estimated as the difference between the rPFS and the OS curves. The extrapolated rPFS and OS curves were utilised to estimate hazards in each model cycle to allow for the estimation of the number of patients transitioning to the progressive disease and death health states, respectively. To maintain the sequential nature of mCRPC within a PartSA structure, the transitions through each subsequent line of therapy were estimated in the same manner as in the Markov model approach. This involved utilising mean health state durations for each of the mCRPC health states taken from previous submissions to estimate constant transition probabilities by applying an exponential distribution to these durations.

B.4.2. Model outcomes

Health effects in the model are calculated in terms of both life years (LYs) and QALYs. Costs and health effects are accrued based on the proportion of patients in the different states over a 20-year time horizon, which is equivalent to lifetime given the starting age of patients with mHSPC (the mean age of patients in the LATITUDE trial was 67 years).

B.4.3. Cycle length

The model cycle length is weekly for the first 52 weeks of the model, increasing to 28 days thereafter in line with the pack size for AA. This allows the model to accurately capture the costs of docetaxel, which is given every three weeks over a maximum of 18 weeks, but also minimises the computational burden of the model.

B.4.4. Clinical parameters and variables

The doses of AAP + ADT and ADT were implemented as per marketing authorisations,[33] the summary of product characteristics (SPC)[1] and the clinical trials which inform clinical effectiveness. Docetaxel + ADT was dosed as per the NHS commissioning policy and was costed accordingly.

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AAP + ADT vs ADT alone

The rPFS data from IA1 and OS data from the final analysis of LATITUDE were utilised to model the clinical and cost-effectiveness of AAP + ADT vs ADT alone. Based on the NICE decision support unit (DSU) technical support document (TSD) 14 guidance on survival analyses, a range of standard parametric distributions (exponential, Weibull, log-logistic, log-normal, Gompertz and generalised gamma) were explored for the extrapolation of rPFS and OS. Both stratified curves for each treatment arm were modelled separately, and unstratified curves in which the treatment arm was included as a covariate were estimated.

All extrapolations were also adjusted for general population mortality; if the predicted hazard based on the parametric survival curves fell below that of the general population, the general population mortality hazard was applied. The functionality was also included to apply KM data directly in the model for a specified period of time before the survival curves were utilised.

In determining the choice of parametric function adopted for the base case extrapolations for each treatment arm, consideration was given to the following, as per the recommendations provided in NICE DSU TSD 14:

- Assessment of proportional treatment effect over time
- Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness-of-fit statistics (i.e. statistical fit)
- Visual inspection against the observed KM curves
- Clinical plausibility for both short-term and long-term estimates of survival

Disease Progression

Upon inspection of the log-cumulative hazard plot for rPFS presented in Figure 10 the proportional hazards assumption does not hold for the full trial duration. Given this, and the fact that patient-level data were available from LATITUDE, stratified curves were utilised in the base case analysis in line with NICE DSU TSD 14 for both rPFS and OS, with unstratified curves applying treatment as a covariate explored in scenario analysis.

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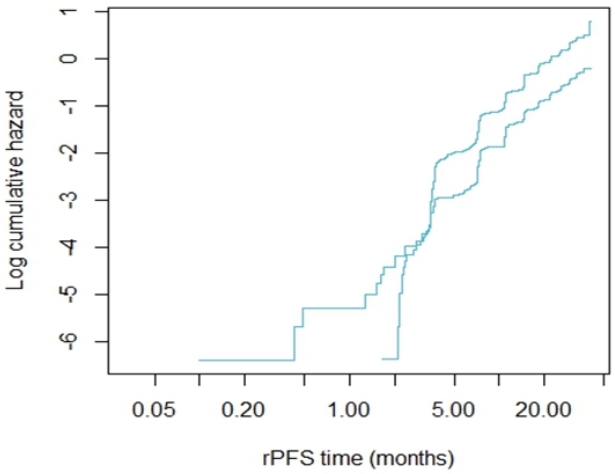
Figure 10: Log-cumulative hazard plot [rPFS]



Key: rPFS, radiographic progression-free survival.

Figure 11 and Figure 12 present the long-term projections of the six parametric functions for rPFS for the AAP + ADT and ADT alone arms, respectively. Additionally, the goodness-of-fit statistics are presented in Table 7 and Table 8 for AAP + ADT and ADT alone, respectively.

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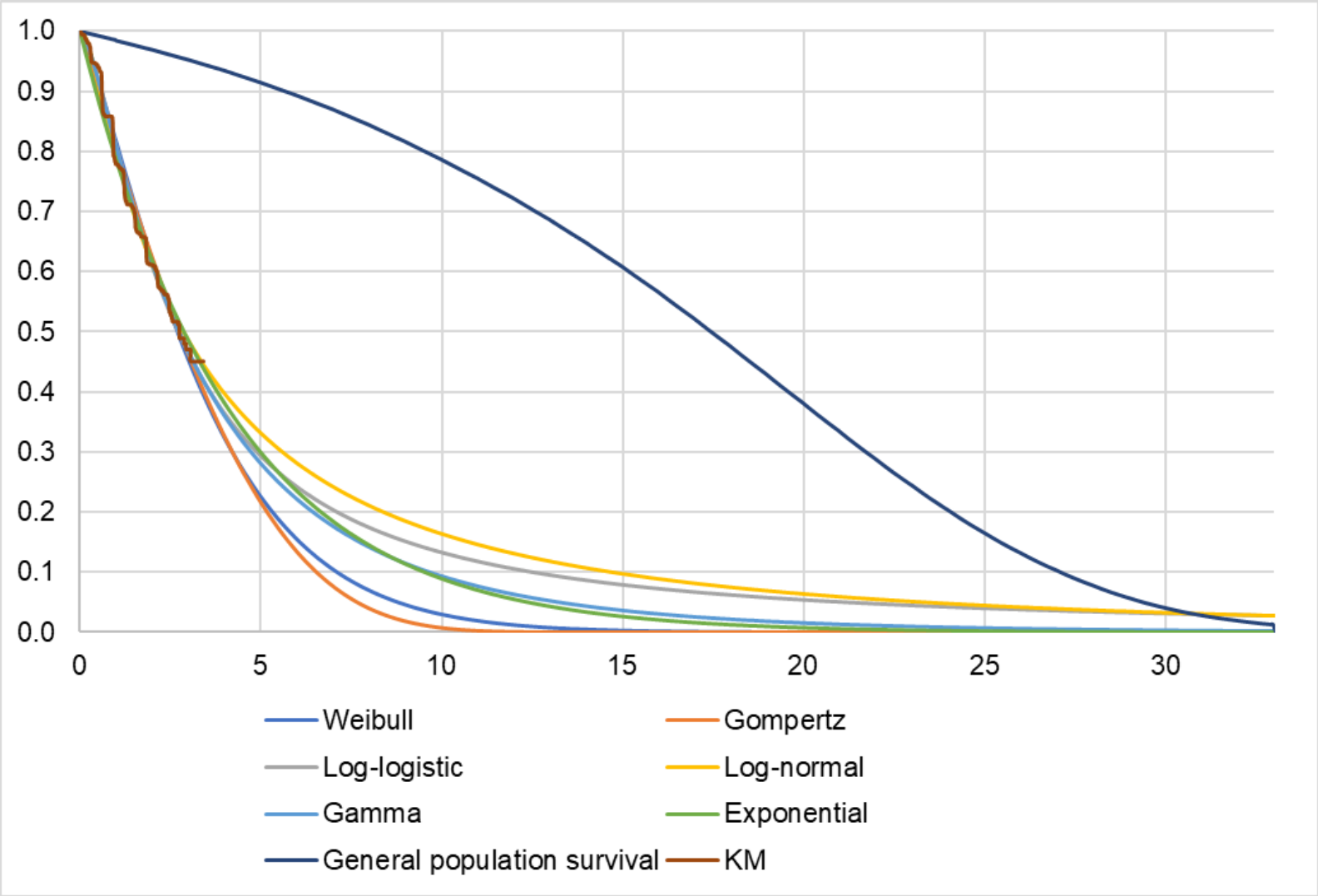
Figure 11: rPFS extrapolation (AAP + ADT)



Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; KM, Kaplan–Meier; rPFS, radiographic progression-free survival.

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Table 7: Goodness of fit statistics & survival projections AAP + ADT (rPFS; stratified)

Analysis	AIC	BIC	% pre-progression at 5 years	% pre-progression at 10 years	% pre-progression at 20 years	Mean time pre-progression (years)
Weibull	2924.104	2932.884	22.0%	2.9%	0.0%	3.35
Log-normal	2885.688	2894.468	32.8%	16.3%	6.4%	5.67
Log-logistic	2899.904	2908.684	28.9%	13.1%	5.3%	5.14
Exponential	2969.111	2973.505	29.5%	8.9%	0.8%	4.11
Generalized gamma	2884.699	2897.859	27.7%	9.3%	1.6%	4.21
Gompertz	2955.765	2964.545	21.0%	0.7%	0.0%	3.16

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; rPFS, radiographic progression-free survival.

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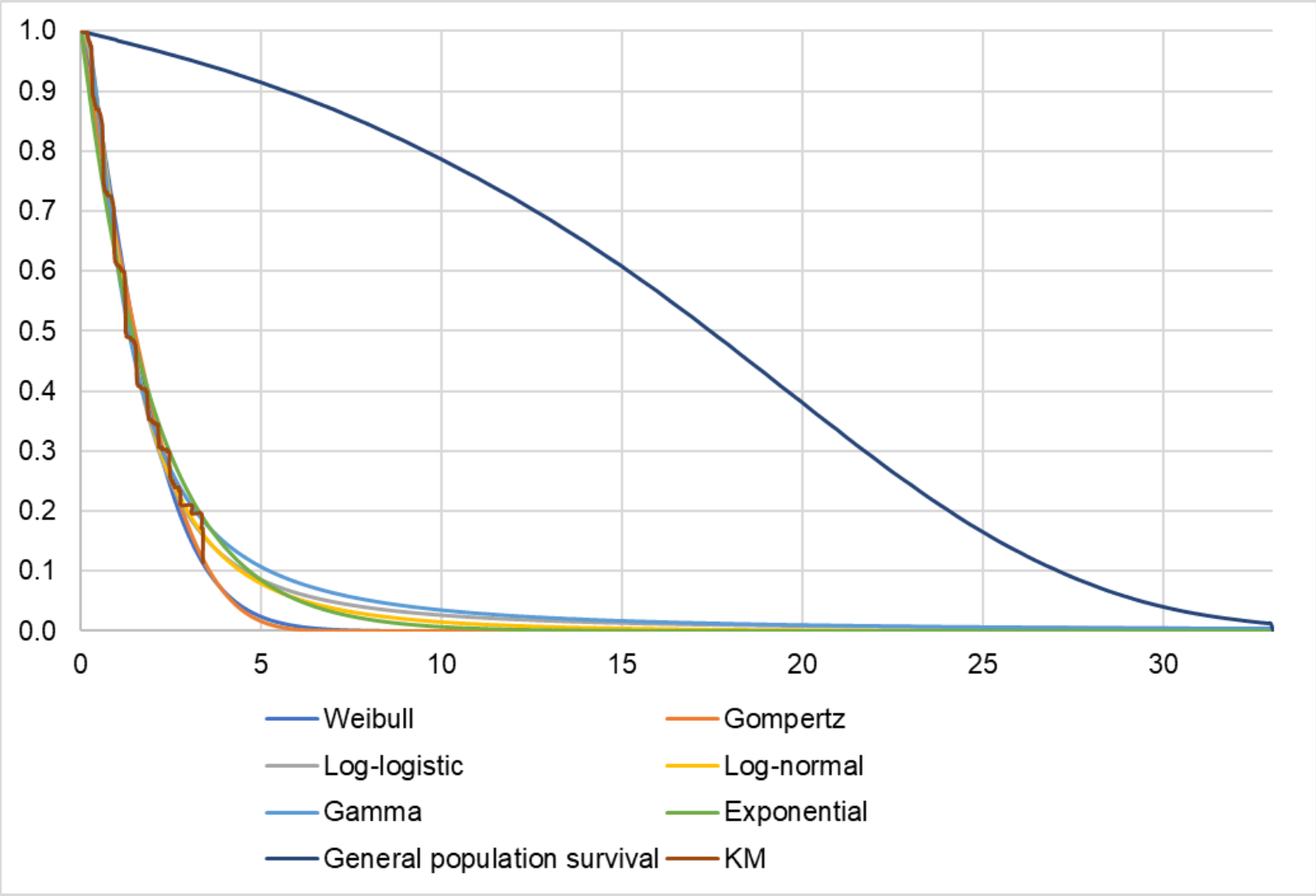
Figure 12: rPFS extrapolation (ADT alone)



Key: ADT, androgen deprivation therapy; KM, Kaplan–Meier; rPFS, radiographic progression-free survival

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Table 8: Goodness of fit statistics & survival projections ADT alone (rPFS; stratified)

Analysis	AIC	BIC	% pre-progression at 5 years	% pre-progression at 10 years	% pre-progression at 20 years	Mean time pre-progression (years)
Weibull	2924.104	2932.884	2.2%	0.0%	0.0%	1.72
Log-normal	2885.688	2894.468	7.7%	1.5%	0.2%	2.05
Log-logistic	2899.904	2908.684	8.3%	2.5%	0.7%	2.21
Exponential	2969.111	2973.505	8.2%	0.7%	0.0%	2.00
Generalized gamma	2884.699	2897.859	10.4%	3.4%	0.9%	2.39
Gompertz	2955.765	2964.545	1.5%	0.0%	0.0%	1.70

Key: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; rPFS, radiographic progression-free survival.

The goodness of statistical fit of the parametric functions for rPFS was broadly consistent across curves for both the AAP + ADT and ADT alone arms, with the lowest AIC/BIC values being for log-normal, log-logistic, gamma and Weibull. Weibull derives the most conservative estimates of rPFS in both arms (AAP+ADT: 3.35 years; ADT alone: 1.72 years), while log-logistic provides more optimistic predictions (AAP + ADT: 5.67; ADT alone 2.05).[34]

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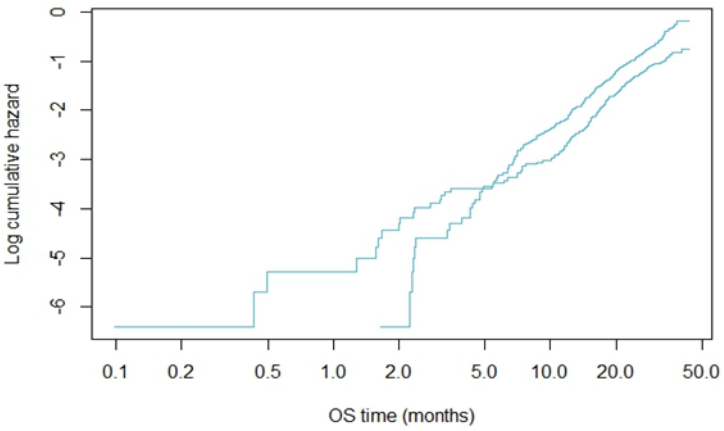
Overall Survival

Similarly to rPFS, inspection of the log-cumulative hazard plot for OS presented in Figure 13 shows that the assumption of proportional hazards does not hold. Therefore, stratified curves were utilised in the base case analysis in line with DSU TSD 14, with unstratified curves applying treatment as a covariate explored in scenario analysis.

Figure 13: Log-cumulative hazard plot [OS]



Key: OS, overall survival.

Figure 14 and Figure 15 present the long-term projections of the six parametric functions for OS for the AAP + ADT and ADT alone arms, respectively. Additionally, the goodness-of-fit statistics are presented in Table 9 and Table 10 for AAP + ADT and ADT alone, respectively.

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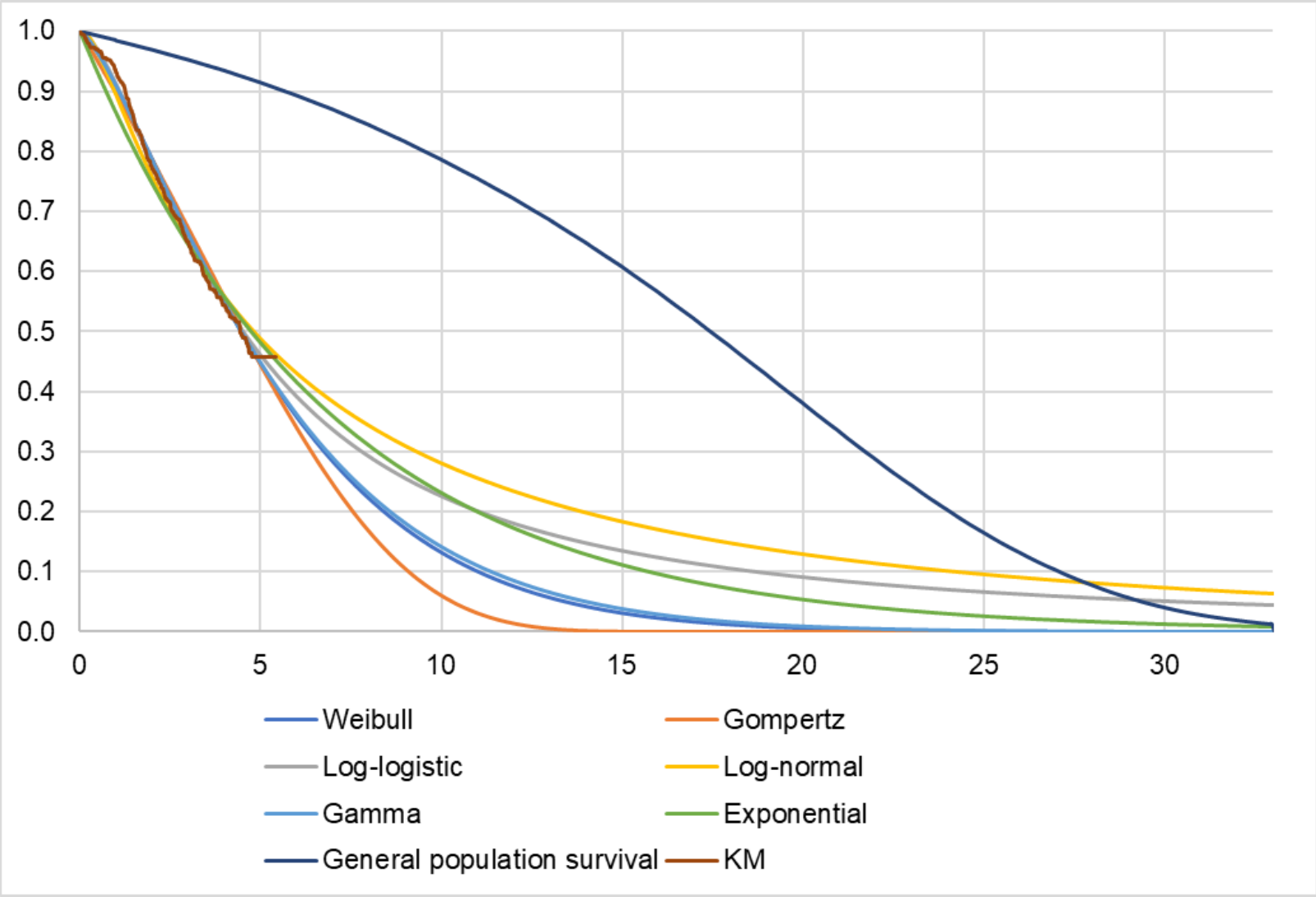
Figure 14: OS extrapolation (AAP + ADT)



Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; KM, Kaplan–Meier; OS, overall survival.

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Table 9: Goodness of fit statistics & survival projections AAP + ADT (OS; stratified)

Analysis	AIC	BIC	% alive at 5 years	% alive at 10 years	% alive at 20 years	Mean survival (years)
Weibull	2952.552	2961.336	44.0%	13.1%	0.6%	5.37
Log-normal	2981.891	2990.674	48.3%	27.9%	12.9%	8.49
Log-logistic	2951.969	2960.753	45.5%	22.4%	9.0%	7.43
Exponential	2974.570	2978.962	47.6%	22.9%	5.3%	6.73
Generalized gamma	2954.446	2967.622	44.2%	14.0%	0.9%	5.48
Gompertz	2960.592	2969.376	43.7%	5.9%	0.0%	4.78

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

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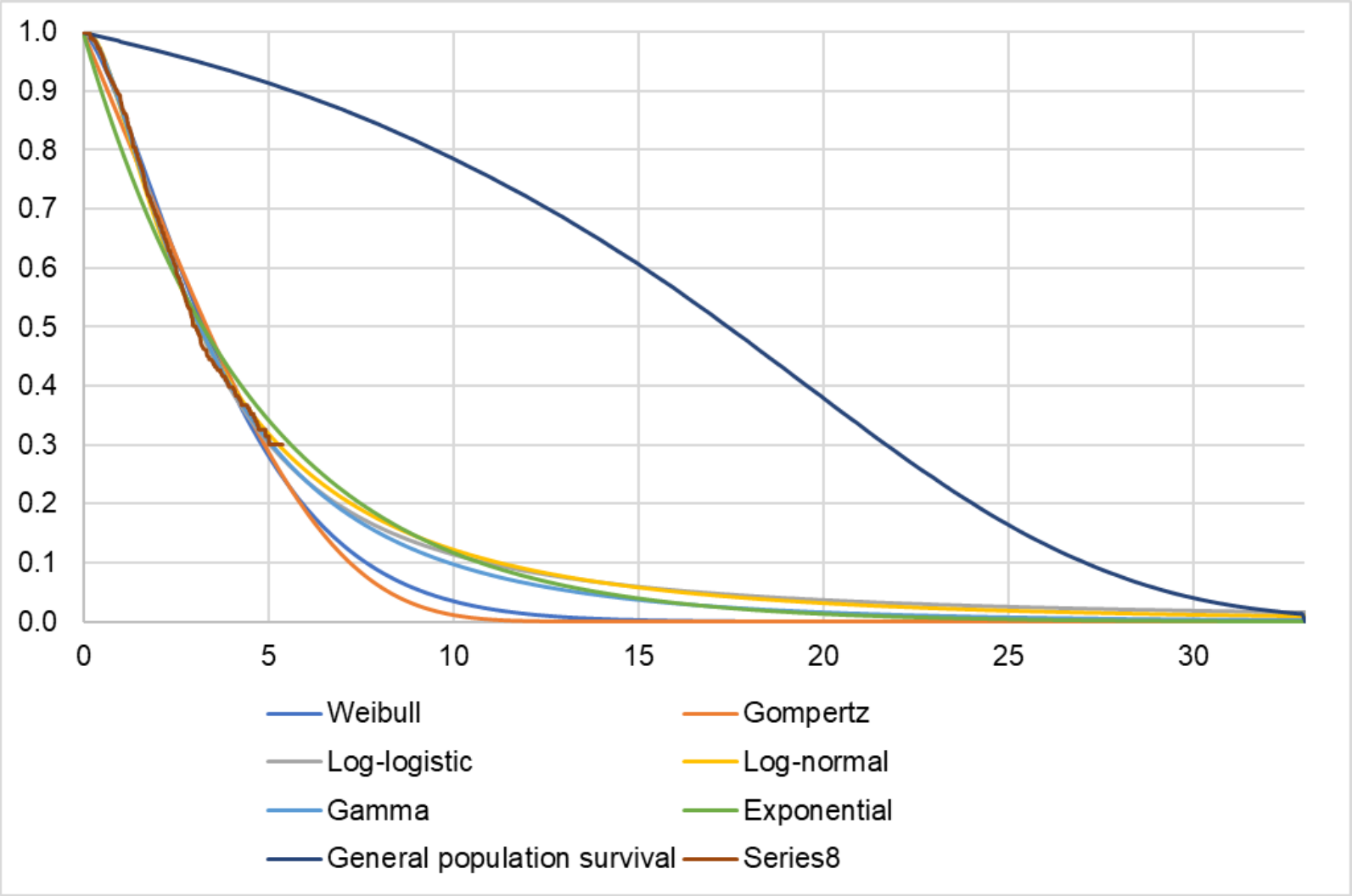
Figure 15: OS extrapolation (ADT alone)



Key: ADT, androgen deprivation therapy; OS, overall survival.

