National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Apalutamide for treating metastatic hormone-sensitive prostate cancer [ID1534]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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.

The appraisals of apalutamide for treating metastatic hormone-sensitive prostate cancer [ID1534] and apalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1174] have been combined into a single appraisal with the title apalutamide for treating prostate cancer [ID1534].

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Janssen-Cilag	None	Comment noted. No action required.
	TACKLE Prostate Cancer	YES	Comment noted. No action required.
Timing Issues	Janssen-Cilag	None	Comment noted. No action required.
	TACKLE Prostate Cancer	NO COMMENT	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit	Janssen-Cilag	No comment	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	• Abiraterone is likely to be similar and could be considered as a comparator • Suggest looking specifically into high volume metastatic disease as benefit seems to be greater in that group • Local RT has been seen as carrying survival in low volume metastatic cap and not included • STAMPEDE may Report enzalutamide and abiraterone combination soon, that may be additional competition in next 6 Months.	Comments noted. Abiraterone is included in the list of comparators "subject to ongoing NICE appraisal". Where evidence allows, subgroup analysis of people with high risk disease will be conducted.
	TACKLE Prostate Cancer	NO COMMENT	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Janssen-Cilag	No comment	Comment noted. No action required.
	TACKLE Prostate Cancer	The latest National Prostate Cancer Audit (pub 2019) indicates that 16% of men already had metastatic disease at the time of diagnosis. Although it is not known how many of these men had hormone (ADT) sensitive disease, it highlights a potentially large therapeutic group of patients. Not all men	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		would be suitable (or be willing to undergo) chemotherapy. Alternatives do exist – Abiraterone and Enzalutamide may be used alongside ADT but as yet have NICE approval or marketing authorisation. With increasing early diagnosis of PCa, it is hoped that the number of men presenting with metastatic disease should fall in the future. This should positively reflect on long-term cost issues.	
The technology/ intervention	Janssen-Cilag	None	Comment noted. No action required.
	TACKLE Prostate Cancer	Yes	Comment noted. No action required.
Population	Janssen-Cilag	None	Comment noted. No action required.
	TACKLE Prostate Cancer	Clarification is needed as to exactly which patient group is being discussed. Appendix B raises the question of distinguishing between 'hormone naïve' and 'hormone sensitive' patients. Since it would seem logical that the label 'hormone sensitive' can only be used once ADT had been commenced and the effects monitored, the group of patients in question would be all newly diagnosed patients with metastatic disease who then showed a response to ADT within the 12 week period recommended in the NICE Guideline.	Comments noted. Hormone-sensitive refers to a broader population that includes people with metastatic prostate cancer who are newly diagnosed and hormone naïve or are continuing to respond to androgen deprivation therapy. This information has been added to the background section.

Section	Consultee/ Commentator	Comments [sic]	Action
Comparators	Janssen-Cilag	Docetaxel with androgen deprivation therapy is only commissioned for patients with newly diagnosed metastatic prostate cancer (https://www.england.nhs.uk/wp-content/uploads/2016/01/b15psa-docetaxel-policy-statement.pdf) Abiraterone with prednisone or prednisolone and androgen deprivation therapy is only licensed for use in newly diagnosed, high risk, metastatic prostate cancer.	Comments noted. No action required.
	TACKLE Prostate Cancer	Commenting from the viewpoint of a patient, I have insufficient clinical experience to comment but I believe the comparators are true.	Comment noted. No action required.
Outcomes	Janssen-Cilag	Janssen propose the following outcome measures to capture the most important health benefits for apalutamide: • Overall survival • **Radiographic** progression free survival • **Second progression free survival** • **Time to subsequent therapy** • Prostate specific antigen (PSA) response • Adverse effects of treatment • Health-related quality of life Janssen propose that “response rate” be removed from the list of outcomes as it is not generally used as an outcome measure in advanced prostate cancer as prostate metastases, particularly bone metastases, generally do not show radiological responses to treatment, even though overall the treatment may be working.	Comments noted. The outcome “progression free survival” captures radiographic and second progression free survival and time to subsequent therapy. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	TACKLE Prostate Cancer	The six outcomes stated are reasonable. From the standpoint of a patient all of these are of equal importance. Cost effectiveness is not specifically mentioned in outcomes. To an extent the cost of treatment is of secondary concern to a patient if the outcomes for treatment are considerably improved compared with current treatments used.	Comments noted. No action required.
Economic analysis	Janssen-Cilag	No comment	Comment noted. No action required.
	TACKLE Prostate Cancer	No Comment. See statement in 'Outcomes'	Comment noted. No action required.
Equality and Diversity	Janssen-Cilag	No comment	Comment noted. No action required.
	TACKLE Prostate Cancer	Although not strictly a standard 'equality' issue, patients are always aware that even when NICE Guidelines / Approval are issued, the ultimate decisions on offering treatments are often made at a local CCG level and considerably biased to cost issues. The term 'Postcode Lottery' is still a phrase still too commonly appropriate in some areas of the UK. There is also often a difference in availability of treatments in Scotland /Wales compared with England. This may not exactly be an 'Equality' issue as defined here, but is very important to patients scattered around the country.	Comments noted. No action required.
Innovation	Janssen-Cilag	Currently the only treatment options available to patients with mHSPC are either ADT or docetaxel. Many men are not able to tolerate docetaxel or have comorbidities that	Comments noted. Innovation will be considered by the