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Table 10: Goodness of fit statistics & survival projections ADT alone (OS; stratified)

Analysis	AIC	BIC	% alive at 5 years	% alive at 10 years	% alive at 20 years	Mean survival (years)
Weibull	3405.541	3414.342	27.7%	3.4%	0.0%	3.82
Log-normal	3393.424	3402.224	31.6%	12.2%	3.2%	4.98
Log-logistic	3392.502	3401.302	29.9%	11.3%	3.6%	4.98
Exponential	3450.879	3455.279	33.9%	11.7%	1.4%	4.64
Generalized gamma	3393.783	3406.984	30.4%	9.7%	1.6%	4.54
Gompertz	3431.409	3440.210	28.3%	1.1%	0.0%	3.66
Key: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.						

According to the goodness-of-fit statistics for OS, AIC/BIC values were broadly consistent with log-normal, log-logistic, gamma and Weibull producing the lowest values. When presented with the extrapolated curves and survival projections, clinical experts suggested, while the log-logistic function may overestimate long-term benefit, the Weibull function may underestimate them.[34] As such, it may be clinically plausible for long-term survival projections reside between the two.

AAP + ADT vs docetaxel + ADT

To estimate comparative PFS and OS for docetaxel + ADT in the model, the HRs derived from the Bayesian NMA for docetaxel + ADT vs. AAP + ADT (described previously in Section B.1) were applied to the estimated survival curves for AAP + ADT in the base case. Janssen maintain that the comprehensive evidence base suggests AAP + ADT is highly likely to be superior at extending OS compared to docetaxel + ADT. Nevertheless, acknowledging the Committee's request, a scenario analysis has been tested in which there is no OS benefit AAP + ADT and docetaxel.

B.4.5. Subsequent treatment durations

In the base case, the modelled time spent in 1L, 2L and 3L mCRPC were estimated by re-weighting (for overall differences in PPS between the TA387 and this submission) mean health state durations derived from TA387.[35] Currently, this method does not account for the fact a proportion of patients will have died prior to disease progression, and as such the calculations may underestimate the time spent

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in the mCRPC health states. Scenario analyses have been explored in attempt to resolve limitations in this method, with a full description of the revised approach outlined in Appendix E. These scenarios demonstrate that the base case cost-effectiveness estimates are likely to be conservative since the subsequent therapy costs in each comparator arm are underestimated.

B.4.6. Safety

As previously, frequencies of grade 3/4 AEs (including skeletal-related events [SREs]) associated with AAP + ADT or ADT alone were taken from LATITUDE, while the frequencies of grade 3/4 AEs/SREs associated with docetaxel + ADT were obtained from published literature. The AE frequencies for each subsequent therapy in mCRPC were also sourced from the literature as before.[2 25 36-39]

B.4.7. Measurement and valuation of health effects

Health-related quality of life

Given the Committee's preference to utilise regression analysis with an AE coefficient which was not separated out by treatment arm, the regression analysis used in the revised model is presented in Table 11 and a summary of all the utility values included in the new model is outlined in Table 12.

Table 11: LATITUDE utility mixed effects model results

Coefficient	Mixed effects model coefficient outputs
mHSPC treatment (baseline)	[redacted]
Intercept	[redacted]
Treatment effect	[redacted]
Baseline EQ-5D	[redacted]
Radiographic progression	[redacted]
AE (ever) | AA	[redacted]
SRE | AA	[redacted]
SRE | placebo	[redacted]

Key: AA, abiraterone acetate; AE, adverse event; mHSPC, metastatic hormone sensitive prostate cancer; SRE, skeletal-related event.

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Table 12: Summary of utility values for cost-effectiveness analysis

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

Key: 1/2/3L, first-/second/third-line; AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; AE, adverse event; mCRPC, metastatic castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; SRE, skeletal-related event.

Adverse reactions

Given the Committee's preference, during the mHSPC phase, AE disutilities associated with AAP + ADT and ADT alone were estimated using data on the proportion of patients who experienced each AE in the LATITUDE trial, alongside the LATITUDE utility regression variables. As previously, AE disutilities were estimated for each mCRPC treatment using data on the proportion of patients who experienced each AE within associated trials.[36 38-40] The duration for which AE disutilities were applied in the model was consistent with each source of the utility values.

Cost and medical resource use

Drug acquisition, medical resource use (MRU) and AE costs detailed in the original submission were updated using the most up-to-date data from each of their relevant sources and reflect the Committee's preferred assumptions for MRU. The key parameters related to drug acquisition, MRU and AEs for each treatment during the mHSPC phase of the model are summarised in Table 13.

An additional cost for granulocyte-colony stimulating factor (G-CSF) of £52.70 was also added per each administration of docetaxel, based on precedent from the recent enzalutamide submission in non-mCRPC [TA580].[41] This was a conservative estimate of the true cost as several higher priced G-CSF treatments are available.

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As advised by the ERG previously, the proportion of patients receiving AAP in the model was derived via the mid-point estimate of compliance from LATITUDE.

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Table 13: Summary of cost parameters

Drug	Abiraterone		Docetaxel		ADT			
	List	CAA			Goserelin	Leuprorelin	Triptorelin	Bicalutamide
Cost per package	£2,735.00	[redacted]	£14.74		£68.49	£194.82	£228.52	£3.96
Package size	56 tablets (500mg)	56 tablets (500mg)	80 mg vial		3.6 mg [a]	11.25 mg [a]	11.25 mg [a]	50 mg [a]
Acquisition cost per dose	£97.68	[redacted]	£28.04		£68.49	£194.82	£228.52	£0.14
Administration cost per dose	£0.00	£0.00	£300.44		£11.63	£11.63	£11.63	£0.00
Number of doses / tx cycles	7.00	7.00	1.00		0.25	0.08	0.08	7.00
Scheduled MRU (4 weekly)	wk 0-12	£300.44	On Tx	£213.53	£77.09			
	wk 13+	£170.31	Off Tx	£87.25				
Unscheduled MRU (annual)	£1213.97		£1213.97		£1535.24			
AEs (annual)	£641.31		£1,120.27		£587.88			

Key: ADT, androgen deprivation therapy; AE, adverse events; CAA, commercial access arrangement; MRU, medical resource use; tx, treatment

Note: [a], A weighted cost was calculated for each ADT therapy using prescription data, therefore the mg differs for each treatment.

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Subsequent Therapies

When patients progress on treatment for mHSPC, there are several subsequent therapies available in mCRPC within the NHS. Janssen acknowledge the Committee's request to test differences in effectiveness of treatments for mCRPC; however, there remains no robust evidence to determine the relative effectiveness of subsequent therapies in mCRPC, specifically after active treatment in mHSPC. To accommodate the Committee's request as best as possible, the PartSA structure allows for the post-progression phase to be varied by changing the OS HR between AAP + ADT vs ADT alone and vs docetaxel + ADT.

Janssen recognise that, since LATITUDE was an international study, the subsequent therapies observed within the trial may not be reflective of UK clinical practice; however, as shown earlier in Figure 7, the survival outcomes of the LATITUDE trial track very closely with the high-risk mHSPC subgroup from STAMPEDE, which the Committee consider most representative of UK practice. This validates the representativeness of LATITUDE outcomes for modelling purposes, provided modelled arms are costed according to UK clinical practice.

At the time this appraisal was suspended, the Committee questioned whether the modelled treatment pathways reflected UK clinical practice. Clinical experts have also advised that treatment practice has evolved over the past year.[34] There has been increased use of cabazitaxel in mCRPC as an alternative, more tolerable taxane to re-challenge with docetaxel (thereby indicating docetaxel re-challenge is very rare). There has also been a decrease in the use of radium-223 as a consequence of new Medicines and Healthcare products Regulatory Agency (MHRA) guidance, issued in September 2018, which restricts the use of radium-223 to after two previous systemic treatments for mCRPC, or in those who cannot receive other systemic treatments.[42] As such, updated expert clinical opinion was sought to ascertain an appropriate simulation of the treatment pathway;[34] the subsequent therapies applied in the PartSA, after each respective treatment in mHSPC, are presented in Figure 16.

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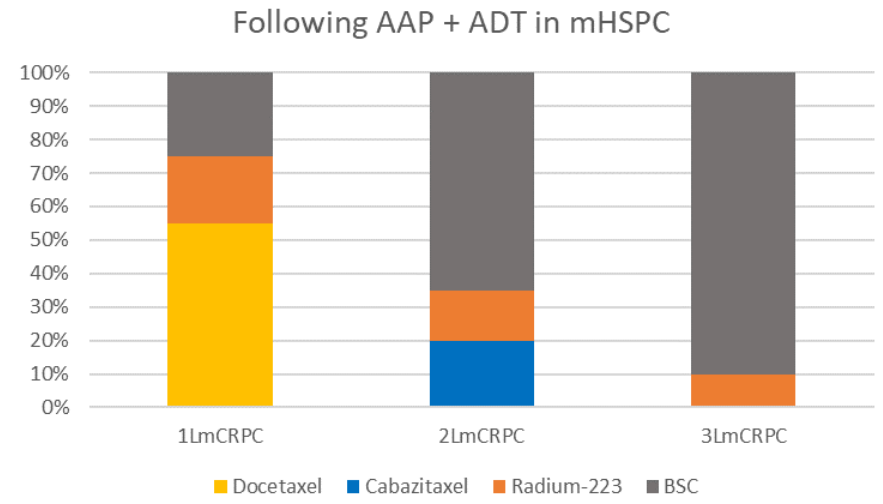
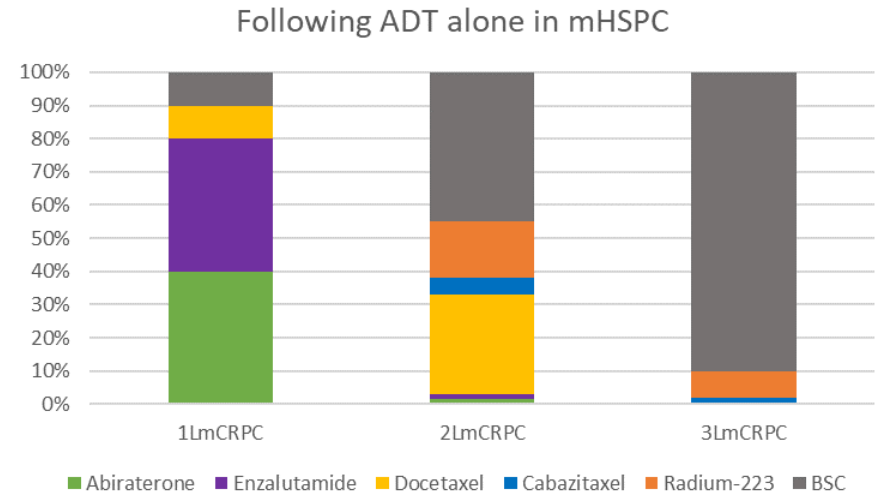
Figure 16: Modelled treatment pathways following mHSPC

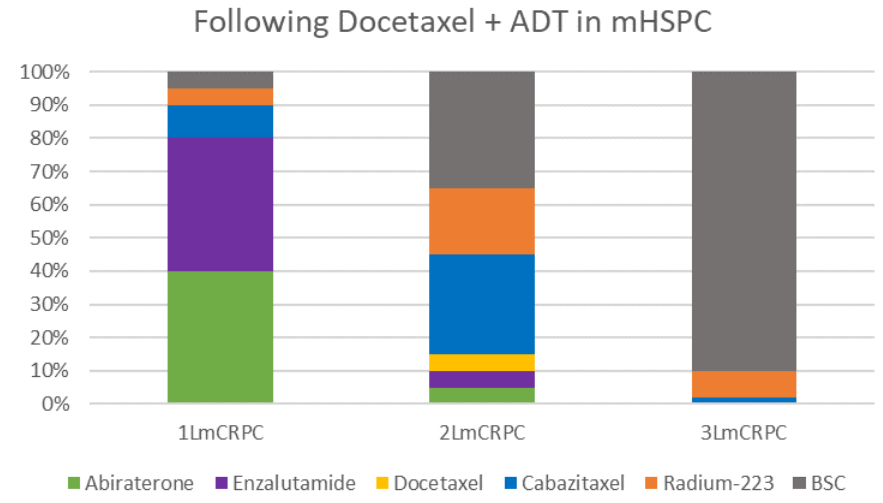
a)



b)



c)



Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; BSC, best supportive care; L, treatment line; mCRPC metastatic castrate-resistant prostate cancer; mHSPC, metastatic hormone sensitive

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B.4.8. Base case results

All results presented herein incorporate the confidential CAA between Janssen and NHS England, extended to include this indication in mHSPC (at NICE's request, results at list price are also presented in Appendix F). Results also acknowledge feedback from the ERG and Committee at the time this appraisal was suspended, as well as updates for new data.

Results in Table 14 show that AAP + ADT is a highly cost-effective use of NHS resources when used in men with high-risk mHSPC who are deemed chemo-ineligible at diagnosis with an ICER between [redacted] per QALY gained. An ICER range has been presented given the feedback on the parametric functions; Weibull may underestimate the long-term benefit of AAP + ADT, while log-logistic may overestimate it.[34] As such, the true ICER is likely to reside between these values, both of which are highly cost-effective. When AAP + ADT is compared against ADT alone, a substantial incremental survival benefit drives significant QALY gains for these men who currently have no life-extending treatment option on the NHS. These significant benefits offset the incremental cost of adding AAP to their ADT to derive a highly cost-effective ICER.

Table 14: Results for AAP + ADT in the chemo-ineligible cohort [with CAA]

Extrapolation	**Log-logistic**		**Weibull**	
Technologies	**ADT alone**	**AAP + ADT**	**ADT alone**	**AAP + ADT**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]		[redacted]	
Incremental LYG	[redacted]		[redacted]	
Incremental QALYs	[redacted]		[redacted]	
ICER	[redacted]		[redacted]	

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CAA, commercial access arrangement; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Results for the comparison of AAP + ADT vs docetaxel + ADT have been presented in a comparable manner. Table 15 show that the ICER for AAP + ADT vs docetaxel + ADT is at the upper-end of NICE's willingness-to-pay threshold when considering patients who are

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currently eligible for chemotherapy. These results demonstrate the significant challenge in determining cost-effectiveness against an inexpensive generic chemotherapy, which is beneficial for those who are fit enough to receive it.

Table 15: Results for AAP + ADT in the chemo-eligible cohort [with CAA]

Extrapolation	Log-logistic		Weibull	
Technologies	**Docetaxel + ADT**	**AAP + ADT**	**Docetaxel + ADT**	**AAP + ADT**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]		[redacted]	
Incremental LYG	[redacted]		[redacted]	
Incremental QALYs	[redacted]		[redacted]	
ICER	[redacted]		[redacted]	

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CAA, commercial access arrangement; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

The life years gained (LYG) accrued in the revised model across each health state by treatment are presented in Figure 17. Docetaxel + ADT and ADT alone are associated with a longer post progression survival (PPS) than AAP + ADT, which stands to reason given that subsequent therapy with novel agents is prohibited for patients treated with AAP + ADT. As noted in Section B.1.7, however, when AAP + ADT is used later in the treatment pathway the incremental benefit with respect to OS is four times lower than when used in mHSPC. As such, the overall LYG is expected to be significantly higher with AAP +ADT versus ADT alone, with modest gains anticipated versus docetaxel + ADT. It is important to note that although PPS is longer following docetaxel + ADT and ADT alone, the time spent progression free is substantially greater with AAP + ADT and it is in this health state that patients experience the best quality of life.

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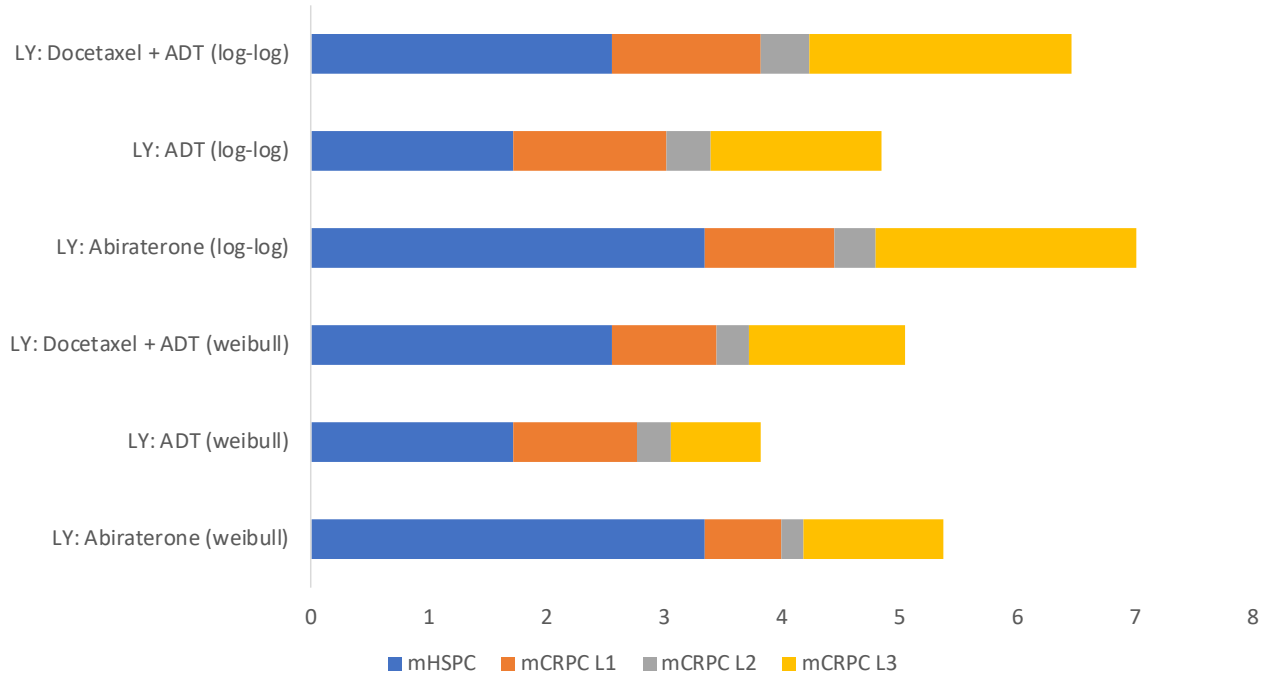
Figure 17: LYG across model health states by treatment arm



Key: ADT, androgen deprivation therapy; LY, life year; LYG, life years gained; mCRPC, metastatic castrate resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer.

B.4.9. One-way Sensitivity Analysis

Tornado diagrams for the comparisons of AAP + ADT vs ADT alone, and vs docetaxel + ADT under the confidential CAA are presented in Figure 18, Figure 19, Figure 20 and Figure 21 (tornado diagrams at list price are also presented in Appendix F).

Figure 18: Tornado diagram for AAP + ADT versus ADT alone in the chemo-ineligible cohort [with CAA and Weibull extrapolation]

[redacted]

Key: AA, Abiraterone acetate; AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; AE, adverse event; CAA, commercial access arrangement; ICER, incremental cost-effectiveness ratio; L1, first-line; L3, third-line; mCRPC, metastatic castrate resistant prostate cancer; QALY, quality adjusted life year; SRE, skeletal related event; trt, treatment.

Figure 19: Tornado diagram for AAP + ADT versus docetaxel + ADT in the chemo-eligible cohort [with CAA and Weibull extrapolation]

[redacted]

Key: AA, Abiraterone acetate; AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; AE, adverse event; CAA, commercial access arrangement; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; L1, first-line; mCRPC, metastatic castrate resistant prostate cancer; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; SRE, skeletal related event; trt, treatment; TTO, time trade off.

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Figure 20: Tornado diagram for AAP + ADT versus ADT alone in the chemo-ineligible cohort [with CAA and log-logistic extrapolation]

Key: AA, Abiraterone acetate; AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; AE, adverse event; CAA, commercial access arrangement; ICER, incremental cost-effectiveness ratio; L1, first-line; mCRPC, metastatic castrate resistant prostate cancer; QALY, quality adjusted life year; SRE, skeletal related event; trt, treatment.

Figure 21: Tornado diagram for AAP + ADT versus docetaxel + ADT in the chemo-eligible cohort [with CAA and log-logistic extrapolation]

Key: AA, Abiraterone acetate; AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CAA, commercial access arrangement; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; L1, first-line; mCRPC, metastatic castrate resistant prostate cancer; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; trt, treatment; TTO, time trade off.

B.4.10. Scenario Analyses

A series of scenario analyses have been explored to assess the impact on the ICER with changing model assumptions. As shown in Table 16, the ICERs for AAP + ADT vs ADT alone are consistently highly cost-effective through all scenarios. The ICERs for AAP + ADT vs docetaxel + ADT are associated with greater uncertainty as noted by a larger range in results from scenario analyses. For both comparisons, the highest ICERs are derived when the modelled time horizon is set to 5 years whilst the NICE reference case stipulates a life-time horizon should always be used. Discarding this outlying scenario, all ICERs for AAP + ADT vs ADT alone range between [redacted] per QALY gained and all ICERs vs docetaxel + ADT range between [redacted] per QALY gained.

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Table 16: Scenario Analyses [with CAA]

Model assumption	Scenario	ICER vs ADT alone	ICER vs dox + ADT	ICER vs ADT alone	ICER vs dox + ADT
Base case		**Loglogistic**		**Weibull**	
		[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	20 years	[redacted]	[redacted]	[redacted]	[redacted]
	10 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
AAP utility increment	Applied until death	[redacted]	[redacted]	[redacted]	[redacted]
	No increment applied	[redacted]	[redacted]	[redacted]	[redacted]
AE disutilities	Using literature values	[redacted]	[redacted]	[redacted]	[redacted]
mCRPC utilities	Assumed constant through mCRPC	[redacted]	[redacted]	[redacted]	[redacted]
Vial wastage	Set to zero	[redacted]	[redacted]	[redacted]	[redacted]
No OS benefit	AAP + ADT v docetaxel + ADT OS HR=1; PFS HR=0.69	[redacted]	[redacted]	[redacted]	[redacted]
NMA at IA1	AAP + ADT v docetaxel + ADT OS HR=0.88; PFS HR=0.72	[redacted]	[redacted]	[redacted]	[redacted]
Survival extrapolation for rPFS	Unstratified	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal (stratified)	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma (stratified)	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz (stratified)	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential (stratified)	[redacted]	[redacted]	[redacted]	[redacted]
Survival extrapolation for OS	Unstratified	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal (stratified)	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma (stratified)	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz (stratified)	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential (stratified)	[redacted]	[redacted]	[redacted]	[redacted]
G-CSF cost	Exclude	[redacted]	[redacted]	[redacted]	[redacted]
mCRPC health state durations	Apply BSC durations from TA387	[redacted]	[redacted]	[redacted]	[redacted]
	Apply AAP durations from TA387	[redacted]	[redacted]	[redacted]	[redacted]

Key: AAP, abiraterone acetate with prednisone; ADT, androgen deprivation therapy; AE, adverse event; BSC, best supportive care; CAA, commercial access arrangement; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; IA1, first interim analysis; ICER, incremental cost-effectiveness ratio; mCRPC, metastatic castrate-resistant prostate cancer; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; rPFS, radiographic progression-free survival

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B.4.11. Probabilistic sensitivity analysis

Table 17: PSA Results for AAP + ADT in the chemo-ineligible cohort [with CAA]

Extrapolation	Log-logistic		Weibull	
Technologies	ADT alone	AAP + ADT	ADT alone	AAP + ADT
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]		[redacted]	
Incremental LYG	[redacted]		[redacted]	
Incremental QALYs	[redacted]		[redacted]	
ICER	[redacted]		[redacted]	

Key: AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CAA, commercial access arrangement; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analyses; QALYs, quality-adjusted life years

Table 18: PSA Results for AAP + ADT in the chemo-eligible cohort [with CAA]

Extrapolation	Log-logistic		Weibull	
Technologies	Docetaxel + ADT alone	AAP + ADT	Docetaxel + ADT alone	AAP + ADT
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]		[redacted]	
Incremental LYG	[redacted]		[redacted]	
Incremental QALYs	[redacted]		[redacted]	
ICER	[redacted]		[redacted]	

Key: AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CAA, commercial access arrangement; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analyses; QALYs, quality-adjusted life years

Figure 22: PSA scatter plots for AAP + ADT versus ADT alone in the chemo-ineligible cohort [with CAA]

[redacted]**Key:** AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CAA, commercial access arrangement; PSA, probabilistic sensitivity analyses, QALY, quality adjusted life year.

Figure 23: PSA scatter plots for AAP + ADT versus docetaxel + ADT in the chemo-eligible cohort [with CAA]

[redacted]**Key:** AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CAA, commercial access arrangement; PSA, probabilistic sensitivity analyses, QALY, quality adjusted life year.

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Figure 24: Cost-effectiveness acceptability curves for AAP + ADT vs ADT alone [with CAA]

[redacted]**Key:** AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CAA, commercial access arrangement; WTP, willingness to pay.

Figure 25: Cost-effectiveness acceptability curves for AAP + ADT vs docetaxel + ADT [with CAA]

[redacted]**Key:** AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CAA, commercial access arrangement; WTP, willingness to pay.

Table 19: Probability of cost-effectiveness [with CAA}

Base-case setting	Comparator	WTP threshold		
		£20,000	£30,000	£50,000
Weibull	Vs ADT alone	[redacted]	[redacted]	[redacted]
	Vs docetaxel + ADT	[redacted]	[redacted]	[redacted]
Log-logistic	Vs ADT alone	[redacted]	[redacted]	[redacted]
	Vs docetaxel + ADT	[redacted]	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; CAA, commercial access arrangement; WTP, willingness to pay

B.4.12. Conclusion

These results provide irrefutable evidence for the cost-effectiveness of AAP + ADT vs ADT alone in patients with high-risk mHSPC, who are chemo-ineligible at diagnosis. Whilst defining explicit criteria for chemo-ineligibility is challenging, promising precedent has been set by NICE within TA587 which recognises the importance of exercising clinical judgement in making treatment decisions regarding patients' eligibility to existing treatments associated with toxicity. This is vital in fulfilling the acute unmet need for a life-extending therapy for those chemo-ineligible men currently dying within three years of their diagnosis.[3 5]

Janssen recognise that the cost-effectiveness of AAP + ADT vs docetaxel + ADT is at the upper-end of NICE's willingness-to-pay threshold when considering patients who are currently eligible for chemotherapy. Given the considerable value being offered to the NHS through the confidential CAA, these results demonstrate the significant challenge in determining cost-effectiveness against an inexpensive generic chemotherapy, which is beneficial for those who are fit enough to receive it.

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The cost-effective use of AAP + ADT in chemo-ineligible cohort of men within the NHS will help fulfil the highest unmet need, will significantly improve these men's quality of life, extend their survival and ultimately benefit societal health outcomes by reducing the burden on carers and allowing men with mHSPC to continue with 'normal life' for as long as possible. Cost-effective treatment with AAP + ADT should not be denied to those who have no alternative life-extending options within the NHS.

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Appendix A. Patient Numbers in England

	2016	2017	2018	2019	2020	2021	2022
Prostate Cancer Incidence England in 2016 [a]	40,489	40,732	40,976	41,222	41,470	41,718	41,969
Newly diagnosed mHSPC [18%] [a]	7,288	7,332	7,376	7,420	7,465	7,509	7,554
Newly diagnosed high-risk mHSPC [50%] [b]	3,644	3,666	3,688	3,710	3,732	3,755	3,777
Chemo-ineligible [20%][c]	729	733	738	742	746	751	755

Population growth assumed 0.6% per year as per Office of National Statistics.

[a] Cancer Research UK – Prostate Cancer incidence statistics [accessed June 2019][6]

[b] Buelens et al. 2018 [7]

[c] UK Advisory Board

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Appendix B. LATITUDE: Results from IA1, IA2 and final analysis

Table 20: Treatment exposure [LATITUDE, ITT population]

	IA1[2]		IA2[27]		Final Analysis[3 29]	
	AAP + ADT (n=597)	**ADT alone (n=602)**	**AAP + ADT (n=597)**	**ADT alone (n=602)**	**AAP + ADT (n=597)**	**ADT alone (n=602)**
Treatment duration, median months (range)	24.0 [redacted]	14.3 [redacted]	25.8 [redacted]	14.4 [redacted]	25.8 (0.1-64.4)	14.4 (0.7-51.3)
Received ≥6 cycles, n (%)	548 (91.8)	518 (86.0)	[redacted]	[redacted]	[redacted]	[redacted]
Received ≥24 cycles, n (%)	325 (54.4)	179 (29.7)	[redacted]	[redacted]	[redacted]	[redacted]
Received ≥36 cycles, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Received dose reductions, n (%)	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Received dose interruptions, n (%)	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Received dose interruptions with prednisolone due to AEs, n (%)	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; AE, adverse event; IA1, first interim analysis; IA2, second interim analysis; ITT, intention-to-treat; NR, not reported.

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Table 21: Overall survival, [LATITUDE, ITT population]

	IA1[2]		IA2[27]		Final Analysis[3 29]	
	AAP + ADT (n=597)	**ADT alone (n=602)**	**AAP + ADT (n=597)**	**ADT alone (n=602)**	**AAP + ADT (n=597)**	**ADT alone (n=602)**
Median follow-up, months	30.4		[redacted]		51.8	
Median OS, months	NR	34.7	[redacted]	[redacted]	53.3	36.5
HR [95% CI]	0.62 [0.51–0.76]		[redacted]		0.66 [0.56, 0.78]	
OS rate at 3 years	66%	49%	[redacted]	[redacted]	[redacted]	[redacted]
OS rate at 4 years	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; IA1, first interim analysis; IA2, second interim analysis; ITT, intention-to-treat; NR, not reached; OS, overall survival.

As illustrated by Figure 26, the significant survival benefit with AAP + ADT vs ADT alone was sustained after a longer duration of follow-up, substantiating the robustness of results.

Figure 26: KM plot of OS at IA1 vs IA2 vs final analysis [LATITUDE, ITT population]

[redacted]**Key**: AA, abiraterone acetate; ADT, androgen deprivation therapy; KM, Kaplan–Meier; NE, not evaluable; OS, overall survival; IA1, first interim analysis; IA2, second interim analysis; ITT, intention-to-treat;

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Table 22: Subsequent therapy [LATITUDE, ITT population]

	IA1[2 43]		IA2[27]		Final analysis[29]	
	AAP + ADT (n=597)	**ADT alone (n=602)**	**AAP + ADT (n=597)**	**ADT alone (n=602)**	**AAP + ADT (n=597)**	**ADT alone (n=602)**
Received subsequent therapy, n (%)	191 (32.0)	322 (53.5)				
Received subsequent systemic therapy, n (%)						
Antineoplastic agents						
Docetaxel						
Cabazitaxel						
Endocrine therapy						
Bicalutamide						
Enzalutamide						
Corticosteroids for systemic use						
Subsequent surgery/procedures, n (%)						
Radiotherapy (to bone)						
Radiotherapy (other than bone)						
Surgery (to bone)						
Surgery (other than bone)						

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; IA1, first interim analysis; IA2, second interim analysis; ITT, intention-to-treat.

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Table 23: Secondary outcomes [LATITUDE, ITT Population]

	IA1[2 43]		IA2[27]		Final analysis[3 29]	
	AAP + ADT (n=597)	**ADT alone (n=602)**	**AAP + ADT (n=597)**	**ADT alone (n=602)**	**AAP + ADT (n=597)**	**ADT alone (n=602)**
Time to pain progression						
Events, n (%)	233 (39.0)	289 (48.0)	NR	NR	245 (41.0)	292 (48.5)
Median months (95% CI)	NR (36.5-NR)	16.6 (11.1-24.0)	47.4	17.9	47.4 (33.2-NE)	16.6 (11.1-24.0)
HR (95% CI) [p-value]	0.70 (0.58–0.83) [p<0.001]		0.72 (0.61–0.86) [p=0.0002]		0.72 (0.6- 0.86) [p=0.0002]	
Time to subsequent prostate cancer therapy						
Events, n (%)	191 (32.0)	322 (53.5)	[redacted]	[redacted]	248 (42.2)	355 (59.0)
Median months (95% CI)	NR (37.9-NR)	21.6 (18.8-23.6)	NR	21.2	54.9 (46.4-NE)	21.2 (18.6-23.5)
HR (95% CI) [p-value]	0.42 (0.35–0.50) [<0.001]		0.43 (0.36–0.51) [p<0.0001]		0.45 (0.38, 0.53) [p<0.0001]	
Time to life-extending subsequent therapy for prostate cancer						
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) [p-value]	[redacted]		[redacted]		[redacted]	
Time to initiation of chemotherapy						
Events, n (%)	109 (18.3)	191 (31.7)	NR	NR	150 (25.1)	218 (36.2)
Median months (95% CI)	NR (NR-NR)	38.9 (33.4-NR)	NR	47.3	NE (62.6-NE)	57.6 (38.2-NE)
HR (95% CI) [p-value]	0.44 (0.35–0.56) [p<0.001]		0.47 (0.38–0.59) [p<0.0001]		0.51 (0.41, 0.63) [p<0.0001]	
Time to PSA progression						
Events, n (%)	241 (40.4)	434 (72.1)	NR	NR	[redacted]	[redacted]

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Median months (95% CI)	33.2 (27.6-NR)	7.4 (7.2-9.2)	NR	NR	[redacted]	[redacted]
HR (95% CI) [p-value]	0.30 (0.26–0.35) [p<0.001]		NR		[redacted]	
Progression-free survival following subsequent therapy (PFS2)						
Events, n (%)	NR	NR	[redacted]	[redacted]	267 (45.0)	336 (56.1)
Median months (95% CI)	NR	NR	[redacted]	[redacted]	53.3	30.1
HR (95% CI) [p-value]	NR		[redacted]		0.58 (0.49, 0.68) [p<0.0001]	
Time to next SRE						
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median months (95% CI)	NR (NR-NR)	NR (NR-NR)	NR	NR	NE (NE-NE)	NE (NE-NE)
HR (95% CI) [p-value]	0.70 (0.54–0.92) [p=0.009]		0.74 (0.58–0.94) [p=0.0148]		0.75 (0.60-0.95) [p=0.0181]	

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; IA1, first interim analysis; IA2, second interim analysis; ITT, intention-to-treat; NE, not evaluable; NR, not reached; PSA, prostate-specific antigen; SRE, skeletal-related event.

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Table 24: Treatment-emergent grade 3–4 AEs reported in at least 1% of patients in either treatment group [LATITUDE, safety population, final analysis]

	IA1[2 28]						Final analysis[3]					
	AAP + ADT (n=597)			ADT Alone (n=602)			AAP + ADT (n=597)			ADT Alone (n=602)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Any TEAE, n (%)	374 (62.6)	342 (57.3)	32 (5.4)	287 (47.7)	265 (44.0)	22 (3.7)	403 (67.5)	[redacted]	[redacted]	299 (49.7)	[redacted]	[redacted]
Vascular disorders	127 (21.3)	126 (21.1)	1 (0.2)	65 (10.8)	64 (10.6)	1 (0.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	121 (20.3)	121 (20.3)	0	60 (10.0)	59 (9.8)	1 (0.2)	131 (20.9)	130 (22.0)	1 (<1)	62 (10.0)	62 (10.0)	1 (<1)
Cardiac disorder	-	-	-	-	-	-	23 (4)	18 (3)	5 (1)	6 (1)	6 (1)	0
Any	74 (12)	15 (3)	5 (1)	47 (8)	6 (1)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	8 (1)	2 (<1)	0	2 (<1)	1 (<1)	0	2 (0.3)	2 (0.3)	0	1 (0.2)	1 (0.2)	0
Metabolism and nutrition disorders	98 (16.4)	90 (15.1)	8 (1.3)	42 (7.0)	39 (6.5)	3 (0.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	62 (10.4)	57 (9.5)	5 (0.8)	8 (1.3)	7 (1.2)	1 (0.2)	70 (11.7)	65 (10.9)	5 (0.8)	10 (1.7)	9 (1.5)	1 (0.2)
Hyperglycaemia	27 (4.5)	26 (4.4)	1 (0.2)	18 (3.0)	18 (3.0)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	7 (1.2)	5 (0.8)	2 (0.3)	9 (1.5)	9 (1.5)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	69 (11.6)	62 (10.4)	7 (1.2)	47 (7.8)	45 (7.5)	2 (0.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT increase	33 (5.5)	31 (5.2)	2 (0.3)	8 (1.3)	8 (1.3)	0	34 (5.7)	32 (5.4)	2 (0.3)	8 (1.3)	8 (1.3)	0

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AST increase	26 (4.4)	25 (4.2)	1 (0.2)	9 (1.5)	9 (1.5)	0	27 (4.5)	26 (4.4)	1 (0.2)	9 (1.5)	9 (1.5)	0
LDH increase	11 (1.8)	10 (1.7)	1 (0.2)	9 (1.5)	9 (1.5)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight increase	6 (1.0)	6 (1.0)	0	6 (1.0)	6 (1.0)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	55 (9.2)	55 (9.2)	0	72 (12.0)	72 (12.0)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone pain	20 (3.4)	20 (3.4)	0	17 (2.8)	17 (2.8)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	14 (2.3)	14 (2.3)	0	19 (3.2)	19 (3.2)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	7 (1.2)	7 (1.2)	0	12 (2.0)	12 (2.0)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	6 (1.0)	6 (1.0)	0	15 (2.5)	15 (2.5)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	4 (0.7)	4 (0.7)	0	6 (1.0)	6 (1.0)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscular weakness	3 (0.5)	3 (0.5)	0	7 (1.2)	7 (1.2)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	35 (5.9)	32 (5.4)	3 (0.5)	35 (5.8)	31 (5.1)	4 (0.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spinal cord compression	12 (2.0)	12 (2.0)	0	10 (1.7)	7 (1.2)	3 (0.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	31 (5.2)	29 (4.9)	2 (0.3)	19 (3.2)	17 (2.8)	2 (0.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	10 (1.7)	9 (1.5)	1 (0.2)	3 (0.5)	3 (0.5)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	6 (1.0)	6 (1.0)	0	5 (0.8)	5 (0.8)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and	30	29	1 (0.2)	29	28	1 (0.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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urinary disorders	(5.0)	(4.9)		(4.8)	(4.7)							
Urinary retention	10 (1.7)	10 (1.7)	0	8 (1.3)	8 (1.3)	0						
Haematuria	6 (1.0)	6 (1.0)	0	3 (0.5)	3 (0.5)	0						
Blood and lymphatic system disorders	26 (4.4)	21 (3.5)	5 (0.8)	35 (5.8)	33 (5.5)	2 (0.3)						
Anaemia	15 (2.5)	12 (2.0)	3 (0.5)	27 (4.5)	26 (4.3)	1 (0.2)						
General disorders and administration site conditions	26 (4.4)	26 (4.4)	0	39 (6.5)	37 (6.1)	2 (0.3)						
Fatigue	10 (1.7)	10 (1.7)	0	14 (2.3)	14 (2.3)	0						
Asthenia	4 (0.7)	4 (0.7)	0	7 (1.2)	7 (1.2)	0						
General physical health deterioration	4 (0.7)	4 (0.7)	0	6 (1.0)	6 (1.0)	0						

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; LDH, lactate dehydrogenase; TEAE, treatment-emergent adverse events.

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A summary of the most common AEs and AEs of special interest is presented in Table 25.

AEs that led to treatment discontinuation were reported in 93 (16%) patients in the AAP + ADT group and 63 (11%) patients in the ADT alone group.[3] The most frequently reported AEs leading to treatment discontinuation (reported in ≥1% of patients in either the AAP + ADT or ADT alone group) were [redacted] and [redacted].[43] Notably, there were only rare cases of discontinuation for the preferred terms of [redacted].[43]

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Table 25: Most common AEs and AEs of special interest [LATITUDE, safety population]

	IA1[2]						Final analysis[29]					
	AAP + ADT (n=597)			ADT alone (n=602)			AAP + ADT (n=597)			ADT alone (n=602)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
AE, n (%)												
Hypertension	219 (37)	121 (20)	0	133 (22)	59 (10)	1 (<1)	[redacted]					
Hypokalaemia	122 (20)	57 (10)	5 (1)	22 (4)	7 (1)	1 (<1)	[redacted]					
ALT increased	98 (16)	31 (5)	2 (<1)	77 (13)	8 (1)	0	[redacted]					
Hyperglycaemia	75 (13)	26 (4)	1 (<1)	68 (11)	18 (3)	0	[redacted]					
AST increased	87 (15)	25 (4)	1 (<1)	68 (11)	9 (1)	0	[redacted]					
Bone pain	74 (12)	20 (3)	0	88 (15)	17 (3)	0	[redacted]					
Cardiac disorder							[redacted]					
Any	74 (12)	15 (3)	5 (1)	47 (8)	6 (1)	0	[redacted]					
Atrial fibrillation	8 (1)	2 (<1)	0	2 (<1)	1 (<1)	0	[redacted]					
Anaemia	54 (9)	12 (2)	3 (1)	85 (14)	26 (4)	1 (<1)	[redacted]					
Back pain	110 (18)	14 (2)	0	123 (2)	19 (3)	0	[redacted]					
Fatigue	77 (13)	10 (2)	0	86 (14)	14 (2)	0	[redacted]					
Spinal-cord	14 (2)	12 (2)	0	12 (2)	7 (1)	3 (<1)	[redacted]					

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compression												

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IA1, first interim analysis; NR, not reported.
Note: [a], Grade ≥4

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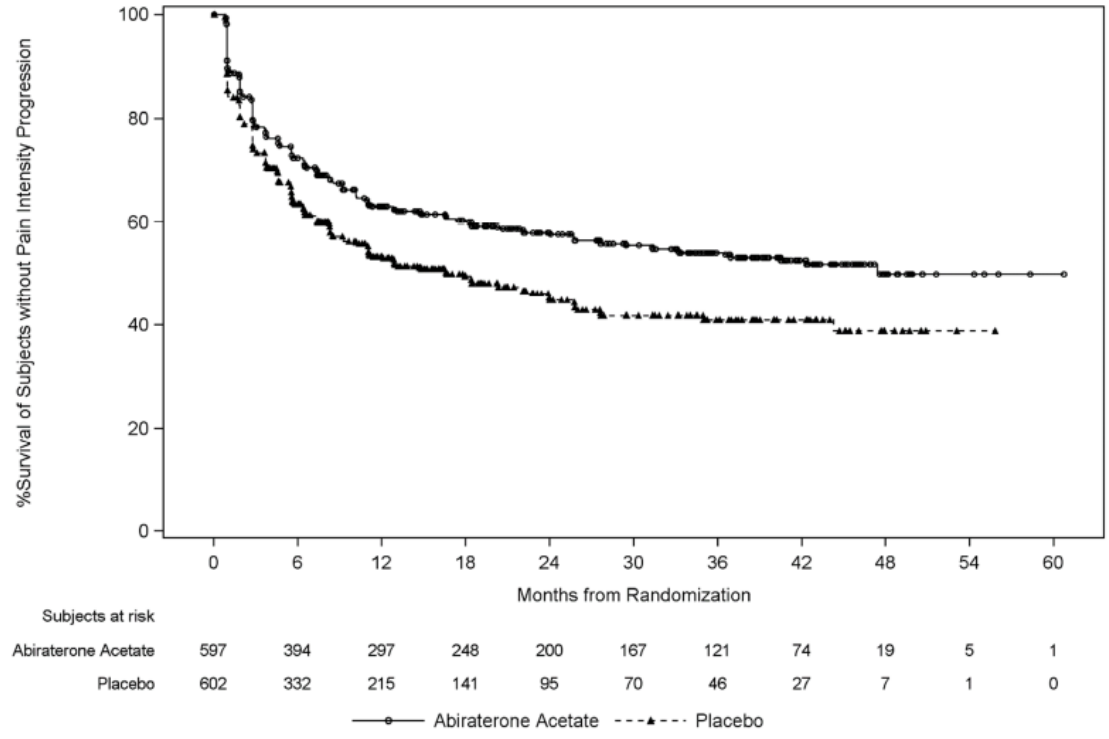
Appendix C. LATITUDE: Secondary Endpoints

Time to pain progression

Time to pain progression was defined as the time interval from randomisation to the first date a patient experiences a ≥30% increase from baseline in the Brief Pain Inventory-Short Form (BPI-SF) worst pain intensity (Item 3) observed at two consecutive evaluations ≥4 weeks apart.[43]

As shown in Figure 27, median time to pain progression was 47.4 months in the AAP + ADT group and 16.6 months in the ADT alone group, resulting in a **28% reduction in the risk of pain progression** (HR=0.72; 95% CI: 0.61–0.86; p=0.0002).[3] The 36-month event-free rate was [redacted]% for AAP + ADT vs. [redacted]% for ADT alone.

Figure 27: Kaplan–Meier plot of time to pain progression [LATITUDE, ITT population, final analysis]



Key: ITT, intention-to-treat.
Source: Fizazi et al. 2019[44].

Time to subsequent therapy for prostate cancer

As shown in Figure 28, the median time to subsequent therapy was 54.9 months in the AAP + ADT group and 21.2 months in the ADT group (HR=0.45; 95% CI: 0.38–

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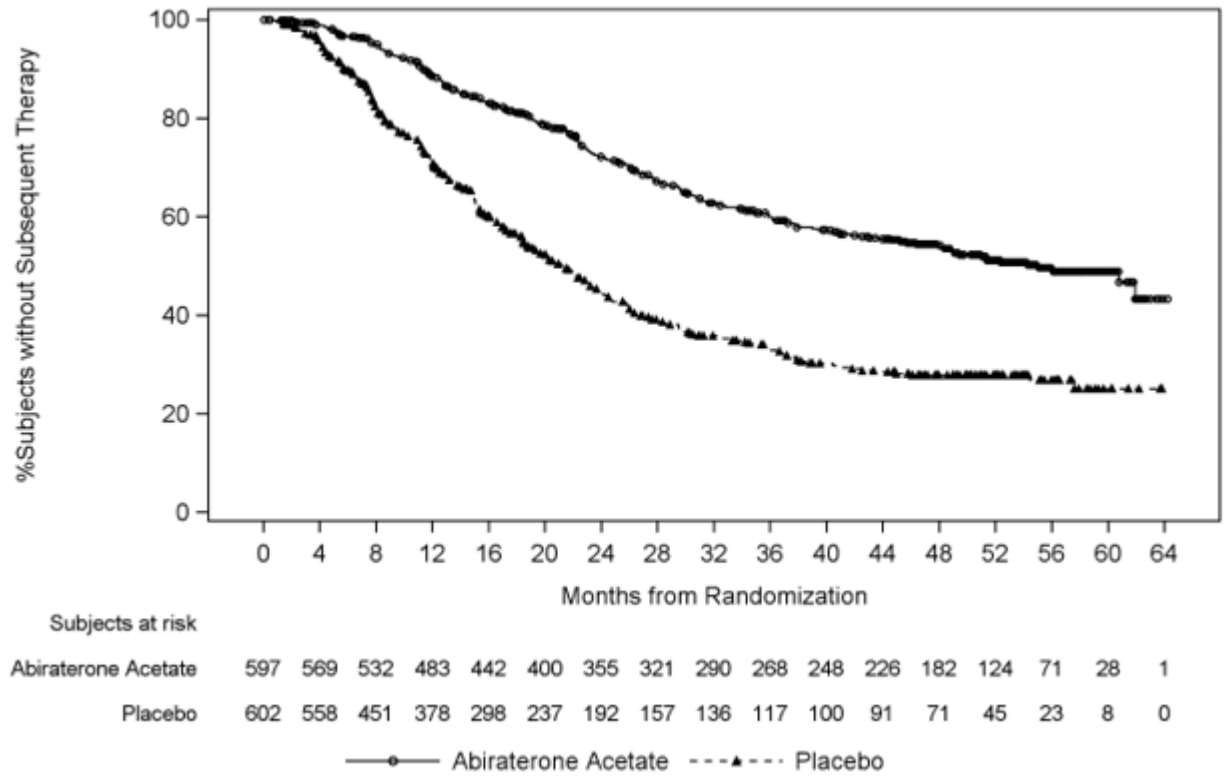
0.53; p<0.0001)[44], demonstrating that AAP + ADT delayed the need for initiation of subsequent therapy by nearly 3 years (33.7 months).[29] The 60-month event-free rate (i.e. percentage of patients for whom any subsequent prostate cancer therapy was not required at 5 years after initiation of study treatment) was [redacted]% for AAP + ADT vs [redacted]% for ADT alone.[29]

Figure 28: Kaplan–Meier plot of time to subsequent prostate cancer therapy [LATITUDE, ITT population, final analysis]



Key: ITT, intention-to-treat.
Source: LATITUDE final clinical study report, 2018.[29]

A summary of subsequent therapy received is presented in Table 26. A total of [redacted]% of AAP + ADT patients and [redacted]% of ADT alone patients received subsequent therapy for prostate cancer.[29] The most common subsequent therapy was docetaxel, received by [redacted]% of patients in the AAP + ADT arm and [redacted]% of patients in the ADT alone arm.