Section	Consultee/ Commentator	Comments [sic]	Action
		preclude it as an option. Furthermore, some men do not meet the inclusion criteria to receive docetaxel as set out in NHSE commissioning policy (https://www.england.nhs.uk/wp-content/uploads/2016/01/b15psa-docetaxel-policy-statement.pdf). There is an unmet need for these men. The only treatment option is ADT until patients progress to metastatic castrate resistant prostate cancer (mCRPC). At this point a non-hormonal therapy is an option but at a more progressed disease state with a reduced quality of life and poorer long-term outlook. Apalutamide is an oral medication with a unique mechanism of action, it blocks androgen receptor (AR) activation, prevents nuclear translocation, inhibits deoxyribonucleic acid (DNA) binding and impedes AR-mediated transcription, inducing cancer cell death, leading to tumour regression. It provides an alternative therapy for patients wanting to take their treatment at home. Apalutamide is generally well tolerated and offers patient benefits such as not having to travel to hospital for treatment and not having to undergo intravenous infusions. The benefits of an oral medication that maintains quality of life and allows patients to continue normal life for longer is unlikely to be accounted for in the QALY calculation.	appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	TACKLE Prostate Cancer	It provides another alternative to the combined use of chemotherapy (docetaxel) and hormone therapy (ADT). There are other drugs undergoing a similar appraisal. It would seem inappropriate to exclude apalutamide from this overall process so that all alternatives can be appraised and the best alternative can be judged.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Other considerations	Janssen-Cilag	No comment	Comment noted. No action required.
	TACKLE Prostate Cancer	No Comment	Comment noted. No action required.
Questions for consultation	Janssen-Cilag	Is the population for this appraisal defined appropriately? • NICE understands that 'hormone-naive' refers to people who are about to start (or who have started within the last 12 weeks) androgen deprivation therapy. 'Hormone-sensitive' is a broader population that refers to all people with metastatic prostate cancer who are having androgen deprivation therapy. In which population is apalutamide expected to be used? **Apalutamide is expected to be used in the broader, 'Hormone sensitive' population. That is, all adult men with metastatic prostate cancer who are hormone naïve or are continuing to respond to androgen deprivation therapy**. Have all relevant comparators for apalutamide been included in the scope? • NICE recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases. Would degarelix and apalutamide be used in the same population? **Janssen does not consider degarelix to be an appropriate comparator. It is used in limited circumstances as an alternative to luteinising hormone-releasing hormone analogues (LHRHA) where there may be a risk of spinal cord compression due to the location of bone metastases.**	Comments noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Have all relevant comparators for apalutamide been included in the scope? Which treatments are considered to be established clinical practice in the NHS for metastatic hormone-sensitive prostate cancer?' **Yes, Androgen deprivation therapy is an appropriate comparator** **Yes, Docetaxel with ADT is an appropriate comparator for patients that meet the inclusion criteria in NHSE commissioning policy** **Abiraterone with prednisone or prednisolone and androgen deprivation therapy is undergoing appraisal by NICE. It is also only licensed in a subset of the population (that is, newly diagnosed, high risk mHSPC patients).**	Comments noted. No action required.
		Are the outcomes listed appropriate? **Janssen has provided more detail on outcomes in the comments above**	Comment noted. Please see above.
		Are there any subgroups of people in whom apalutamide is expected to be more clinically effective and cost effective or other groups that should be examined separately? **There are no groups within the treatment population under consideration that should be considered separately.**	Comment noted. Subgroups of high-risk and newly diagnosed prostate cancer have been added.
		Where do you consider apalutamide will fit into the existing NICE pathway,	

Section	Consultee/ Commentator	Comments [sic]	Action
		Prostate cancer? **Apalutamide is relevant either for newly diagnosed mHSPC patients or for mHSPC patients who became metastatic after experiencing biochemical recurrence following treatment for localised or locally advanced prostate cancer.** 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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which apalutamide will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. 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. **No comment** Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. **No comment**	Comment noted. No action required. Comment noted. No action required. Comment noted. No