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Table 26: Subsequent therapy for prostate cancer [LATITUDE, ITT population, final analysis]

	AAP + ADT (n=597)	ADT alone (n=602)
Received subsequent therapy, n (%)	[redacted]	[redacted]
Received subsequent systemic therapy, n (%)	[redacted]	[redacted]
Antineoplastic agents	[redacted]	[redacted]
Docetaxel	144 (24.1)	212 (35.2)
Cabazitaxel	25 (4.2)	50 (8.3)
Endocrine therapy	[redacted]	[redacted]
Bicalutamide	[redacted]	[redacted]
Enzalutamide	57 (9.5)	99 (16.4)
Corticosteroids for systemic use	[redacted]	[redacted]
Subsequent surgery/procedures, n (%)	[redacted]	[redacted]
Radiotherapy (to bone)	[redacted]	[redacted]
Radiotherapy (other than bone)	[redacted]	[redacted]
Surgery (to bone)	[redacted]	[redacted]
Surgery (other than bone)	[redacted]	[redacted]

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; ITT, intention-to-treat.
Source: LATITUDE final clinical study report, 2018.[29]

Time to life extending subsequent therapy for prostate cancer

As shown in Figure 29, the median time to life-extending subsequent therapy was [redacted] in the AAP + ADT group but was [redacted] months in the ADT alone group, demonstrating that AAP + ADT delayed the need for initiation of life-extending subsequent therapy (HR=[redacted]; 95% CI: [redacted]; p[redacted]).[29]

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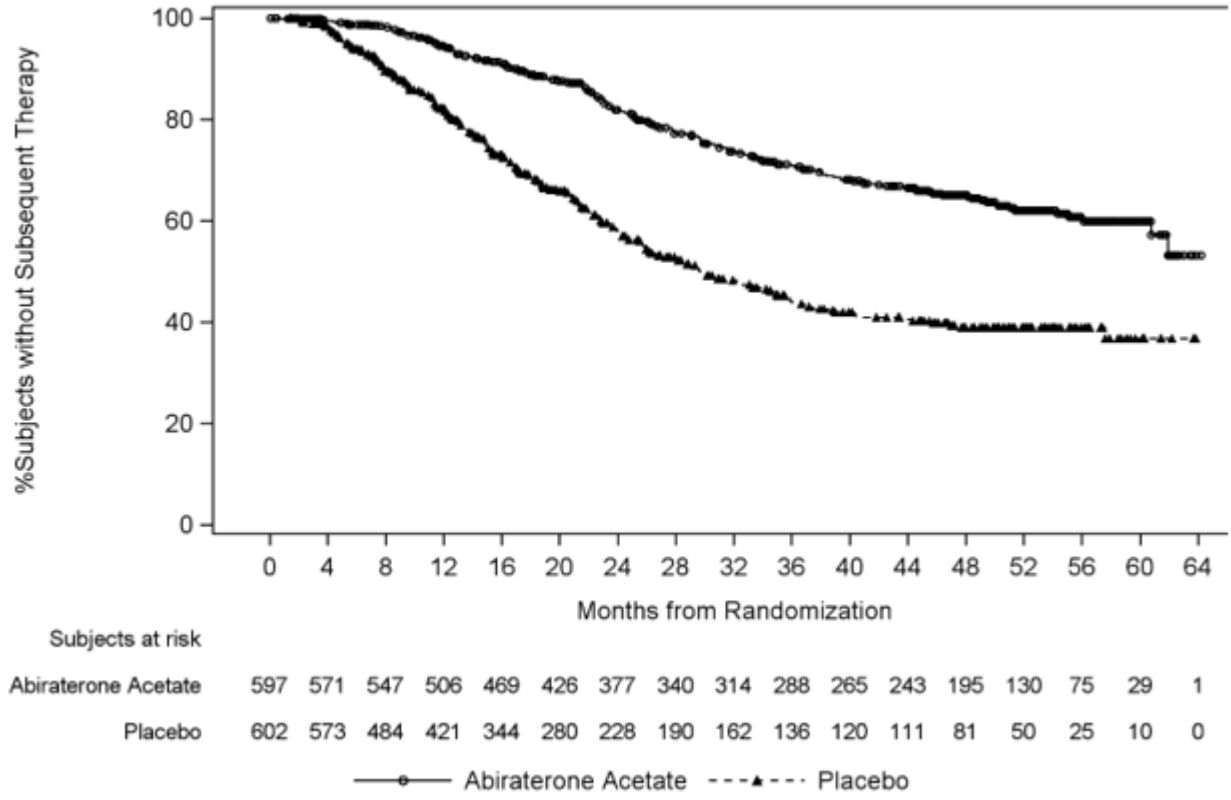
Figure 29: Kaplan–Meier plot of time to life-extending subsequent prostate cancer therapy [LATITUDE, ITT population, final analysis]



Key: ITT, intention-to-treat.
Source: LATITUDE final clinical study report, 2018.[29]

Table 27 provides an updated summary of life-extending subsequent therapy for prostate cancer. Life-extending therapy was reported for [redacted]% of patients in the AAP + ADT group compared with [redacted] % of patients in the ADT alone group.[29] The most frequently used life-extending therapy was docetaxel ([redacted] % AAP + ADT and [redacted] % ADT alone), followed by enzalutamide ([redacted]% and [redacted]%, respectively) and AAP ([redacted]% and [redacted]%, respectively).

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Table 27: Life-extending subsequent therapy [LATITUDE, ITT population, final analysis]

	AAP + ADT (n=597)	ADT alone (n=602)
Received life-extending subsequent therapy, n (%)	176 (29.5)	273 (45.3)
Docetaxel	144 (24.1)	212 (35.2)
Enzalutamide	57 (9.5)	99 (16.4)
AAP	18 (3.0)	84 (14.0)
Cabazitaxel	25 (4.2)	50 (8.3)
Radium-223	27 (4.5)	44 (7.3)

Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; ITT, intention-to-treat.
Source: Fizazi et al. 2019[44].

Time to initiation of chemotherapy

As shown in Figure 30, the median time to initiation of chemotherapy was not reached in the AAP + ADT group but was 57.6 months in the ADT alone group, demonstrating that treatment with AAP + ADT significantly delayed the time until patients required chemotherapy (HR=0.51; 95% CI: 0.41–0.63; p<0.0001).[44] This translated to a 49% reduction in the risk of initiation of chemotherapy. This is of utmost importance to men in England who are not willing to undertake the course of cytotoxic chemotherapy too early in their treatment pathway.

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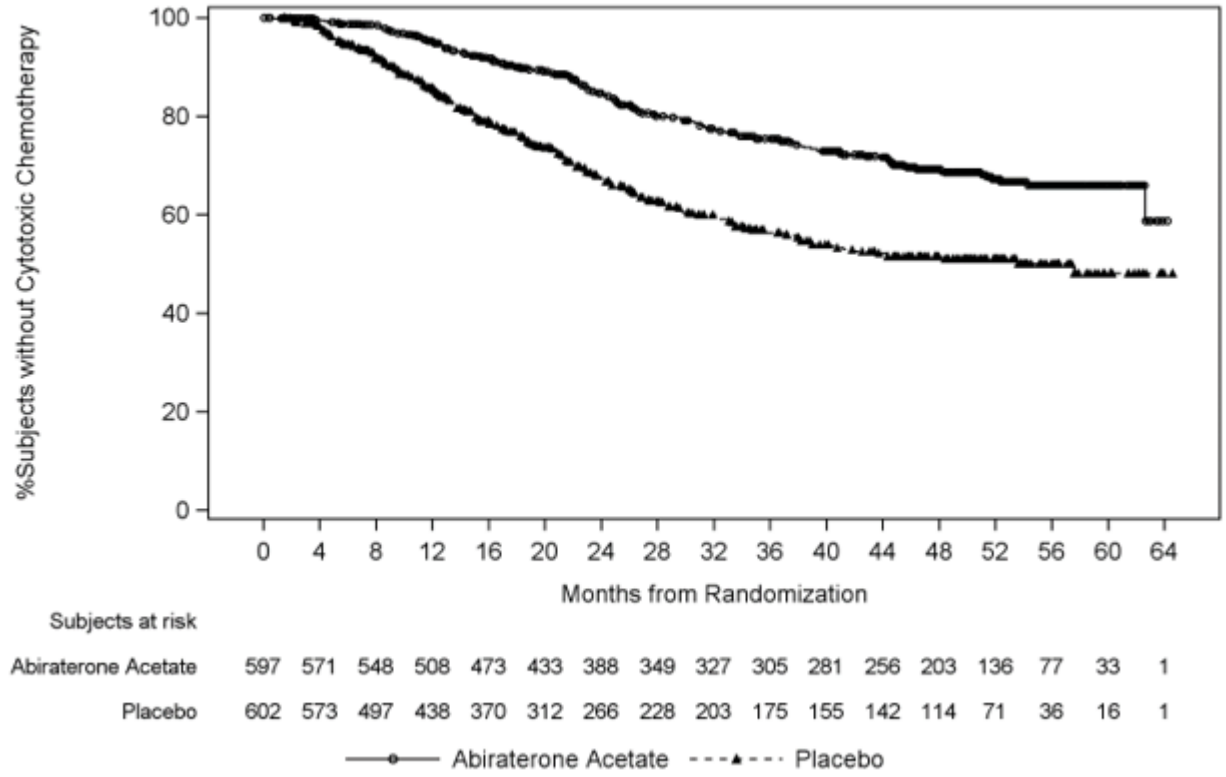
Figure 30: Kaplan–Meier plot of time to initiation of chemotherapy [LATITUDE, ITT population, final analysis]



Key: ITT, intention-to-treat.
Source: LATITUDE final clinical study report, 2018.[29]

Time to PSA progression

Time to prostate specific antigen (PSA) progression was assessed according to Prostate Cancer Working Group 2 (PCWG2) criteria. Based on these criteria, progression was defined as a 25% increase in PSA from baseline, along with an increase in absolute value of 2ng/mL or more, after 12 weeks of treatment.[45]

Results showed treatment with AAP + ADT significantly delayed PSA progression by [redacted] months (p<0.0001) compared to ADT alone.[29] As shown in Figure 31, the median time to PSA progression was [redacted] months in the AAP + ADT arm compared to [redacted] months in the ADT alone arm (HR=[redacted]; 95% CI: [redacted]; p[redacted]).

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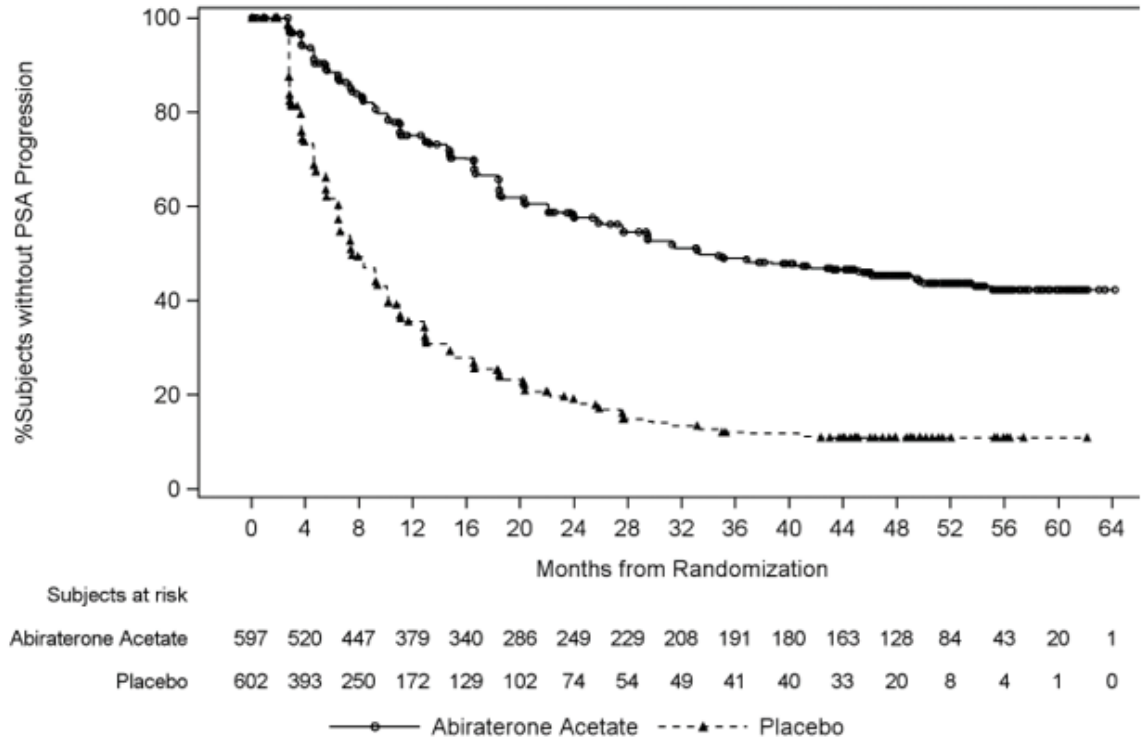
Figure 31: Kaplan–Meier plot of time to PSA progression [LATITUDE, ITT population, final analysis]



Key: ITT, intention-to-treat; PSA, prostate-specific antigen.
Source: LATITUDE final clinical study report, 2018[29]

Time to next skeletal-related event

As shown in Figure 32, treatment with AAP + ADT significantly reduced the risk of SREs by 24% (HR=0.76; 95% CI: 0.60–0.96; p=0.0208), although the median time to SRE was not reached in either arm.[44]

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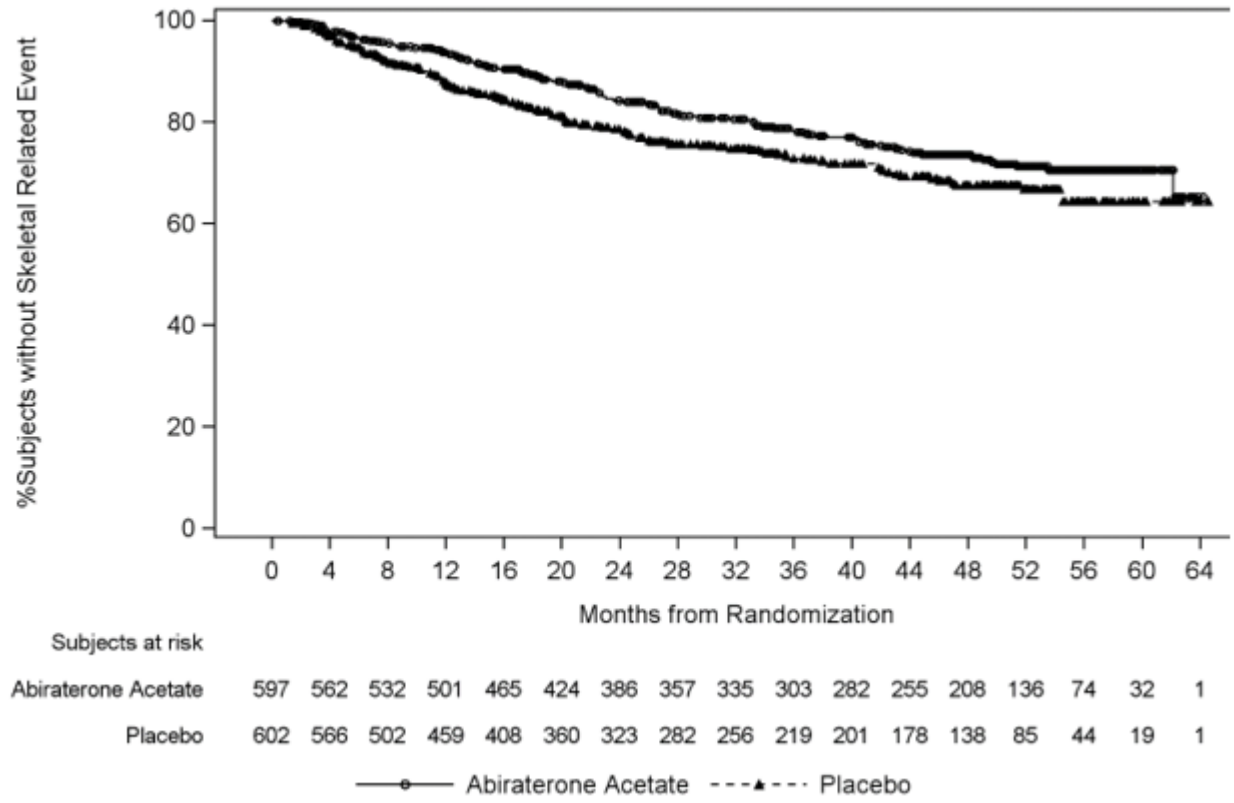
Figure 32: Kaplan–Meier plot of time to next SRE [LATITUDE, ITT population, final analysis]



Key: ITT, intention-to-treat; SRE, skeletal-related event.
Source: LATITUDE final clinical study report, 2018.[29]

Prostate cancer-specific survival

At the time of IA1, deaths due to prostate cancer occurred [redacted] in the AAP + ADT group than in the ADT alone group ([redacted]% vs [redacted]%, respectively). This resulted in a [redacted] in prostate cancer-specific survival for the AAP + ADT group compared to the ADT alone group (HR=[redacted]; 95% CI: [redacted]; p<[redacted])[43], meaning men with newly diagnosed high-risk mHSPC were less likely to die from their prostate cancer compared with those treated with ADT alone.

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Appendix D. STAMPEDE: *post-hoc* high-risk mHSPC subgroup analyses

Baseline Characteristics

Table 28: Baseline Characteristics of STAMPEDE high-risk mHSPC subgroup

	High-risk mHSPC (n=473)		
	ADT (n=232)	ADT+AAP (n=241)	p-value
Age at randomization			
Median (Range)	67 (39-84)	67 (42-85)	0.75
PSA prior to ADT			
Median (Range)	174 (3.3-8028)	126 (3.6-21460)	0.28
WHO performance status			
0	163	177	0.44
01-Feb	69	64	
Gleason Sum			
<=7	3	2	0.62
08-Oct	229	239	
Primary Tumour stage			
£T2	23	21	0.32
T3	116	141	
T4	68	59	
TX	25	20	
Regional node status			
N0	78	84	0.36
N+	137	131	
NX	17	26	
Primary or Progression			
M+, new	229	238	0.96
Previously treated	3	3	
Metastatic Site			
Node	-	-	0.77
Bone	154	169	
Visceral	1	-	
Bone + Node	60	52	
Bone + Visceral	9	12	
Visceral + Node	1	1	
Bone + Node + Visceral	7	7	

Key: AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate specific antigen; WHO, World Health Organisation

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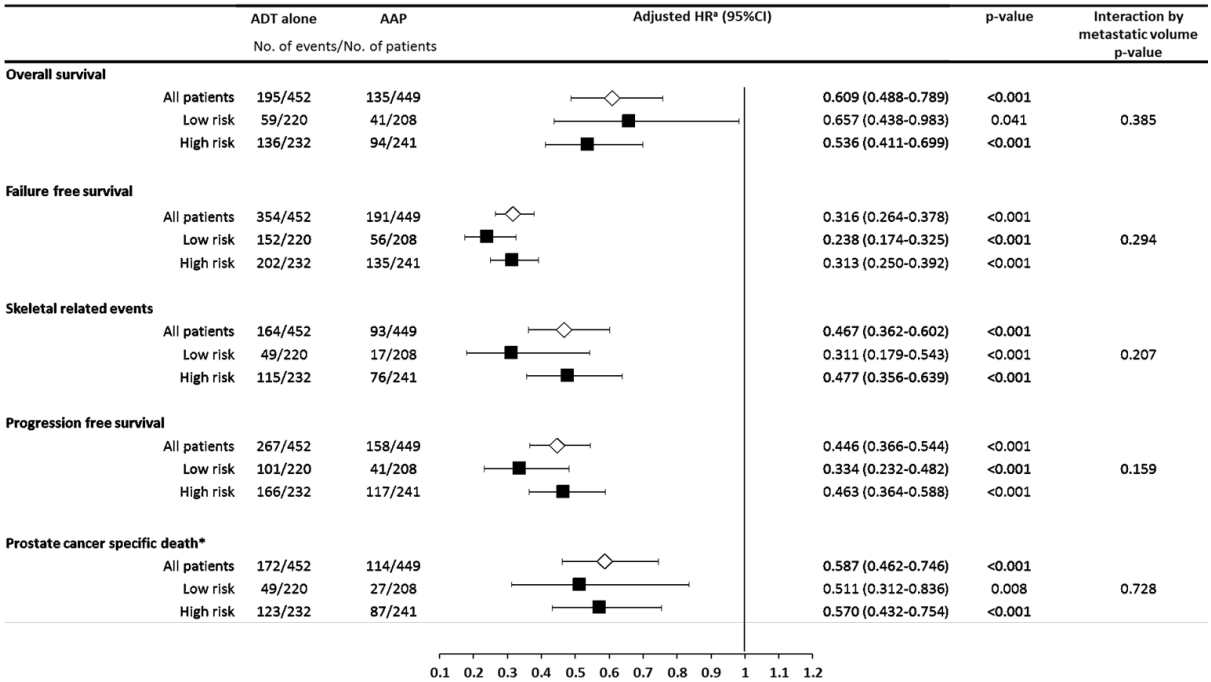
Source: Hoyle et al. (2018)[5]

Figure 33: Secondary endpoints for STAMPEDE high-risk mHSPC subgroup



Key: AAP, Abiraterone acetate (AA) plus prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer.
Source: Hoyle et al. (2018)[5]

Appendix E. Subsequent treatment durations

In the base case, the modelled time spent in 1L, 2L and 3L mCRPC were estimated by re-weighting mean health state durations derived from TA387.[2] Constant transition probabilities were estimated by applying an exponential distribution to the mean time in state values for each treatment arm. This approach involved taking the sum of the durations from 1L, 1L-off treatment and 2L mCRPC from TA387, dividing this figure by the predicted mean time spent in the post-progression survival health state in the model to adjust for any population differences between patients in LATITUDE and those modelled in the TA387 submission. This value was then used to adjust each health state durations using the following formula:

$$1L\ mCRPC\ duration = 1L\ mCRPC\ duration\ (TA387) * \frac{1L + 1L\ off\ treatment + 2L\ mCRPC\ durations\ (TA387)}{Mean\ post\ progression\ survival\ \ (model)}$$

There are, however, three limitations with this method:

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- The calculation does not account for the fact a proportion of patients will have died prior to disease progression, which may result in an underestimation of the mean post-progression survival time applied in the formulae.
- The calculation uses mean health state durations from the comparator arm from the TA387 submission rather than the intervention arm which may underestimate the time patients spend in the 1L mCRPC health state.
- The sum of the 1L, 1L off-treatment and 2L mCRPC health states from TA387 does not capture the full time spent in mCRPC as the TA387 model included additional health states that are not accounted for in this model.

As such, scenario analyses have been presented which address these limitations. The alternative formulae utilise total life years from TA387, instead of the sum of the 1L, 1L-off treatment and 2L mCRPC health states, to capture the full post-progression survival time from TA387. It also adjusts the health state durations to account for the fact that a proportion of patients will die prior to disease progression. These proportions cannot be estimated within the PartSA framework because the relationship between progression status and death is not modelled explicitly. As such, estimates must be taken from the extrapolations of the previously submitted model. A summary of the parameters utilised in these scenarios are presented in Table 29. Two scenarios are presented: one utilising the health state durations from the best supportive care arm from TA387 and the other using the estimates from the AAP arm.

Table 29: Parameters to inform time in mCRPC health states

Health state	Base-case	Scenario analyses	
		Comparator arm scenario	Intervention arm scenario
% deaths pre-progression	0%	AAP + ADT: 41% ADT alone: 33% Docetaxel + ADT: 37%	AAP + ADT: 41% ADT alone: 33% Docetaxel + ADT: 37%
mCRPC LYs	2.62	2.94	3.71
1L mCRPC	1.1	1.1	1.97
1L off-trt	0.61	0.61	0.68
2L mCRPC	0.91	0.91	0.76

Key: 1/2L, 1st, 2nd line; AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; LYs, life years; mCRPC, metastatic castrate resistant prostate cancer; trt, treatment

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A summary of the adjusted mean health state durations applied in each scenario of the model are summarised in Table 30. These results indicate that the base case analysis likely underestimates the time patients spend in the 1L mCRPC state and thereby underestimates subsequent therapy costs for the comparator therapies. The results of these scenarios are presented in Table 16.

Table 30: Mean health state durations (years)

Scenario	Treatment	Health state		
		1L mCRPC	1L off-trt	2L mCRPC
Base-case	AAP + ADT	0.76	0.42	0.63
	ADT alone	1.20	0.66	0.99
	Docetaxel + ADT	0.96	0.53	0.79
BSC scenario	AAP + ADT	1.15	0.64	0.95
	ADT alone	1.61	0.89	1.33
	Docetaxel + ADT	1.35	0.75	1.12
AAP scenario	AAP + ADT	1.64	0.56	0.63
	ADT alone	2.28	0.79	0.88
	Docetaxel + ADT	1.92	0.66	0.74

Key: 1/2L, 1st, 2nd line; AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; BSC, best supportive care; mCRPC, metastatic castrate resistant prostate cancer

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Appendix F: Results at List-Price [CONFIDENTIAL]

Table 31: Results for AAP + ADT vs ADT alone in a chemo-ineligible cohort [List Price]

Extrapolation	Weibull		Log-logistic	
Technologies	**ADT alone**	**AAP + ADT**	**ADT alone**	**AAP + ADT**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total LYG	4.85	7.01	3.82	5.38
Total QALYs	2.62	3.99	2.24	3.25
Incremental costs	[redacted]		[redacted]	
Incremental LYG	2.16		1.56	
Incremental QALYs	1.37		1.01	
ICER	£98,704		£100,323	

Key: AAP, Abiraterone acetate (AA) plus prednisolone; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 32: Results for AAP + ADT vs docetaxel + ADT in a chemo-eligible cohort [List Price]

Extrapolation	Weibull		Log-logistic	
Technologies	**Docetaxel + ADT**	**AAP + ADT**	**Docetaxel + ADT**	**AAP + ADT**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total LYG	6.49	7.01	5.07	5.38
Total QALYs	3.38	3.99	2.85	3.25
Incremental costs	[redacted]		[redacted]	
Incremental LYG	0.52		0.32	
Incremental QALYs	0.61		0.41	
ICER	£210,643		£234,443	

Key: AAP, Abiraterone acetate (AA) plus prednisolone; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

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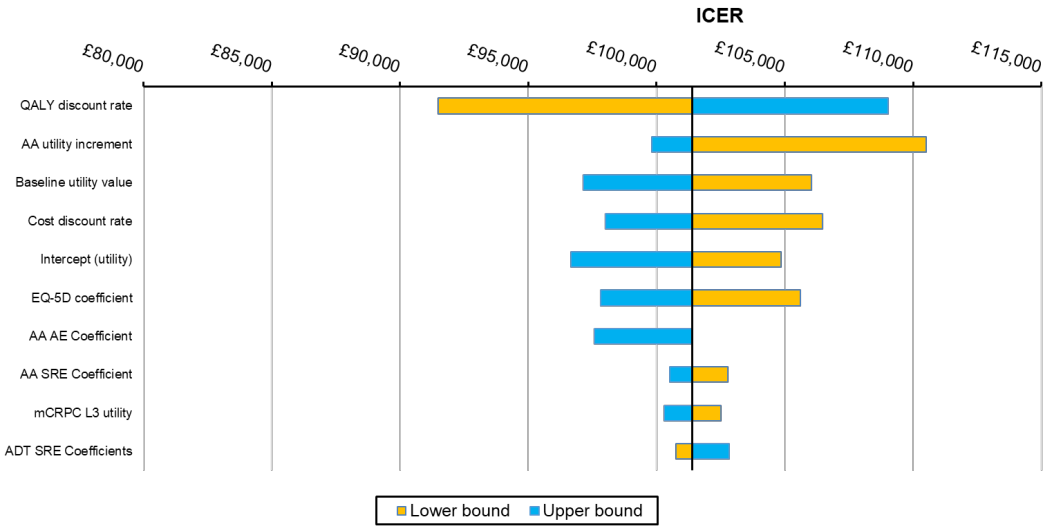
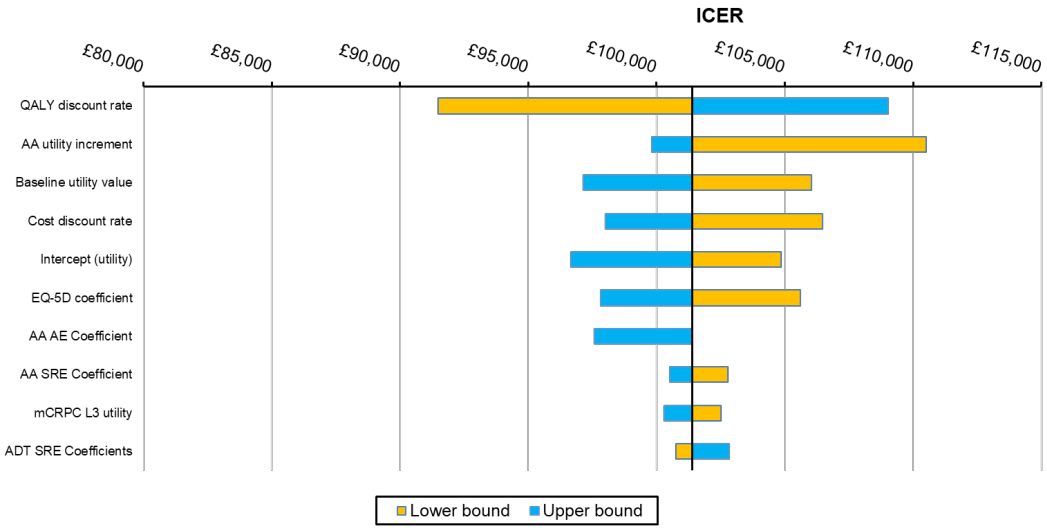
Figure 34: Tornado diagram for AAP + ADT in the chemo-ineligible cohort [List Price and Weibull extrapolation]



Key: AA, Abiraterone acetate; AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; AE, adverse event; ICER, incremental cost-effectiveness ratio; L3, third-line; mCRPC, metastatic castrate resistant prostate cancer; QALY, quality adjusted life year; SRE, skeletal related event.

Figure 35: Tornado diagram for AAP + ADT versus docetaxel + ADT in the chemo-eligible cohort [List Price and Weibull extrapolation]



Key: AA, Abiraterone acetate; AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; AE, adverse event; ICER, incremental cost-effectiveness ratio; L3, third-line; mCRPC, metastatic castrate resistant prostate cancer; QALY, quality adjusted life year; SRE, skeletal related event.

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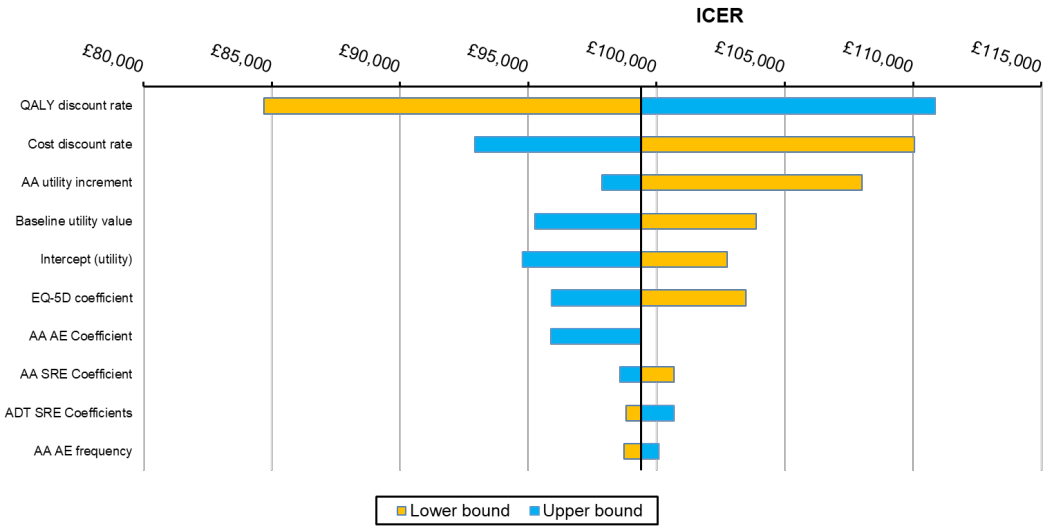
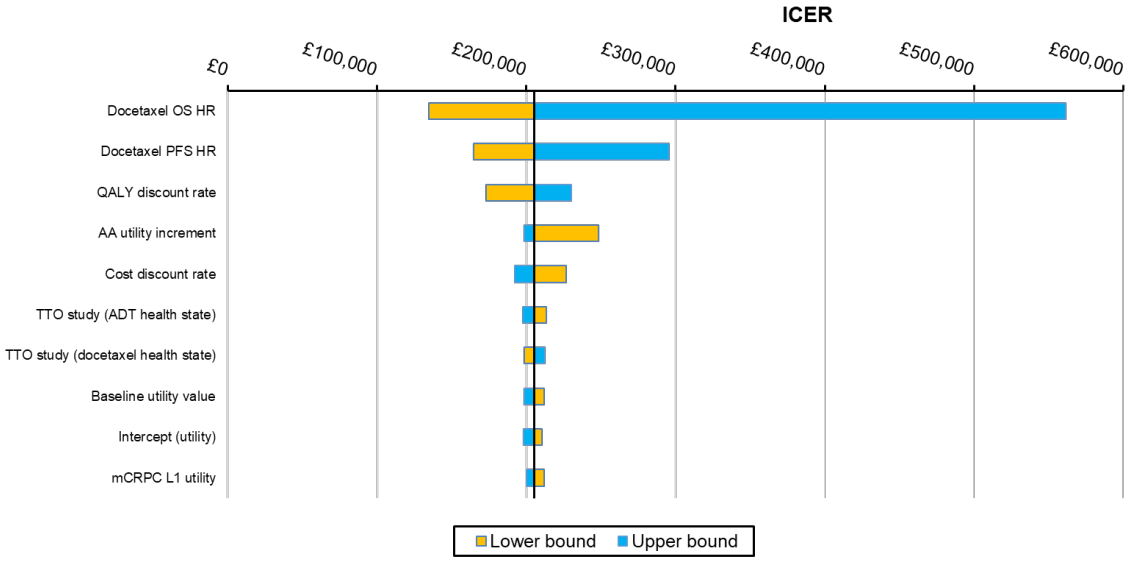
Figure 36: Tornado diagram for AAP + ADT in the chemo-ineligible cohort [List Price and log-logistic extrapolation]



Key: AA, Abiraterone acetate; AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; AE, adverse event; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SRE, skeletal related event.

Figure 37: Tornado diagram for AAP + ADT versus docetaxel + ADT in the chemo-eligible cohort [List Price and log-logistic extrapolation]



Key: AA, Abiraterone acetate; AAP, Abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; L1, first line; mCRPC, metastatic castrate resistant prostate cancer; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; TTO, time trade off.

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Table 33: Scenario analyses [List Price]

Model assumption	Scenario	ICER vs ADT alone	ICER vs dox + ADT	ICER vs ADT alone	ICER vs dox + ADT
Base case		**Loglogistic**		**Weibull**	
		£99,395	£205,185	£101,398	£231,678
Time horizon	20 years	£102,166	£215,864	£101,688	£232,428
	10 years	£120,231	£266,960	£111,763	£252,931
	5 years	£168,494	£366,439	£164,034	£341,462
AAP utility increment	Applied until death	£95,294	£187,588	£95,738	£202,508
	No increment applied	£98,902	£202,980	£100,878	£228,802
AE disutilities	Using literature values	£96,230	£199,594	£98,214	£224,229
mCRPC utilities	Assumed constant through mCRPC	£98,660	£241,388	£95,937	£259,737
Vial wastage	Set to zero	£99,143	£205,666	£100,839	£232,156
No OS benefit	AAP + ADT v docetaxel + ADT OS HR=1; PFS HR=0.69	£99,395	£272,523	£101,398	£317,396
NMA at IA1	AAP + ADT v docetaxel + ADT OS HR=0.88; PFS HR=0.72	£99,395	£179,457	£101,398	£200,879
Survival extrapolation for rPFS	Unstratified	£100,422	£198,892	£100,659	£230,618
	Log-normal (stratified)	£99,140	£210,442	£109,345	£251,789
	Gamma (stratified)	£99,670	£202,894	£110,838	£237,904
	Gompertz (stratified)	£83,315	£193,336	£99,644	£231,089
	Exponential (stratified)	£94,413	£203,990	£109,503	£235,922
Survival extrapolation for OS	Unstratified	£111,550	£209,610	£105,737	£235,576
	Log-normal (stratified)	£86,427	£198,222	£72,141	£183,160
	Gamma (stratified)	£129,791	£239,824	£118,038	£228,216
	Gompertz (stratified)	£121,968	£266,141	£116,573	£255,638
	Exponential (stratified)	£100,232	£211,925	£87,891	£199,450
G-CSF cost	Exclude	£99,382	£205,575	£101,359	£232,213
mCRPC health state durations	Apply BSC durations from TA387	£98,502	£207,675	£99,282	£230,817
	Apply AA durations from TA387	£97,148	£206,843	£97,118	£228,302

Key: AAP, abiraterone acetate with prednisone; ADT, androgen deprivation therapy; AE, adverse event; CAA, commercial access arrangement; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; IA1, first interim analysis; mCRPC, metastatic castrate-resistant prostate cancer; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

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Table 34: PSA results for AAP + ADT in the chemo-ineligible patient cohort [List Price]

Extrapolation	Loglogistic		Weibull	
Technologies	**ADT alone**	**AAP + ADT**	**ADT alone**	**AAP + ADT**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total LYG	4.85	7.01	3.82	5.38
Total QALYs	2.62	3.99	2.24	3.25
Incremental costs	[redacted]		[redacted]	
Incremental LYG	2.16		1.56	
Incremental QALYs	1.37		1.01	
ICER	£98,704		£100,323	

Key: AAP, Abiraterone acetate (AA) plus prednisolone; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 35: PSA results for AAP + ADT in the chemo-eligible patient cohort [List Price]

Extrapolation	Loglogistic		Weibull	
Technologies	**Docetaxel + ADT**	**AAP + ADT**	**Docetaxel + ADT**	**AAP + ADT**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total LYG	6.49	7.01	5.07	5.38
Total QALYs	3.38	3.99	2.85	3.25
Incremental costs	[redacted]		[redacted]	
Incremental LYG	0.52		0.32	
Incremental QALYs	0.61		0.41	
ICER	£210,643		£234,443	

Key: AAP, Abiraterone acetate (AA) plus prednisolone; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

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Figure 38: PSA scatter plots for AAP + ADT in the chemo-ineligible cohort [List Price]

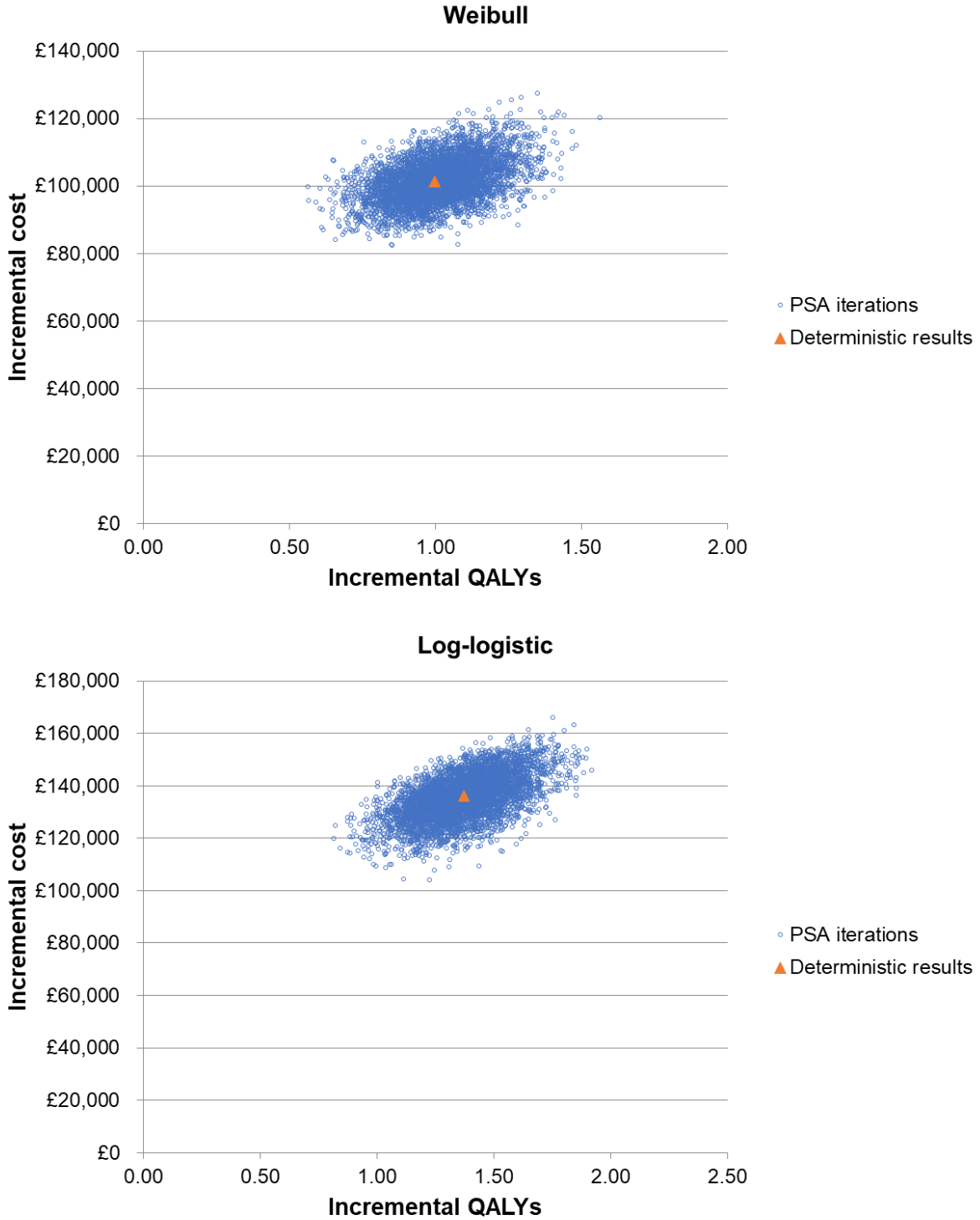

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Figure 39: PSA scatter plots for AAP + ADT in the chemo-eligible cohort [List Price]

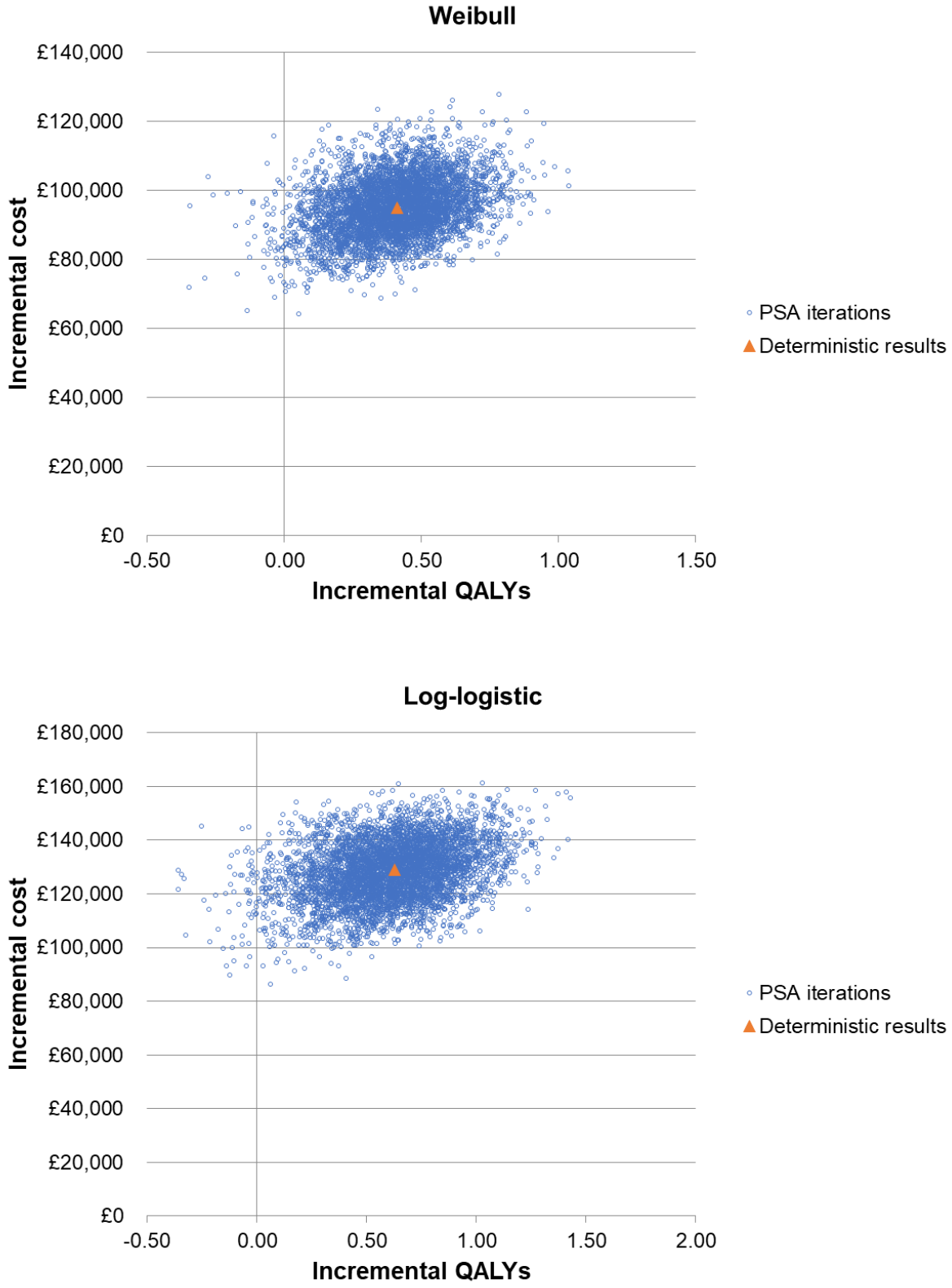

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Figure 40: Cost-effectiveness acceptability curves for AAP + ADT vs ADT alone [list price]