Section	Consultee/ Commentator	Comments [sic]	Action
			action required.
		Do you consider apalutamide to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? **Yes, see innovation comments above.**	Comment noted. Please see above.
		Do you consider that the use of apalutamide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? **Yes, the benefit of maintaining normal life is unlikely to be captured in the QALY calculation**	Comments noted. No action required.
		Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. **No comment**	Comment noted. No action required.
		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. **No**	Comments noted. No action required.
		NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at	

Section	Consultee/ Commentator	Comments [sic]	Action
		http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). **Janssen considers the STA process to be appropriate to appraise apalutamide.** NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. • Would it be appropriate to use the cost comparison methodology for this topic? **No, the efficacy of apalutamide is likely to differ from the standard of care (ADT)** • Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? **No, the efficacy of apalutamide is likely to differ from the standard of care (ADT)** • Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? **Yes** • Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?	Comment noted. No action required. Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Yes, the STAMPEDE trial	
	TACKLE Prostate Cancer	No extra comment at this stage	Comment noted. No action required.
Additional comments on the draft scope	TACKLE Prostate Cancer	No comment	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Ipsen Ltd

National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Apalutamide for treating non-metastatic, hormone-relapsed prostate cancer [ID1174]

Response to consultee and commentator comments on the draft remit and draft scope

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The appraisals of apalutamide for treating metastatic hormone-sensitive prostate cancer [ID1534] and apalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1174] have been combined into a single appraisal with the title apalutamide for treating prostate cancer [ID1534].

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	No. Janssen suggests the wording of the remit should reflect the anticipated license as follows: To appraise the clinical and cost effectiveness of apalutamide within its marketing authorisation for treating adult men with non-metastatic castration-resistant prostate cancer who are at a high risk of developing metastatic disease.	Comment noted. The remit has been left broad to ensure that if apalutamide receives a marketing authorisation in the UK for this indication, the appraisal

Section	Consultee/ Commentator	Comments [sic]	Action
			covers the whole licensed population. As detailed in the scope, the term 'hormone relapsed prostate cancer' is preferred.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
	Prostate Cancer UK	Our understanding is that apalutamide is being considered for the treatment of non-metastatic hormone-relapsed prostate cancer, not localised hormone-relapsed prostate cancer. Non-metastatic prostate cancer includes locally advanced prostate cancer which has spread to the lymph nodes in the pelvic region (N1 vs. N0). It is likely that the license will also only apply to 'high-risk' non-metastatic hormone-relapsed prostate cancer. 'High risk' is defined in the SPARTAN trial a PSA doubling time of less than 10 months for men receiving hormone therapy.	Comments noted. 'Localised' has been removed from the text. The scope has been left broad to ensure that the appraisal covers the population in the marketing authorisation.
Timing Issues	Astellas Pharma	No Comment	Comment noted. No action required.
	Bayer	There are currently no licensed treatments for this stage of prostate cancer but three treatments (apalutamide, enzalutamide and darolutamide) are likely to be licensed within the next two years.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website:

Section	Consultee/ Commentator	Comments [sic]	Action
			https://www.nice.org.uk/guidance/indevelopment/gid-ta10377. No action required.
	Janssen-Cilag	There is no licensed medication in this disease setting despite the known risk of rapid progression to metastasis which impacts patients significantly. There is therefore an unmet need.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10377. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
	Prostate Cancer UK	Men with localised and locally advanced prostate cancer, whose PSA levels indicate that they are no longer hormone sensitive will, if no visible metastases are identified have no treatment options available to them. They must wait, receiving periodic scans, to determine whether their prostate cancer has metastasised before any further treatment options are open to them. Current imaging used to diagnose advanced prostate cancer is limited in its ability to detect metastases. This means that men can be left in limbo without access to treatment and the potential to gain additional months of life from the treatments available for castrate-resistant metastatic prostate cancer. Apalutamide gives these men the opportunity to access a treatment that can delay progression. Further research is needed to determine	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10377. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		whether, for those men with undetected metastases, this treatment could also provide clinical benefit.	
Additional comments on the draft remit	Bayer	No comments.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	The epidemiology data in this section relates to a population with non-metastatic prostate cancer; whereas apalutamide will be indicted for a smaller subgroup of this population namely adult men with non-metastatic castration-resistant prostate cancer who are at a high risk of developing metastatic disease. Clarifications included in bold below 3rd paragraph: Hormone-relapsed prostate cancer is diagnosed by rising prostate-specific antigen levels **despite treatment with ADT or orchidectomy**. 5th paragraph: stopping hormone therapy completely would increase	Comments noted. This section of the scope aims to provide a brief overview of the background for the appraisal. The text has been amended as suggested.