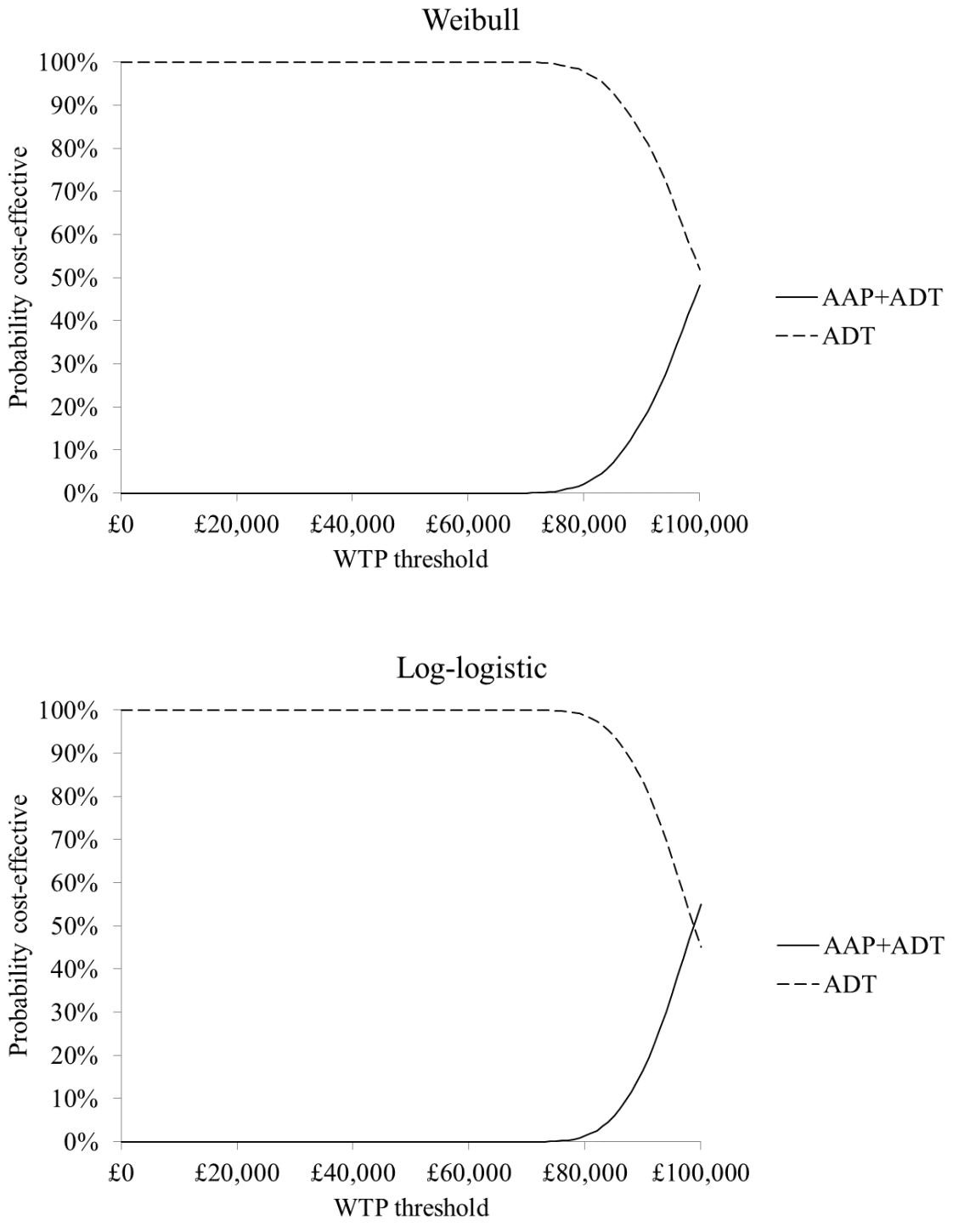

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Figure 41: Cost-effectiveness acceptability curves for AAP + ADT vs docetaxel + ADT [list price]

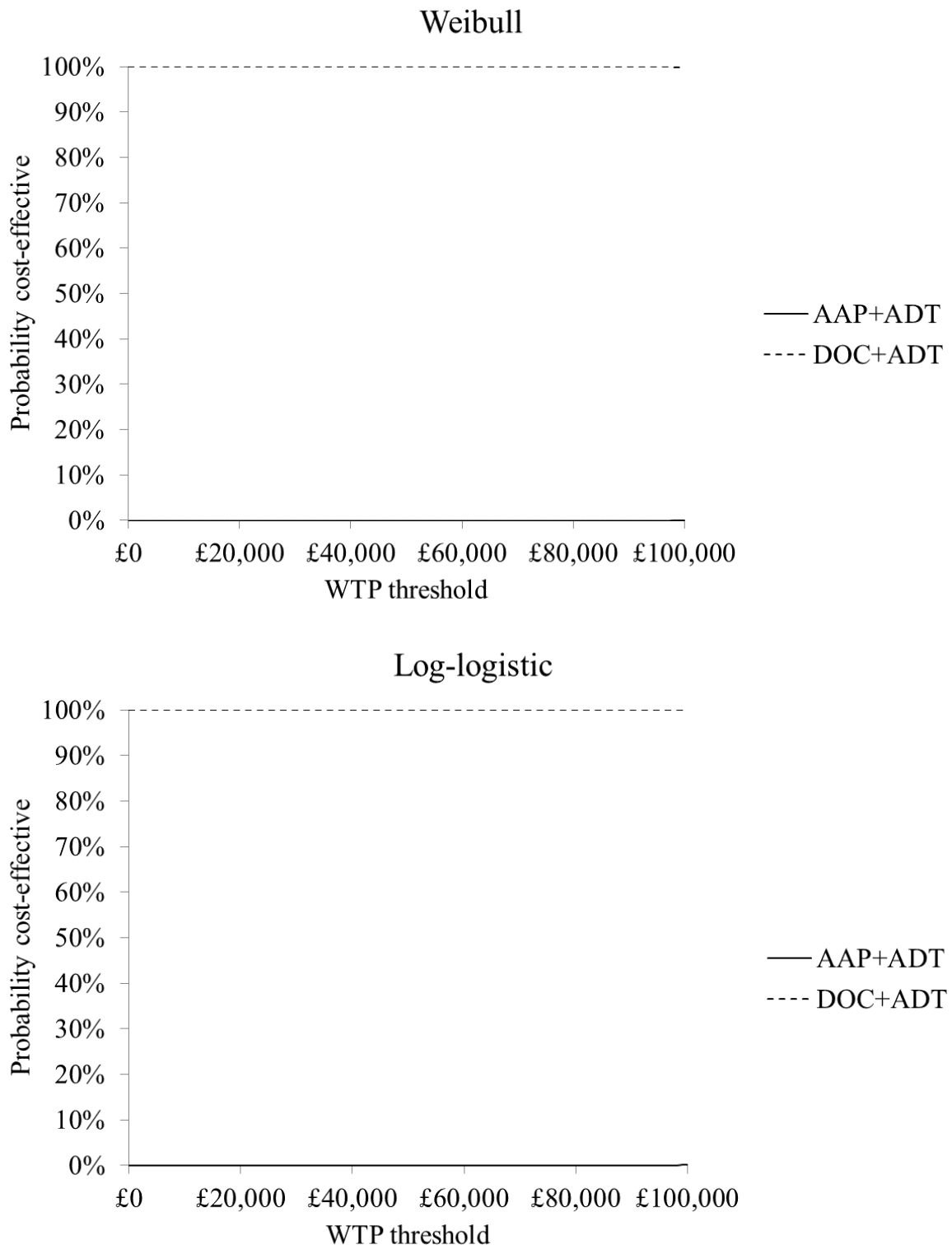

Table 36: Probability of cost-effectiveness [list price]

Base-case setting	Comparator	WTP threshold

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		£20,000	£30,000	£50,000
Weibull	Vs ADT alone	0%	0%	0%
	Vs docetaxel + ADT	0%	0%	0%
Log-logistic	Vs ADT alone	0%	0%	0%
	Vs docetaxel + ADT	0%	0%	0%

Key: ADT, androgen deprivation therapy; WTP, willingness to pay

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Appendix A:

Updated Network Meta-Analysis (NMA) following the release of new *post-hoc* STAMPEDE analysis of docetaxel + ADT vs ADT alone within the subgroup of patients with high-burden hormone-sensitive metastatic prostate cancer.

Janssen welcome that the ERG have stated within their review:

"Overall, whilst there are substantial uncertainties regarding comparison with docetaxel + ADT, the ERG has a preference towards the company's base case approach of using the hazard ratios from the NMA over sole reliance on the limited direct head-to-head data from STAMPEDE." [page 6]

In concordance with this, following Janssen's re-submission to NICE in July 2019, *post-hoc* subgroup analysis for the clinical effectiveness of docetaxel + ADT in patients with high-burden (which is similar to high-risk) disease was published by STAMPEDE in Clarke et al. (2019).[1] These data are more relevant to the decision problem, and thus more useful in deriving the comparative effectiveness of AAP + ADT vs docetaxel + ADT, than data previously included from James et al. (2016)[2], which only presented evidence in all metastatic patients. Additionally, Clarke et al. (2019) now provides a longer median duration of follow-up (78.2 months)[1] than James et al. (2015) did previously (43.0 months).[2]

As such, Janssen have conducted subsequent updates to the NMA for OS and PFS, which are represented in Table 2 and Table 3 herein. These updated analyses show AAP + ADT has an even greater probability of being superior to docetaxel + ADT at both delaying disease progression (HR=[redacted], prob HR < 1 = [redacted]%) and extending survival (HR=[redacted], prob HR < 1 = [redacted]%), compared to that previously presented.

Furthermore, the incorporation of this new evidence means that all relevant data from *post-hoc* STAMPEDE analyses within high-risk (or similarly high-burden) have now been included via Hoyle et al. (2019)[3] and Clarke et al. (2019).[1] Given the nature of STAMPEDE, we note that the head-to-head data in Sydes et al. (2018)[4] are not mutually exclusive to these other STAMPEDE data included within the network. As such, this analysis may now be extraneous to the decision problem and an additional sensitivity analysis has been conducted to remove any occurrence of 'double-counting' of data within the NMA. The result of this sensitivity analysis has also been presented in Table 2 and Table 3 and it also shows an improvement in the probability of AAP + ADT being superior to docetaxel + ADT at delaying disease progression (prob HR < 1 = [redacted]%) and extending survival (prob HR < 1 = [redacted]%).

The subsequent impact of incorporating these updated NMA results into the model have been presented alongside the base case in Table 1 and demonstrate further improvements in the ICER, in favour of the cost effectiveness of AAP + ADT vs docetaxel + ADT. Importantly, both updated ICERs are below £30,000/QALY.

Table 1: Impact of updated NMA results on the ICER vs docetaxel + ADT

Scenario	Inputs	ICER vs D+ADT
Base Case	OS HR = [redacted] PFS HR = [redacted]	[redacted]
Updated 1 inc. Sydes et al. (2018)	OS HR = [redacted] PFS HR = [redacted]	[redacted]
Updated 2 exc. Sydes et al. (2018)	OS HR = [redacted] PFS HR = [redacted]	[redacted]
Key: ADT, androgen deprivation therapy; D, docetaxel; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival, PFS, progression-free survival		

Table 2: Updated OS NMA with Clarke et al. (2019)

	Direct evidence, HR [95% CI]						NMA results	
	AAP+ADT vs ADT		D+ADT vs ADT			AAP+ADT vs D+ADT	AAP+ADT vs D+ADT	
Population	**NDx HR**	**M1 HR**	**NDx HVD**	**NDx HVD**	**M1**	**M1**	**HR [95% CrI]**	**Probability HR<1**
Submitted (July'19) OS NMA w. LATITUDE FA -	0.66 [0.57; 0.78]	0.54 [0.41, 0.70]	0.63 [0.49, 0.81]	0.78 [0.54, 1.12]	0.76 [0.62, 0.92]	1.13 [0.77, 1.66]	[redacted]	[redacted]
Population	**NDx HR**	**M1 HR**	**NDx HVD**	**NDx HVD**	**M1 HBD**	**M1**	**HR [95% CrI]**	**Probability HR<1**
Updated[1] (Nov'19) OS NMA w. LATITUDE FA	0.66 [0.57; 0.78]	0.54 [0.41, 0.70]	0.63 [0.49, 0.81]	0.78 [0.54, 1.12]	0.81 [0.64-1.02]	1.13 [0.77, 1.66]	[redacted]	[redacted]
Updated[2] (Nov'19) OS NMA w. LATITUDE FA	0.66 [0.57; 0.78]	0.54 [0.41, 0.70]	0.63 [0.49, 0.81]	0.78 [0.54, 1.12]	0.81 [0.64-1.02]		[redacted]	[redacted]
Updated[1] – including the OS HR from Sydes et al. (2018) Updated[2] – excluding the OS HR from Sydes et al. (2018)								
Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; CrI, credible interval; D, docetaxel; FA, final analysis; HR, hazard ratio; HBD, high-burden disease; HRD, high-risk disease; HVD, high-volume disease; M1, metastatic; NDx, newly diagnosed; NMA, network meta-analysis; OS, overall survival.								

Table 3: Updated PFS NMA with Clarke et al. (2019)

	Direct evidence, HR [95% CI]						NMA results	
	AAP+ADT vs ADT		D+ADT vs ADT			AAP+ADT vs D+ADT	AAP+ADT vs D+ADT	
Trial	**LATITUDE (IA1)**	**STAMPEDE**	**CHAARTED**	**GETUG-AFU 15**	**STAMPEDE**	**STAMPEDE**	**HR [95% CrI]**	**Probability HR<1**
Population	**NDx HRD**	**HRD**	**NDx HVD**	**NDx HVD**	**M1 HBD**	**M1**		
Submitted (July'19) PFS NMA	0.47 [0.39, 0.55]	0.46 [0.36, 0.59]	NR	0.61 [0.44, 0.83]	NR	0.69 [0.50, 0.95]	[redacted]	[redacted]
Updated[1] (Nov'19) PFS NMA	0.47 [0.39, 0.55]	0.46 [0.36, 0.59]	NR	0.61 [0.44, 0.83]	0.68 [0.54, 0.85]	0.69 [0.50, 0.95]	[redacted]	[redacted]
Updated[2] (Nov'19) PFS NMA	0.47 [0.39, 0.55]	0.46 [0.36, 0.59]	NR	0.61 [0.44, 0.83]	0.68 [0.54, 0.85]		[redacted]	[redacted]
Updated[1] – including the OS HR from Sydes et al. (2018) Updated[2] – excluding the OS HR from Sydes et al. (2018)								
Key: AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; CrI, credible interval; D, docetaxel; HR, hazard ratio; HBD, high-burden disease; HRD, high-risk disease; HVD, high-volume disease; M1, metastatic; NDx, newly diagnosed; NMA, network meta-analysis; PFS, progression-free survival.								

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

ADDENDUM to the ERG report

ERG's critique of the company's addendum submitted in July 2019

Produced by Aberdeen HTA Group

Date Completed 31 October 2019

Contains AIC/CIC

This report provides the ERG's commentary and critique of new evidence submitted by the company (Janssen) in July 2019 as documents:
"ID945_Abiraterone mHSPC_Final Analysis Addendum_ACIC 12072019 [ACIC].docx" and "[ID945] Abiraterone CE model_addendum [ACiC]_12072019 - JP 180719 [ACIC].xlsm".

The clinical evidence, revised model and results are discussed in following sections. This commentary should be read in conjunction with the company's addendum.

1. Clinical effectiveness

1.1 Summary of new clinical effectiveness evidence submitted by the company

The company present data from the pre-planned final analysis of the LATITUDE trial (Fizazi et al., 2019) and the published post-hoc analyses of STAMPEDE that specifically look at AAP + ADT vs ADT alone in the metastatic high-risk subgroup of prostate cancer patients (Hoyle et al., 2018). Although the enrolled population of STAMPEDE is broader than the licensed indication for ASP + ADT, the STAMPEDE subgroup is considered comparable to the LATITUDE population (patients with newly diagnosed high-risk mHSPC). The company refer the Committee's interest in attaining HRQOL data from STAMPEDE but note that these data remain unpublished at this time.

The LATITUDE final analysis cut-off date was 15th August 2018, which provides a median follow-up period of 51.8 months. The ITT and safety populations comprised 1199 patients: 597 AAP + ADT patients and 602 ADT alone patients. The company note that treatment crossover was permitted after the trial was unblinded at the first interim analysis. At time of final analysis, 72 patients (12%) in the ADT alone group had crossed over to receive open-label treatment with AAP + ADT. The company present comparative results of OS and other secondary endpoint results between the IA1, IA2 and final analyses in Appendix B of the company addendum.

Primary endpoint - overall survival

At the time of final analysis, the majority ([redacted]%) of patients in the LATITUDE AAP + ADT group were still alive, compared to [redacted] % of patients in the ADT alone group. The comparative OS data at IA1, IA2 and final analysis, presented in Table 21 and Figure 26 of the company addendum, show that the survival benefit of AAP + ADT versus ADT alone remained at 4 years. The hazard ratio at final analysis was 0.66 (95% CI: 0.56 - 0.78), compared to 0.64 (95% CI: 0.54 - 0.76) at IA2.

Subgroup analyses were consistent with the overall LATITUDE results, except for patients with an ECOG score of 2 (HR=1.42), for which eight additional deaths were reported; however, the company state that this was a small subgroup of 40 patients, thus precluding meaningful conclusions. The forest plot for the subgroup analyses is presented as Figure 3 in the company addendum.

The LATITUDE results are consistent with the most recent post-hoc analysis of OS data from the STAMPEDE trial subgroup of high-risk mHSPC patients. This analysis showed that AAP + ADT was also associated 46% reduction in the risk of death compared to ADT alone (HR=0.54 [0.41-0.70]; p<0.001) (Hoyle et al., 2015). This compares with a HR of 0.61 (0.49-0.75) previously reported for the STAMPEDE metastatic subgroup as a whole. The company state that 95% of the STAMPEDE high-risk mHSPC subgroup were newly diagnosed and are, therefore, comparable with the licensed indication for AAP + ADT. The company also highlight that a statistically significant result was obtained despite the analysis being underpowered to detect a between group difference in OS, indicating a large treatment effect. The Kaplan Meier data for OS in STAMPEDE are presented as Figure 4 in the company addendum.

Secondary endpoints

The company present a summary of the LATITUDE secondary endpoints at time of final analysis in Table 1 and Appendix C of their addendum. AAP + ADT was significantly superior to ADT alone for all secondary efficacy endpoints. Data for prostate cancer-specific survival at the time of IA1 show a [redacted] in prostate cancer-specific survival for the AAP + ADT group compared to the ADT alone group (HR=[redacted]; 95% CI: [redacted]; [redacted] (Janssen Research and Development). The company state this means that men with newly diagnosed high-risk mHSPC were less likely to die from their prostate cancer compared with those treated with ADT alone.

The company present secondary endpoint data for the STAMPEDE subgroup in Appendix D. AAP + ADT was favoured compared to ADT alone for all subgroups.

Exploratory endpoints

Progression-free survival following subsequent therapy

The company present the LATITUDE final analysis Kaplan Meier data for progression-free survival following subsequent therapy (PFS2) as Figure 5 in their addendum. Treatment with AAP + ADT statistically significantly extended PFS2 by 42% compared with ADT alone (HR=0.58 [95% CI:0.49-0.68]; p<0.0001).

Safety endpoints

Summaries of adverse reactions for the LATITUDE safety population are presented in Table 2 and Appendix B of the company's addendum. Patients treated with AAP + ADT had more drug-related TEAEs and grade 3-4 TAEs than patients treated with ADT, although a comparable number of drug-related deaths was observed (0.5% for both arms). The final analysis results are broadly similar to those from IA1.

1.2 ERG critique of new clinical effectiveness evidence submitted by the company

Overall, the final analysis results from the LATITUDE trial provide evidence of benefits of AAP + ADT compared with ADT alone for the treatment of patients with mHSPC in terms of OS, PFS and most secondary outcomes. Since the company argue that the direct evidence for AAP+ADT versus ADT alone should be used to inform decision making in those who are chemo-ineligible, such as those with poor ECOG performance status, it is somewhat problematic that LATITUDE will have recruited a relatively small number of patients that would be considered chemo-ineligible. For example, all patients in LATITUDE had ECOG performance status of 2 or below. There does not appear to be any published data to confirm the generalisability of the LATIDUE efficacy data to chemo-ineligible patients.

The recently published OS results for the high-risk mHSPC subgroup of the STAMPEDE trial also favour AAP + ADT compared with ADT alone, although it should be noted that the STAMPEDE analysis was conducted post hoc on a subgroup of the trial population. Similarly, all patients in STAMPEDE had WHO performance status of 2 or below, and so generalisability to a chemo-ineligible population may again be questionable.

2. Comparative effectiveness

2.1 Summary of revised comparative effectiveness analysis submitted by the company

The company updated their NMA to include the final analysis of OS data form LATITUDE, and the OS data for AAP+ADT versus ADT alone in the high-risk mHSPC subgroup of STAMPEDE. The company also include a new estimate from STAMPEDE for the effect of AAP+ADT versus ADT on rPFS in the high-risk subgroup (HR=0.46; 95% CI: 0.36 – 0.59). The revised network also retains the head-to-head data relating to the AAP + ADT versus docetaxel + ADT comparison for the mHSPC subgroup of STAMPEDE as a whole. See Table 4 and 5 of the company's submitted addendum for the NMA inputs.

Results of a meta-analysis combining final data for LATITUDE and data from the high-risk mHSPC STAMPEDE subgroup, reaffirm the superiority of AAP + ADT versus ADT (Table 3 of the company addendum).

The updated NMA for comparison AAP + ADT versus docetaxel + ADT, generates similar estimates of benefit to the company's original NMA. The HR estimates carried forward into the company model are [redacted]

2.2 ERG critique of the company's revised comparative effectiveness analysis

As indicated, the company rely on the NMA for estimating the comparative efficacy of docetaxel + ADT versus AAP + ADT. The company offer further arguments as to why the direct evidence on OS and rPFS from STAMPEDE may not be the most reliable source. They note an inconsistency in the proportion of censoring events in the AAP + ADT and docetaxel + ADT arms, with significantly more occurring in the docetaxel + ADT arm. They further argue that this may be due to significantly more patients in the docetaxel + ADT arm withdrawing from follow-up as a result of experiencing toxicities, excluding some higher risk patients from follow-up and biasing results in favour of docetaxel. The company also show a comparison of OS Kaplan Maier data for AAP + ADT versus ADT, and docetaxel + ADT versus ADT, both from the STAMPEDE mHSPC subgroups (see Figure 8 of the company's addendum document). Naive indirect comparison of the OS curves for AAP + ADT and docetaxel + ADT is suggestive of a benefit for AAP + ADT. Overall, whilst there are substantial uncertainties regarding comparison with docetaxel + ADT, the ERG has a preference towards the company's base case approach of using the hazard ratios from the NMA over sole reliance on the limited direct head-to-head data from STAMPEDE.

3. Cost-effectiveness

3.1 Summary and critique of the revised economic model submitted by the company

Model structure

The company submitted a revised economic model which can now utilise a partitioned survival approach in addition to the original Markov modelling approach. The state-based structure of the model remains unchanged (Figure 1). As before, all patients start progression free in the mHSPC state where they receive AAP + ADT or one of the two comparators (ADT alone or docetaxel + ADT).

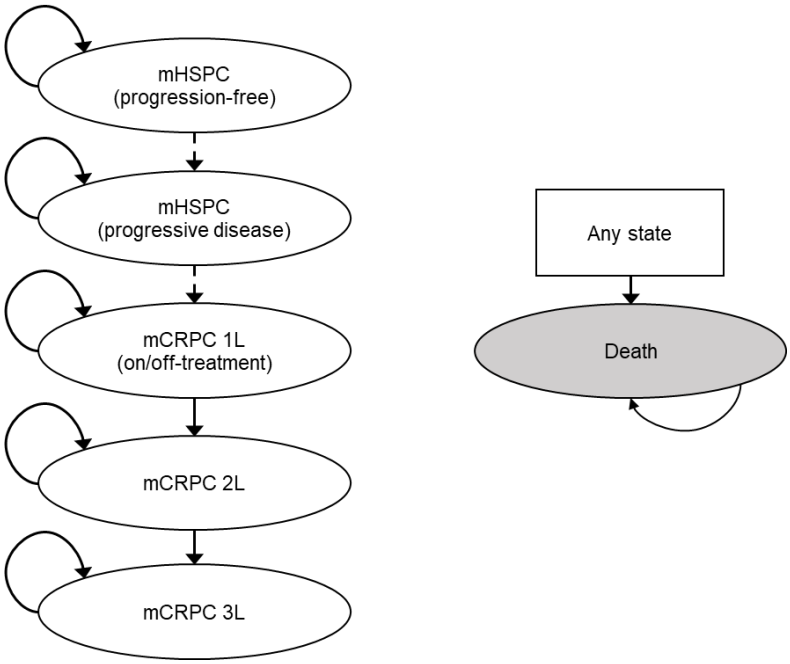

Figure 1 Company model structure (Source: Figure 9 of the company addendum, July 2019)

The revised cost-effectiveness results presented in the company addendum utilise the partitioned survival approach. For AAP + ADT and ADT alone, the company use parametric survival curves fitted to rPFS data from interim analysis one (IA1) of LATITUDE, and OS data from the final analysis data cut. The final analysis cut was released following suspension of the appraisal in July 2018 (clinical cut-off date: 15 August., 2018). The company explain that the purpose of the final analysis was to obtain results for updated OS and other secondary endpoints. They further note that the final analysis of rPFS was planned for after 565 events, which was reached at the time of the first interim analysis (IA1). Therefore, the rPFS analysis is not revisited or re-summarised in the company's new addendum. For docetaxel + ADT, the company apply hazard ratios versus AAP + ADT derived from the revised network meta-analysis summarised above. Whilst OS benefits for AAP + ADT are maintained over docetaxel + ADT in the company's revised base case, the new model structure does allow for OS to equalized in this comparison whilst maintaining the rPFS benefits for AAP + ADT. This addresses one of the committee's key concerns with the previous model structure.

The model maintains the same cycle length as the previously submitted model; weekly for the first 52 weeks, increasing to 28 days thereafter. The model population is in line with the

population recruited to the LATITUDE trial; i.e. adults (mean age 67 years) with newly diagnosed high risk mHSPC. Costs and health effects (life years and QALYs) are accrued based on the sate distribution over a 33-year time horizon. This applied time horizon is at odds with 20-year duration that is stated in the company's submitted addendum.

ERG Commentary

The ERG believes that the partitioned survival approach provides a useful addition to the modelling presented in the previous submissions. One minor issue relates to the time horizon in the company's revised base case being set to 33 years rather than the stated 20 years. However, the company present scenarios where this is set to 20 years, and it has a minimal impact on the ICERs.

Clinical parameters and variables

Parametric distributions were fitted to the rPFS (IA1) and OS (final cut) data for AAP + ADT and ADT alone. Standard parametric distributions were considered as independently fitted curves and unstratified curves with treatment arm included as a covariate. The company state that they followed NICE DSU guidance when considering the choice of parametric function for their base case. Following rejection of the proportional hazards assumption for both rPFS and OS, the company used independently fitted curves.

For rPFS the company determined that the log-normal, log-logistic, Gamma and Weibull curves had the lowest AIC/BIC values for both AAP + ADT and ADT alone (see Tables 7 and 8 of the company addendum). Rather than selecting a single best fitting curve for each arm in the model, they presented one scenario using log-logistic curves for rPFS and OS in both arms and another scenario using Weibull curves for all the extrapolations. Of all the parametric distributions assessed, the log-logistic provided the second most optimistic rPFS projections for both AAP + ADT and ADT alone, whilst the Weibull provided the second most pessimistic rPFS projections for both treatments. With respect to OS, the same approach was taken, with log-logistic curves being selected as an optimistic scenario and Weibull curves being selected as a pessimistic scenario (see Tables 9 and 10 of the company addendum).

To estimate the comparative effectiveness of docetaxel, the company applied the hazard ratios from the NMA described above.

ERG commentary

The ERG finds it useful that the company have presented results for curves that offer both optimistic and pessimistic rPFS and OS extrapolations for both treatments. However, there was no discussion in the company addendum regarding the clinical plausibility of the alternative projections in the different treatment arms. Since the population is a group with high-risk metastatic disease, the ERG's clinical advisor believed that the log-logistic curves offered overly optimistic projections of rPFS and OS, and that the Weibull extrapolations were more plausible. Further, the ERG's clinical expert was of the opinion that even the most pessimistic projections offered by the Gompertz distributions were not completely implausible for a high-risk cohort with metastatic disease.

A further issue relating to the extrapolation of survival data from LATITUDE to inform cost-effectiveness versus ADT alone, is that the fitted curves are relevant to a group high-risk mHSPC patients who would generally be considered eligible for docetaxel. The ERG's expert advice was that patients considered ineligible for docetaxel would be generally sicker, with ECOG performance status of 3 or more. The projections based on the LATIDUDE trial, in which all patients were ECOG 2 or lower, may therefore overestimate rPFS and OS in both arms. Furthermore, there is a lack of data to determine if the relative treatment effects (i.e. the hazard ratios for rPFS and OS) are generalizable to a sicker cohort.

Based on the above points, the ERG believes that there are remaining uncertainties in the comparison versus ADT alone for chemo-ineligible patients, and that the Weibull curves offer the more plausible extrapolations for chemo-eligible patients.

There are also further uncertainties relating to the longer-term relative efficacy of AAP+ADT versus ADT alone and docetaxel + ADT. The company reject the assumption of proportional hazards in their base case and use independently fitted curves for AAP + ADT and ADT alone. As a result, the cycle specific proportional reduction in the hazard of progression and mortality versus the ADT alone increases over the entire time horizon in the model. The ERG has assessed the robustness of the findings to alternative assumptions about loss of relative treatment effects over time, by equalizing the hazards of progression and mortality across treatment arms from five and ten years.

Subsequent castrate resistant prostate cancer (CRPC) states

Within the partitioned survival approach, the company estimated transitions through subsequent lines of therapy for mCRPC. This involved using mean mCRPC health state durations derived from the comparator arm of the discrete event simulation model for TA387 (NICE TA 387, Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated) and reweighting these to the mCRPC survival time in each arm of the current model. The state durations from TA387 were for 1L mCRPC (on treatment), 1L mCRPC (off-treatment) and 2L mCRPC. It is not clear to the ERG if these durations from TA387 represent time in state for state survivors, or if they also account for pre-progression mortality.

The reweighting was done by multiplying the mCRPC state durations from TA387 by the overall arm specific mCRPC survival time from the current model, divided by the sum of time in 1L, 1L off-treatment, and 2L mCRPC from TA387. For example:

$$1L\ mCRPC\ duration = 1L\ mCRPC\ duration\ (TA387) * \frac{Mean\ post\ progression\ survival\ \ (current\ model)}{1L + 1L\ off treatment + 2L\ mCRPC\ durations\ (TA387)}$$

Exponential distributions were then fitted to the reweighted mCRPC state durations to estimate constant transitions probabilities to the next mCRPC state.

<u>*ERG commentary*</u>

The ERG notes that the comparator arm of TA387 was best supportive care followed by docetaxel followed by abiraterone. In this context, it is the ERGs understanding that 1L in TA387 relates to a treatment period with prednisolone + placebo, 1L (off-treatment) relates to a period of BSC (without prednisolone) prior to docetaxel therapy, and 2L relates to time on docetaxel and BSC following docetaxel treatment and prior to commencing a subsequent therapy. The applicability of these state durations to the current modelled treatment sequences is therefore questionable. For example, 1st line treatment for mCRPC in the DOCETAXEL+ ADT arm of the current model is abiraterone (40%), enzalutamide (40%) BSC (5%), cabazitaxel (10%) and radium-223 (5%).

The company note that use of the comparator arm state durations from TA387 may lead to underestimation of the time patients spend on 1st line treatment for mCRPC. They further

note that their base case reweighting of the state durations, does not account for pre-progression deaths in current model. This may serve to overestimate the rate of transition through the mCRPC states in the current model, and underestimate time spent in the 1L and 2L states. However, a further issue with the company base case adjustment is that it divides the total duration across all mCRPC states, accounting for pre-progression mortality, by time spent across an incomplete set of mCRPC states from TA387. The ERG believes this could potentially serve to bias the adjustment of state durations upwards in the current model.

To address these issues, the company have provided further adjustment scenarios where they reweight state durations from TA387 by multiplying them by total mCRPC state duration (with pre-progression mortality factored out), divided by total life years from TA387.

$$1L\ mCRPC\ duration\ (TA387) * \frac{Mean\ post\ progression\ survival\ \ (current\ model\ adjusted\ for\ pre\_prog\ mortality)}{Total\ life\ years\ (TA387)}$$

The alternative adjustment is applied using state durations from either the BSC arm of TA387, or the Treatment arm of TA387.

The ERG is of the opinion that this alternative approach also has its problems, since it adjusts outs pre-progression mortality from overall mCRPC duration in the current model, and divides this by total life years from TA387, which would be expected to account for pre-progression morality. This approach could serve to over-adjust mCRPC state durations in the current model. It also relies on estimates of pre-progression mortality which are derived from the company's original state transition MSM model, which introduces further uncertainty. In addition, it seems somewhat unintuitive to use the same unadjusted mCRPC state durations across the different arms of the current model, since the mCRPC treatment sequences are different across the different arms.

Therefore, the ERG has conducted some further exploratory analyses regarding mCRPC state durations. These include: removing the adjustment for pre-progression mortality in the company's additional scenarios; applying no adjustments to the BSC state durations from TA387; applying no adjustments to the treatment arm state durations from TA387; and

applying unadjusted treatment arm durations from TA387 to the ADT alone and docetaxel + ADT arms of the current model, and unadjusted BSC state durations from TA387 to the AAP + ADT arm. This latter scenario is justified by the fact the 1L treatment in the treatment arm of TA387 (abiraterone) matches better with the 1L mCRPC treatment in the comparator arms of the current model.

On balance the ERG believe that is more likely that the company's base case underestimates time in 1L in the comparator arms of the model, which may be conservative in favour of the comparators, but the extent of that underestimation is uncertain.

Health related quality of life

The company note that they have adopted the committees preferred approach to health state utilities, with respect to utilising a regression-based approach to the LATITUDE EQ-5D data that doesn't separate out an AE coefficient by treatment arm. They continue to apply an on-treatment utility increment for Abiraterone versus ADT (0.04), and a utility decrement for docetaxel versus ADT (0.07) only whilst on treatment as per committee preferences. Whilst the company recognise the committee's preference for using EQ 5D data from the subgroup of people from STAMPEDE with metastatic and high-risk hormone-sensitive prostate cancer - because comparable data were available for abiraterone plus ADT, docetaxel plus ADT and ADT alone – they reiterate that this data remains unpublished.

With respect to adverse events, the proportions of patients on AAP + ADT and ADT alone who experience an AE are taken from LATITUDE and combined with the LATITUDE regression coefficient for AEs. Frequencies of grade 3/4 AEs for DOCETAXEL+ ADT are taken from the literature, as are AE frequencies for subsequent therapies.

ERG commentary

The utility assumptions appear to be in line with the assumptions applied by the company in their revised base case at the second AC meeting. These assumptions took on board several preferences expressed by the committee at the first AC meeting. Whilst EQ-5D data from the metastatic and high-risk hormone-sensitive prostate cancer sub-group of STAMPEDE remains unpublished, it is worth noting that the recently published economic evaluation of docetaxel + ADT versus ADT based on the whole STAMPEDE population, estimated a smaller utility decrement for docetaxel (0.02) than the one applied in the company model

(0.07)(Woods et al., 2018). This was adjusted for age and health state, but not AEs, and lasted for one year. Therefore, the ERG explores the impact of applying a smaller decrement of 0.02. It is also notable that no treatment utility increments or decrements are applied to patients modelled to receive abiraterone for mCRPC in the comparator arms, or those receiving docetaxel following progression (more common in the AAP + ADT arm).

Resource use and costs

Resource use and costs in the company's revised model are generally in line with those applied in the company's revised base case at the second appraisal committee meeting. Changes include the following

- Use of the mid-point compliance estimate from LATITUDE for the proportion of patients receiving abiraterone. This in line the committee's preference as expressed in the ACD.
- Updating of all costs to reflect most recent available prices.
- Applying an additional cost of £52.70 for granulocyte-colony stimulating factor (G-CSF) per docetaxel administration (to lower the risk of febrile neutropenia). The company note this to be based on precedent from the enzalutamide submission for no-mCRPC (TA580).
- Applying revised distributions of subsequent treatments in mCRPC1, mCRPC2 and mCRPC3 (see figure 16 of the company's addendum).

ERG commentary

The ERG is generally satisfied that costs in the model have been applied in line with the committees previously expressed preferences. With respect to the updating of unit costs, these primarily affect the AE and MRU data as drug prices remain largely unchanged.

With respect to the addition of G-CSF prophylaxis per docetaxel administration, it is the ERGs understanding that this is used in the NHS, but not universally for all patients with mHSPC receiving docetaxel. The ESMO Clinical Practice Guidelines on the management of febrile neutropenia suggest that G-CSF is recommended for primary prophylaxis where the febrile neutropenia risk is >20% based on the planned regimen and patient characteristics (e.g. age > 65, other co-morbidities)(Klastersky et al., 2016). Based on retrospective analysis of 198 mHSPC patients receiving upfront docetaxel between April 2013 and April 2017 at three Cancer Centres in South Central England, only 16 (8.1%) reportedly received

prophylactic G-CSF (Bennet et al., 2018). Thus, its universal application in the model is highly questionable. However, its removal has only a small impact on the ICER as shown in the company's scenario analysis.

Regarding the distributions of subsequent therapies applied in the model, these were generally in line with the expectations of the ERGs clinical advisor, except when considering a sub-population of mHSPC patients ineligible for chemotherapy. If it is argued that ADT alone is the relevant comparator for patients with newly diagnosed high-risk mHSPC who are ineligible for docetaxel, it seems inconsistent to assume that substantial proportions of these patients would receive it following progression to mCRPC. The same arguments may also apply for cabazitaxel, which has restrictions relating to ECOG performance status (one of the factors that may result in a patient being deemed ineligible for docetaxel). Thus, greater use of BSC and perhaps radium-223 might be expected in patients considered chemo-ineligible.

3.2 Company revised cost-effectiveness results

The company present revised base case results versus ADT alone and versus docetaxel + ADT, using both log-logistic and Weibull extrapolations of PFS and OS. As the company rely on LATUTUDE for the ADT alone comparison, and the NMA for comparison with docetaxel, they do not report a fully incremental, probabilistic analysis as per the committees stated preference in the ACD. Rather, the company make the case that results versus ADT alone should be used to inform decision making in those who are chemo-ineligible at diagnosis. For those who are fit enough to have chemotherapy, the results against docetaxel are provided.

Results of all the company's analyses can be found in sections B.4.8 to B.4.11 of their submitted addendum. These results incorporate the commercial access agreement for abiraterone, but not the available PAS discounts for modelled subsequent therapies. The results incorporating available discounts for radium-223, cabazitaxel and enzalutamide are provided in the accompanying confidential appendix produced by the ERG using the company's model.

3.3 Further exploratory analysis conducted by the ERG

The ERG conducted some additional scenario analysis to further assess the robustness of the results to several uncertainties identified above:

1. The on-treatment utility decrement for docetaxel + ADT versus ADT alone
2. The rPFS and OS extrapolations in the AAP + ADT and ADT arms of the model
    a. Selection of Gompertz curves for both PFS and OS
    b. Selection of unstratified rPFS and OS curves together (log-logistic and Weibull)
3. Unstratified Weibull curves with downward adjustment of rPFS and OS, and reliance on proportional hazards for AAP + ADT versus ADT alone. This was done to assess the possible implications of shorter rPFS and OS in a chemo-ineligible cohort, whilst maintaining relative treatments effects.
4. Assessing potential impact of relative treatment effect waning, by assuming equal hazards of progression and death across all arms of the model from:
    a. Five years
    b. Ten years
5. The hazard ratio applied for abiraterone versus docetaxel, to explore the impact of a HR for OS = 1 (assuming no benefit), combined with a HR for rPFS = [redacted] (from the NMA).
6. Removal of the docetaxel and cabazitaxel subsequent treatment shares following progression on AAP + ADT and ADT alone in the chemo-ineligible population.
    a. Replacement with BSC
    b. Replacement with R-223 in 1L of the AAP + ADT arm, and 1L and 2L of the ADT alone arm, and 100% BSC in 3L (both arms).
7. Adjustment to mCRPC state durations
    a. Removal of the adjustment for pre-progression mortality but retained use of total life years from TA387 to reweight state durations from the BSC arm of TA387
    b. Removal of adjustment for pre-progression mortality but retained use of total life years from TA387 to reweight state durations from the treatment arm of TA387
    c. Applying unadjusted BSC arm state durations from TA387
    d. Applying unadjusted treatment arm state durations from TA387

e. Applying unadjusted treatment arm state durations from TA387 to the ADT alone and docetaxel + ADT arms, and unadjusted BSC state durations from TA387 to the AAP + ADT arm.

The results of these scenarios are provided in Table 1 below using the PAS price for abiraterone but list prices for subsequent therapies. Results are reproduced in the cPAS appendix using available PAS prices for subsequent treatments.

It can be noted from the results in Table 1 that the ICERs all remain below £30,000 for AAP + ADT versus ADT alone. However, as acknowledged by the company, there is greater uncertainty surrounding the comparison with docetaxel + ADT. When applying the ERGs preferred Weibull distributions, the ICER versus docetaxel + ADT falls by the greatest amount when applying unadjusted probabilities of progression through the mCRPC states using T387 treatment arm state durations (Table 1, scenarios 7d and 7e). The results of all these scenarios are provided in the cPAS appendix with relevant discounts in the subsequent therapies.

Table 1 Further exploratory scenarios undertaken by the ERG

Model assumption	Scenario	ICER vs ADT alone	ICER vs dox + ADT	ICER vs ADT alone	ICER vs dox + ADT
Base case		**Loglogistic**		**Weibull**	
		£14,899	**£21,002**	**£19,120**	**£31,222**
1. On-treatment utility decrement for docetaxel	Decrement = 0.02	NA	£21,576	NA	£32,543
2. OS and PFS extrapolation	a) Gompertz (stratified) for rPFS with Gompertz (stratified) for OS	£22,960	£37,762	£22,960	£37,762
	b) Unstratified curves for both rPFS and OS*	£19,848	£21,923	£21,150	£32,879
3. Proportional downward adjustment of rPFS and OS on ADT alone*	a) 10% proportional increase in hazards of rPFS and OS in chemo-ineligible	NC	NC	£22,368	£34,929
	b) 25% proportional increase in hazards of rPFS and OS in chemo-ineligible	NC	NC	£24,080	£37,778
4. Loss of relative efficacy by equalising hazards of progression and death from:	a) 5 years	£18,811	£30,892	£26,463	£44,246
	b) 10 years	£15,654	£23,299	£20,342	£33,684
5. HRs for AAP + ADT v docetaxel + ADT	OS HR=1; PFS HR=[redacted]	NA	£22,321	NA	£37,079
6. Removal of docetaxel and cabazitaxel as subsequent treatments in the chemo-ineligible population	a) Replacement with BSC	£14,677	NA	£18,424	NA
	b) Replacement with R-223 in 1L (AAP + ADT), and 1L and 2L ADT alone; 100% BSC in 3L	£14,545	NA	£18,833	NA
7. mCRPC state durations	a) Remove adjustment for pre-progression mortality but retain use of life years from TA387 to reweight durations (BSC durations)	£15,363	£21,855	£19,770	£32,488
	b) Remove adjustment for pre-progression mortality but retain use of life years from TA387 to reweight durations (Treatment arm durations)	£13,799	£19,073	£17,564	£28,305
	c) Apply unadjusted BSC state durations from TA387	£15,710	£21,076	£18,796	£27,977
	d) Applying unadjusted treatment arm state durations from TA387	£13,236	£16,226	£15,079	£19,764

	e) Apply unadjusted treatment arm state durations from TA387 for ADT alone and docetaxel arms, and unadjusted BSC state durations from TA387 for AAP + ADT arm	£13,515	£16,997	£15,690	£21,842
Key: AAP, abiraterone acetate with prednisone; ADT, androgen deprivation therapy; AE, adverse event; BSC, best supportive care; CAA, commercial access arrangement; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; IA1, first interim analysis; ICER, incremental cost-effectiveness ratio; mCRPC, metastatic castrate-resistant prostate cancer; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; rPFS, radiographic progression-free survival; NA, not applicable; NC, not conducted.					

Note: *Uses unstratified Weibull curves with proportional hazards assumption rather than the stratified base case curves

References

1. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. The Lancet Oncology 2019;20(5):686-700. doi: 10.1016/s1470
2. Hoyle A, Ali A, James N, et al. Role of Abiraterone Acetate + Prednisolone + ADT in High and Low Risk Metastatic Hormone Naïve Prostate Cancer European Society for Medical Oncology. Munich: Germany, 2018.
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7. Bennet J, Ajayi C, Muller D, Longley J, Yousuf A, Silva A, et al. Real world experience of upfront docetaxel in metastatic hormone-sensitive prostate cancer: a 4-year multi-centre review. NCRI Cancer Conference, 2018, Poster session. Conference abstract available at: https://abstracts.ncri.org.uk/year_published/2018/ [accessed October 2019].

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

ERG's critique of the company's addendum submitted in July 2019

Erratum

Produced by Aberdeen HTA Group

Completed December 11, 2019

Contains CIC/AIC

This document is intended to replace pages 3, 4, 9, 11, 13, 17, 18 and 19 of the ERGs critique of the company's addendum submitted in July 2019. These changes were due to a few inaccuracies in the ERG report, and a referencing error.

1. Clinical effectiveness

1.1 Summary of new clinical effectiveness evidence submitted by the company

The company present data from the pre-planned final analysis of the LATITUDE trial (Fizazi et al., 2019) and the published post-hoc analyses of STAMPEDE that specifically look at AAP + ADT vs ADT alone in the metastatic high-risk subgroup of prostate cancer patients (Hoyle et al., 2019). Although the enrolled population of STAMPEDE is broader than the licensed indication for ASP + ADT, the STAMPEDE subgroup is considered comparable to the LATITUDE population (patients with newly diagnosed high-risk mHSPC). The company refer the Committee's interest in attaining HRQOL data from STAMPEDE but note that these data remain unpublished at this time.

The LATITUDE final analysis cut-off date was 15th August 2018, which provides a median follow-up period of 51.8 months. The ITT and safety populations comprised 1199 patients: 597 AAP + ADT patients and 602 ADT alone patients. The company note that treatment crossover was permitted after the trial was unblinded at the first interim analysis. At time of final analysis, 72 patients (12%) in the ADT alone group had crossed over to receive open-label treatment with AAP + ADT. The company present comparative results of OS and other secondary endpoint results between the IA1, IA2 and final analyses in Appendix B of the company addendum.

Primary endpoint - overall survival

At the time of final analysis, the majority ([redacted]%) of patients in the LATITUDE AAP + ADT group were still alive, compared to [redacted]% of patients in the ADT alone group. The comparative OS data at IA1, IA2 and final analysis, presented in Table 21 and Figure 26 of the company addendum, show that the survival benefit of AAP + ADT versus ADT alone remained at 4 years. The hazard ratio at final analysis was 0.66 (95% CI: 0.56 - 0.78), compared to 0.64 (95% CI: 0.54 - 0.76) at IA2.

Subgroup analyses were consistent with the overall LATITUDE results, except for patients with an ECOG score of 2 (HR=1.42), for which eight additional deaths were reported; however, the company state that this was a small subgroup of 40 patients, thus precluding meaningful conclusions. The forest plot for the subgroup analyses is presented as Figure 3 in the company addendum.

The LATITUDE results are consistent with the most recent post-hoc analysis of OS data from the STAMPEDE trial subgroup of high-risk mHSPC patients. This analysis showed that AAP + ADT was also associated 46% reduction in the risk of death compared to ADT alone (HR=0.54 [0.41-0.70]; p<0.001) (Hoyle et al., 2019). This compares with a HR of 0.61 (0.49-0.75) previously reported for the STAMPEDE metastatic subgroup as a whole. The company state that 95% of the STAMPEDE high-risk mHSPC subgroup were newly diagnosed and are, therefore, comparable with the licensed indication for AAP + ADT. The company also highlight that a statistically significant result was obtained despite the analysis being underpowered to detect a between group difference in OS, indicating a large treatment effect. The Kaplan Meier data for OS in STAMPEDE are presented as Figure 4 in the company addendum.

Secondary endpoints

The company present a summary of the LATITUDE secondary endpoints at time of final analysis in Table 1 and Appendix C of their addendum. AAP + ADT was significantly superior to ADT alone for all secondary efficacy endpoints. Data for prostate cancer-specific survival at the time of IA1 show a [redacted] in prostate cancer-specific survival for the AAP + ADT group compared to the ADT alone group (HR=[redacted] 95% CI: [redacted]; [redacted]) (Janssen Research and Development). The company state this means that men with newly diagnosed high-risk mHSPC were less likely to die from their prostate cancer compared with those treated with ADT alone.

The company present secondary endpoint data for the STAMPEDE subgroup in Appendix D. AAP + ADT was favoured compared to ADT alone for all subgroups.

Exploratory endpoints

Progression-free survival following subsequent therapy

The company present the LATITUDE final analysis Kaplan Meier data for progression-free survival following subsequent therapy (PFS2) as Figure 5 in their addendum. Treatment with AAP + ADT statistically significantly extended PFS2 by 42% compared with ADT alone (HR=0.58 [95% CI:0.49-0.68]; p<0.0001).

ERG commentary

The ERG finds it useful that the company have presented results for curves that offer both optimistic and pessimistic rPFS and OS extrapolations for both treatments. The company provided reference to an assessment of the clinical plausibility of the alternative projections in the different treatment arms. Since the population is a group with high-risk metastatic disease, the ERG's clinical advisor believed that the log-logistic curves offered overly optimistic projections of rPFS and OS, and that the Weibull extrapolations were more plausible. Since the population is a group with high-risk metastatic disease, the ERG's clinical advisor believed that the log-logistic curves offered overly optimistic projections of rPFS and OS, and that the Weibull extrapolations were more plausible. Further, the ERG's clinical expert was of the opinion that even the most pessimistic projections offered by the Gompertz distributions were not completely implausible for a high-risk cohort with metastatic disease.

A further issue relating to the extrapolation of survival data from LATITUDE to inform cost-effectiveness versus ADT alone, is that the fitted curves are relevant to a group high-risk mHSPC patients who would generally be considered eligible for docetaxel. The ERG's expert advice was that patients considered ineligible for docetaxel would be generally sicker, with ECOG performance status of 3 or more. The projections based on the LATIDUDE trial, in which all patients were ECOG 2 or lower, may therefore overestimate rPFS and OS in both arms. Furthermore, there is a lack of data to determine if the relative treatment effects (i.e. the hazard ratios for rPFS and OS) are generalizable to a sicker cohort.

Based on the above points, the ERG believes that there are remaining uncertainties in the comparison versus ADT alone for chemo-ineligible patients, and that the Weibull curves offer the more plausible extrapolations for chemo-eligible patients.

There are also further uncertainties relating to the longer-term relative efficacy of AAP+ADT versus ADT alone and docetaxel + ADT. The company reject the assumption of proportional hazards in their base case and use independently fitted curves for AAP + ADT and ADT alone. As a result, the cycle specific proportional reduction in the hazard of progression and mortality versus the ADT alone increases over the entire time horizon in the model. The ERG has explored the robustness of the findings to alternative assumptions about loss of relative treatment effects over time, by equalizing the hazards of progression and mortality across treatment arms from eight and ten years.

note that their base case reweighting of the state durations, does not account for pre-progression deaths in current model. This may serve to overestimate the rate of transition through the mCRPC states in the current model, and underestimate time spent in the 1L and 2L states. However, a further issue with the company base case adjustment is that it divides the total duration across all mCRPC states, accounting for pre-progression mortality, by time spent across an incomplete set of mCRPC states from TA387. The ERG believes this could potentially serve to bias the adjustment of state durations upwards in the current model.

To address these issues, the company have provided further adjustment scenarios where they reweight state durations from TA387 by multiplying them by total mCRPC state duration (with pre-progression mortality factored out), divided by total life years from TA387.

$$1L\ mCRPC\ duration\ (TA387) * \frac{Mean\ post\ progression\ survival\ \ (current\ model\ adjusted\ for\ pre\_prog\ mortality)}{Total\ life\ years\ (TA387)}$$

The alternative adjustment is applied using state durations from either the BSC arm of TA387, or the Treatment arm of TA387.

The ERG is of the opinion that this alternative approach still also has its problems, as it still relies on estimates of pre-progression mortality which are derived from the company's original state transition MSM model, which introduces further uncertainty. In addition, it seems somewhat unintuitive to use the same unadjusted mCRPC state durations across the different arms of the current model, since the mCRPC treatment sequences are different across the different arms.

Therefore, the ERG has conducted some further exploratory analyses regarding mCRPC state durations. These include: removing the adjustment for pre-progression mortality in the company's additional scenarios; applying no adjustments to the BSC state durations from TA387; applying no adjustments to the treatment arm state durations from TA387; and

(0.07)(Woods et al., 2018). This was adjusted for age and health state, but not AEs, and lasted for one year. Therefore, the ERG explores the impact of applying the smaller decrement up to one year in the mHSPC state. Since no specific treatment utility increments or decrements are applied to patients receiving abiraterone for mCRPC in the comparator arms, or those receiving docetaxel for mCRPC (more common in the AAP + ADT arm), the ERG scenario does not apply a decrement beyond progression for those receiving docetaxel for mHSPC.

Resource use and costs

Resource use and costs in the company's revised model are generally in line with those applied in the company's revised base case at the second appraisal committee meeting. Changes include the following

- Use of the mid-point compliance estimate from LATITUDE for the proportion of patients receiving abiraterone. This in line the committee's preference as expressed in the ACD.
- Updating of all costs to reflect most recent available prices.
- Applying an additional cost of £52.70 for granulocyte-colony stimulating factor (G-CSF) per docetaxel administration (to lower the risk of febrile neutropenia). The company note this to be based on precedent from the enzalutamide submission for no-mCRPC (TA580).
- Applying revised distributions of subsequent treatments in mCRPC1, mCRPC2 and mCRPC3 (see figure 16 of the company's addendum).

ERG commentary

The ERG is generally satisfied that costs in the model have been applied in line with the committees previously expressed preferences. With respect to the updating of unit costs, these primarily affect the AE and MRU data as drug prices remain largely unchanged.

With respect to the addition of G-CSF prophylaxis per docetaxel administration, it is the ERGs understanding that this is used in the NHS, but not universally for all patients with mHSPC receiving docetaxel. The ESMO Clinical Practice Guidelines on the management of febrile neutropenia suggest that G-CSF is recommended for primary prophylaxis where the febrile neutropenia risk is >20% based on the planned regimen and patient characteristics (e.g. age > 65, other co-morbidities)(Klastersky et al., 2016). Based on retrospective analysis of 198 mHSPC patients receiving upfront docetaxel between April 2013 and April 2017 at three Cancer Centres in South Central England, only 16 (8.1%) reportedly received

The ERG conducted some additional scenario analysis to further assess the robustness of the results to several uncertainties identified above:

1. The on-treatment utility decrement for docetaxel + ADT versus ADT alone
2. The rPFS and OS extrapolations in the AAP + ADT and ADT arms of the model
    a. Selection of Gompertz curves for both PFS and OS
    b. Selection of unstratified rPFS and OS curves together (log-logistic and Weibull)
3. Unstratified Weibull curves with downward adjustment of rPFS and OS, and reliance on proportional hazards for AAP + ADT versus ADT alone. This was done to assess the possible implications of shorter rPFS and OS in a chemo-ineligible cohort, whilst maintaining relative treatments effects.
4. Assessing potential impact of relative treatment effect waning, by assuming equal hazards of progression and death across all arms of the model from:
    a. Eight years
    b. Ten years
5. The hazard ratio applied for abiraterone versus docetaxel, to explore the impact of a HR for OS = 1 (assuming no benefit), combined with a HR for rPFS = [redacted] (from the NMA).
6. Removal of the docetaxel and cabazitaxel subsequent treatment shares following progression on AAP + ADT and ADT alone in the chemo-ineligible population.
    a. Replacement with BSC
    b. Replacement with R-223 in 1L of the AAP + ADT arm, and 1L and 2L of the ADT alone arm, and 100% BSC in 3L (both arms).
7. Adjustment to mCRPC state durations
    a. Removal of the adjustment for pre-progression mortality but retained use of total life years from TA387 to reweight state durations from the BSC arm of TA387
    b. Removal of adjustment for pre-progression mortality but retained use of total life years from TA387 to reweight state durations from the treatment arm of TA387
    c. Applying unadjusted BSC arm state durations from TA387
    d. Applying unadjusted treatment arm state durations from TA387

Table 1 Further exploratory scenarios undertaken by the ERG

Model assumption	Scenario	ICER vs ADT alone	ICER vs dox + ADT	ICER vs ADT alone	ICER vs dox + ADT
Base case		**Loglogistic**		**Weibull**	
		£14,899	**£21,002**	**£19,120**	**£31,222**
1. Utility decrement for docetaxel	Decrement = 0.02 for one year mHSPC	NA	£20,715	NA	£30,569
2. OS and PFS extrapolation	a) Gompertz (stratified) for rPFS with Gompertz (stratified) for OS	£22,960	£37,762	£22,960	£37,762
	b) Unstratified curves for both rPFS and OS*	£19,848	£21,923	£21,150	£32,879
3. Proportional downward adjustment of rPFS and OS on ADT alone*	a) 10% proportional increase in hazards of rPFS and OS in chemo-ineligible	NC	NC	£22,368	NA
	b) 25% proportional increase in hazards of rPFS and OS in chemo-ineligible	NC	NC	£24,080	NA
4. Loss of relative efficacy by equalising hazards of progression and death from:	a) 8 years	£16,298	£24,938	£21,546	£35,966
	b) 10 years	£15,654	£23,299	£20,342	£33,684
5. HRs for AAP + ADT v docetaxel + ADT	OS HR=1; PFS HR=[redacted]	NA	£22,321	NA	£37,079
6. Removal of docetaxel and cabazitaxel as subsequent treatments in the chemo-ineligible population	a) Replacement with BSC	£14,677	NA	£18,424	NA
	b) Replacement with R-223 in 1L (AAP + ADT), and 1L and 2L ADT alone; 100% BSC in 3L	£14,512	NA	£18,776	NA
7. mCRPC state durations	a) Remove adjustment for pre-progression mortality but retain use of life years from TA387 to reweight durations (BSC durations)	£15,363	£21,855	£19,770	£32,488
	b) Remove adjustment for pre-progression mortality but retain use of life years from TA387 to reweight durations (Treatment arm durations)	£13,799	£19,073	£17,564	£28,305
	c) Apply unadjusted BSC state durations from TA387	£15,710	£21,076	£18,796	£27,977
	d) Applying unadjusted treatment arm state durations from TA387	£13,236	£16,226	£15,079	£19,764

	e) Apply unadjusted treatment arm state durations from TA387 for ADT alone and docetaxel arms, and unadjusted BSC state durations from TA387 for AAP + ADT arm	£13,515	£16,997	£15,690	£21,842
Key: AAP, abiraterone acetate with prednisone; ADT, androgen deprivation therapy; AE, adverse event; BSC, best supportive care; CAA, commercial access arrangement; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; IA1, first interim analysis; ICER, incremental cost-effectiveness ratio; mCRPC, metastatic castrate-resistant prostate cancer; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; rPFS, radiographic progression-free survival; NA, not applicable; NC, not conducted.					

Note: *Uses unstratified Weibull curves with proportional hazards assumption rather than the stratified base case curves

References

1. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. The Lancet Oncology 2019;20(5):686-700. doi: 10.1016/s1470
2. Hoyle AP, Ali A, James ND, Cook A, Parker CC, de Bono JS, Attard G, Chowdhury S, Cross WR, Dearnaley DP, Brawley CD, Gilson C, Ingleby F, Gillessen S, Aebersold DM, Jones RJ, Matheson D, Millman R, Mason MD, Ritchie AWS, Russell M, Douis H, Parmar MKB, Sydes MR, Clarke NW; STAMPEDE Investigators. Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer. Eur Urol. 2019 Dec;76(6):719-728 [Epub 2019 Aug 23].
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4. NICE TA 387. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated https://www.nice.org.uk/guidance/ta387 [accessed October 2019]
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7. Bennet J, Ajayi C, Muller D, Longley J, Yousuf A, Silva A, et al. Real world experience of upfront docetaxel in metastatic hormone-sensitive prostate cancer: a 4-year multi-centre review. NCRI Cancer Conference, 2018, Poster session. Conference abstract available at: https://abstracts.ncri.org.uk/year_published/2018/ [accessed October 2019].

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

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

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on 12 November 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Janssen wish to thank the ERG for conducting their review of our submission addendum and welcome the opportunity to conduct a factual accuracy check of the content. Additionally, following the publication of further STAMPEDE data which NICE may consider relevant to the decision problem, Janssen have provided Appendix A in conjunction with this document to compliment the ongoing appraisal.

Issue 1 LATITUDE data to inform AAP + ADT within chemo-ineligible patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states: *"Furthermore, there is a lack of data to determine if the relative treatment effects (i.e. the hazard ratios for rPFS and OS) are generalizable to a sicker cohort."* [page 9] Janssen wish to signpost the expert opinion which can support the use of LATITUDE to inform the use of AAP + ADT in chemo-ineligible patients.	Janssen ask that the text on page 9 of the ERG report be amended as follows: *"Whilst there is a lack of data to determine if the relative treatment effects (i.e. the hazard ratios for rPFS and OS) are generalizable to a sicker cohort, clinical experts have explained there is no reason to believe that the treatment effect of abiraterone would differ based on a patient's eligibility for chemotherapy."*	Whilst eligibility for chemotherapy may not be determined within the LATITUDE population, separate expert clinical opinions (at a Clinical Advisory Board and at the NICE appraisal committee meeting) have previously suggested that there is no clinical reason why the treatment effect of abiraterone would differ based of a patient's eligibility for chemotherapy. This was explicitly acknowledged within the Appraisal Consultation Document which stated: *"Two clinical experts, who were also investigators in STAMPEDE, explained that there was no reason to believe that there was any subgroup of people for whom abiraterone was more or less effective"* Indeed, precedent within TA587 (provided on page 14 of the re-	Not a factual -inaccuracy. There is a lack of data to confirm generalisability. If used in a sicker population with more comorbidities and higher competing risk of death from other causes, it is possible that the hazard ratio of abiraterone for OS could be diluted.

		submission dossier) suggests that clinical expert opinion is sufficient to support the generalisability of trial results to a particular cohort of interest.	

Issue 2 Clarification of modelled time horizon

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state: *"This applied time horizon is at odds with 20-year duration that is stated in the company's submitted addendum."* [page 8] And: *"One minor issue relates to the time horizon in the company's revised base case being set to 33 years rather than the stated 20 years."* [page 8] Janssen wish to clarify the necessary revision to the modelled time horizon, in light of the revised model structure.	Janssen ask that the text on page 8 be removed/revised as follows: ~~*"This applied time horizon is at odds with 20-year duration that is stated in the company's submitted addendum."*~~ And: *"The time horizon in the company's revised base case has been set to 33 years rather than the previously used 20 years because the revised model structure, now incorporating a range of parametric survival projections, requires a longer time horizon to fulfil a 'life-time' as per the NICE reference case."*	The revised model structure adopts a partitioned survival approach which incorporates a range of parametric survival extrapolations. As such, what constitutes as a life-time horizon depends on the extrapolation used and therefore setting the model time horizon to 33 years is necessary to fulfil the NICE reference case.	Not a factual inaccuracy. Quoting section B4.2. of the company's submitted addendum (July 2019) describing the model, which states: "*Costs and health effects are accrued based on the proportion of patients in the different states over a 20-year time horizon, which is equivalent to lifetime given the starting age of patients with mHSPC (the mean age of patients in the LATITUDE trial was 67 years)*."

Issue 3 Clinical plausibility assessment of survival projections

Description of problem	Description of proposed amendment	Justification for amendment	
The ERG state: *"However, there was no discussion in the company addendum regarding the clinical plausibility of the alternative projections in the different treatment arms."* [page 9] Janssen wish to highlight that the clinical plausibility of survival projections was assessed through face-to-face discussion with clinical experts prior to the re-submission to NICE in July 2019.	Janssen ask that the text on page 9 be revised as follows: *"The company provided reference to an assessment of the clinical plausibility of the alternative projections in the different treatment arms. Since the population is a group with high-risk metastatic disease, the ERG's clinical advisor believed that the log-logistic curves offered overly optimistic projections of rPFS and OS, and that the Weibull extrapolations were more plausible."*	Janssen did engage clinical experts to assess the clinical plausibility of modelled survival projections and this was highlighted on page 40 and page 45 of the re-submission dossier, with accompanying reference #34 provided. Of note, in no instance was Gompertz preferred for any extrapolation. With consideration for the statistical fit and feedback from clinical experts, Janssen presented an optimistic scenario using log-logistic curves and a pessimistic scenario using Weibull curves and we are pleased this approach has been welcomed by the ERG.	Correction acepted (see erratum)

Issue 4 Survival projection for chemo-ineligible patients

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th></th></tr>
<tr>
<td>
The ERG state:

“Unstratified Weibull curves with downward adjustment of rPFS and OS, and reliance on proportional hazards for AAP + ADT versus ADT alone. This was done to assess the possible implications of shorter rPFS and OS in a chemo-ineligible cohort, whilst maintaining relative treatments effects.” [page 15]

And present the following results [page 17]
<table>
<tr><th>Model assumption</th><th>Scenario</th><th>ICER vs ADT alone</th><th>ICER vs dox + ADT</th><th>ICER vs ADT alone</th><th>ICER vs dox + ADT</th></tr>
<tr><td colspan="2">Base case</td><td>Loglogistic</td><td></td><td>Weibull</td><td></td></tr>
<tr><td colspan="2"></td><td>£14,899</td><td>£21,002</td><td>£19,120</td><td>£31,222</td></tr>
<tr><td rowspan="2">3. Proportional downward adjustment of rPFS and OS on ADT alone*</td><td>a) 10% proportional increase in hazards of rPFS and OS in chemo-ineligible</td><td>NC</td><td>NC</td><td>£22,368</td><td>£34,929</td></tr>
<tr><td>b) 25% proportional increase in hazards of rPFS and OS in chemo-ineligible</td><td>NC</td><td>NC</td><td>£24,080</td><td>£37,778</td></tr>
</table>
</td>
<td>
Janssen ask that the ICERs versus docetaxel + ADT be removed from Table 1, page 17, of the ERG report and Scenario 3 to be revised as follows:
<table>
<tr><th>Model assumption</th><th>Scenario</th><th>ICER vs ADT alone</th><th>ICER vs dox + ADT</th><th>ICER vs ADT alone</th><th>ICER vs dox + ADT</th></tr>
<tr><td colspan="2">Base case</td><td>Loglogistic</td><td></td><td>Weibull</td><td></td></tr>
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<tr><td rowspan="2">3. Proportional downward adjustment of rPFS and OS on ADT alone*</td><td>a) 10% proportional increase in hazards of rPFS and OS in chemo-ineligible</td><td>NC</td><td>NC</td><td>£22,368</td><td>N/A</td></tr>
<tr><td>b) 25% proportional increase in hazards of rPFS and OS in chemo-ineligible</td><td>NC</td><td>NC</td><td>£24,080</td><td>N/A</td></tr>
</table>
</td>
<td>Scenario 3 has been explored by the ERG to test whether chemo-ineligible patients may have a shorter rPFS and OS. However, this scenario is not relevant to the comparison of AAP + ADT vs docetaxel + ADT, since these patients (by default) are eligible for chemotherapy. As such, Janssen believe it is misleading to present ICERs vs</td>
<td>Correction accepted. This was an oversight and not intended. The ERG agree this analysis is irrelevant for to the docetaxel compariso n (see erratum).</td>
</tr>
</table>

		docetaxel + ADT for this scenario analysis.	

Issue 5 Modelled relative treatment effect over time

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state: *"The ERG has assessed the robustness of the findings to alternative assumptions about loss of relative treatment effects*	Janssen ask that the text on page 9 be revised as follows: *"The ERG has assessed the robustness of the findings to alternative assumptions about loss of relative treatment effects over time, by*	Janssen understands the rationale for conducting scenario analysis around the longevity of relative treatment effect; however, we believe that Scenario 4a. (which	Not strictly a factual inaccuracy. The analyses are exploratory. The KM data presented in the submission show rPFS to less

over time, by equalizing the hazards of progression and mortality across treatment arms from five and ten years.“ [page 9]	*equalizing the hazards of progression and mortality across treatment arms at ten years.“* [page 9] And: *“4. Assessing potential impact of relative treatment effect waning, by assuming equal hazards of progression and death across all arms of the model from:* ~~*a. Five years*~~ *b. Ten years”* [page 15] Furthermore, Janssen ask that Scenario 4a. be removed from Table 1, page 17, of the ERG report as it lacks clinically plausibility.	sets the hazards for progression and mortality for AAP + ADT to be the same as ADT alone at 5 years) lacks clinical plausibility. Median follow-up at LATITUDE final analysis was 51.8 months, with some patients followed up for up to 65.2 months, and the Kaplan-Meier curves for both rPFS and OS show no evidence of any convergence. As such, the observed data show it is highly unlikely that the hazards would be equal between treatments at 5 years.	than 5 years and OS data to around five years. What happens beyond that in terms of relative hazards remains uncertain. However, the ERG accept that equalisation of hazards from 5 years may be an overly pessimistic scenario, and have revised the lower timepoint to be 8 years rather than 5 years.

Issue 6 Modelled mCRPC state durations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state: *"The ERG is of the opinion that this alternative approach also has its problems, since it adjusts outs pre-progression mortality from overall mCRPC duration in the current model, and divides this by total life years from TA387, which would be expected to account for pre-progression morality. This approach could serve to over-adjust mCRPC state durations in the current model."* [page 11]	Janssen ask that the text on page 11 be removed as it is mis-leading. ~~*"The ERG is of the opinion that this alternative approach also has its problems, since it adjusts outs pre-progression mortality from overall mCRPC duration in the current model, and divides this by total life years from TA387, which would be expected to account for pre-progression morality. This approach could serve to over-adjust mCRPC state durations in the current model."*~~	Janssen wish to clarify that the life years predicted in TA387 represent the average time patients spend with mCRPC from the point at which they are diagnosed with mCRPC; however, the life years spent with mCRPC predicted by our model represent the average time patients, who initially entered the model with mHSPC, specifically spend in the mCRPC health states. As such, patients with mHSPC who die prior to disease progression are included within these calculations. To ensure the mCRPC life year calculations in the model align with those in TA387, patients who die pre-progression need to be removed from the estimation. To do this, the mCRPC life years are adjusted by the proportion of patients that are assumed to die pre-progression. This approach does not over-adjust the mCRPC state durations as stated by the ERG, but instead ensures that there is consistency between the life year calculations and corrects the base-case approach, which underestimates the mCRPC life years. That said, Janssen note other statements from the ERG regarding the uncertainty that exists around the percentage of patients who	Accepted (see erratum)

		die prior to mCRPC are indeed accurate.	

Issue 7 On-treatment disutility associated with docetaxel

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state: *"..it is worth noting that the recently published economic evaluation of docetaxel + ADT versus ADT based on the whole STAMPEDE population, estimated a smaller utility decrement for docetaxel (0.02) than the one applied in the company model (0.07)(Woods et al., 2018). This was adjusted for age and health state, but not AEs, and lasted for one year. Therefore, the ERG explores the impact of applying a smaller decrement of 0.02."* [page 12-13] Janssen wish to highlight that Woods et al. (2018) reported the utility decrement of docetaxel over a full year, which does not distinguish between on- and off-treatment.	Janssen ask that the ICERs in Table 1, page 17, of the ERG report be revised for Scenario 1 to appropriately reflect the application of the decrement (0.02) for the full year.	The utility decrement of 0.02 estimated from STAMPEDE was applied for one year in the model presented in Woods et al. (2018), however, the ERG has only applied this decrement for 18 weeks in their scenario analysis. As such, this scenario significantly underestimates the true utility decrement applied in the STAMPEDE analysis and thus the impact of docetaxel on patients' HRQL. Of note, our base-case analysis currently applies a decrement of 0.07 over 18 weeks, which is roughly equivalent to a decrement of 0.02 applied over one year in the STAMPEDE analysis.	Point acknowledged. Scenario 2 has been revised and an erratum page 13 has been added to clarify the scenario. Note, the scenario has been updated so that utility for the mHSPC state in the docetaxel arm is 0.02 lower than it is for ADT alone for 1 year.

Issue 8 Minor amendments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 3 – *"Hoyle et al. (2018)"* Page 4 – *"Hoyle et al. (2015)"*	Page 3 – *"Hoyle et al. (2019)"* Page 4 – *"Hoyle et al. (2019)"*	Hoyle et al. (2018) was the original congress presentation of the post-hoc subgroup analysis from STAMPEDE, however the full publication of Hoyle et al. (2019) is now available and was cited within the re-submission dossier.	Corrected and reference list updated.
Page 3 – "ASP + ADT"	Page 3 – "AAP + ADT"	Typo	Does not impair meaning
Page 3 – *"The company refer the Committee's interest…"*	Page 3 – *"The company refer to the Committee's interest..."*	Word(s) missing	Does not impair meaning
Page 4 – *"This analysis showed that AAP + ADT was also associated 46% reduction in the risk of death…"*	Page 4 – *"This analysis showed that AAP + ADT was also associated with a 46% reduction in the risk of death…"*	Word(s) missing	Does not impair meaning
Page 5 – "*…generalisability of the LATIDUE efficacy data to chemo-ineligible patients"*	Page 5 – "*… generalisability of the LATITUDE efficacy data to chemo-ineligible patients"*	Typo	Does not impair meaning

Additional issue identified by the ERG

When checking the numbers in Table 1 of its critique, the ERG identified a minor error in its implementation of scenario 6b, which has also been correct in the erratum. This only changes the corresponding ICERs by a few pounds.