Section	Consultee/ Commentator	Comments [sic]	Action
		testosterone levels and **decrease** the likely time to metastatic disease	
	NCRI-ACP-RCP-RCR	Satisfactory	Comment noted. No action required.
	Prostate Cancer UK	In the UK, men with hormone sensitive intermediate or high risk non-metastatic prostate cancer should not be offered hormone therapy alone. These men will be offered radical treatment and will only receive hormone therapy alone if they are unable to receive radical treatment. However, it is correct that men will become castrate-resistant after taking hormone therapy.	Comments noted. This information has been included in the background section.
The technology/ intervention	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	The description of the technology is accurate. Janssen suggests the following wording in line with the anticipated license: Apalutamide does not currently have a marketing authorisation in the UK for the treatment of high-risk non-metastatic castration-resistant prostate cancer.	The wording in this section is aligned with the remit for consistency. Please see the response above relating to the wording of the remit.
	NCRI-ACP-RCP-RCR	Yes	Comment noted. No action required.
	Prostate Cancer	Yes	Comment noted. No

Section	Consultee/ Commentator	Comments [sic]	Action
	UK		action required.
Population	Astellas Pharma	Patients for inclusion to the pivotal phase 3 study for apalutamide (SPARTAN)* were classified as 'high-risk' defined in terms of PSA doubling time and Astellas Pharma Ltd would recommend that the appraised population reflects this. *Ref. Mathew R. Smith et al. Apalutamide Treatment and Metastasis-free Survival in prostate cancer. N Engl J med 2018;378:1408-18	The scope has been left broad to ensure that the appraisal covers the population in the marketing authorisation.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	The words 'localised' and 'non-metastatic' are used interchangeably in the draft scope. Localised disease tends to refer to an earlier stage in the prostate cancer pathway than the indication under review. Janssen proposes use of non-metastatic for consistency, and in line with other NICE technology appraisals in this disease setting. As noted in the background section, the words 'hormone-relapsed' and 'castration-resistant' are also used interchangeably in the literature. Janssen proposes the use of castration-resistant for consistency with the anticipated license. The population under consideration is: Adult men with non-metastatic castration-resistant prostate cancer who are at a high risk of developing metastatic disease. There are no groups within this population that should be considered separately.	Comments noted. 'Localised' has been removed and 'non-metastatic' has been added to the description. As detailed in the scope, the term 'hormone relapsed prostate cancer' is preferred.

Section	Consultee/ Commentator	Comments [sic]	Action
	NCRI-ACP-RCP-RCR	Yes: Typographical error – adults with non-metastatic hormone (sensitive? Missing) relapsed localised prostate cancer Within the population consideration to histology (adenocarcinoma) and how aggressively prostate cancer is (in studies, PSA doubling time used)	Comments noted. 'Hormone-relapsed' refers to prostate cancer that no longer responds to hormone therapy. Our understanding is that most prostate cancers are adenocarcinomas so it is not clear that a subgroup based on histology would add value. PSA doubling time in less than 10 months is defined as 'high risk' in the trial and so is likely to already be accounted for in the evidence. No action required.
	Prostate Cancer UK	It will primarily be men who are non-metastatic castrate-resistant who receive this treatment. This includes men with locally advanced disease which has spread to lymph nodes in the pelvic region. To avoid confusion the word 'localised' should be removed. More advanced imaging modalities give increased diagnostic scanning accuracy. It is possible that the men in this indication already have	Comments noted. 'Localised' has been removed from the description.

Section	Consultee/ Commentator	Comments [sic]	Action
		advanced prostate cancer, but current imaging techniques are unable to identify metastases.	
Comparators	Astellas Pharma	We agree that enzalutamide plus ADT would be an appropriate comparator for apalutamide plus ADT in this population (subject to ongoing NICE appraisal).	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	Androgen deprivation therapy is the standard treatment currently used in the NHS. Enzalutamide is currently unlicensed in the UK for this indication and is scheduled for appraisal by NICE. As such it cannot currently be considered a standard or alternative treatment in the NHS and is therefore not a relevant comparator for this appraisal.	Comments noted. To ensure the timeliness of the scope in the event of any possible scenarios such as delays in the submission, the scope has been kept broad and comparators in relevant appraisals have been included "(subject to ongoing NICE appraisal)". No action required.
	NCRI-ACP-RCP-RCR	Yes Currently (UK) patients are treated with androgen deprivation (usually injectable LHRH analogue) MRC STAMPEDE study has recruited patients with N0M0 disease and is due to report results "soon." Arm J included adding abiraterone and	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		enzalutamide	
	Prostate Cancer UK	Enzalutamide is not currently used in the NHS in this indication, as the parenthesis explain Once radical treatment options have been exhausted or ruled out and the man has become castrate-resistant, there are no further treatment options for men until the prostate cancer metastasises elsewhere in the body. Patients are left in limbo, periodically receiving bone scans to determine whether the cancer has metastasised. Once the cancer progresses, treatment options for metastatic prostate cancer will be available to these patients.	Comments noted. No action required.
Outcomes	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	Janssen propose the following outcome measures to capture the most important health benefits of apalutamide: • Metastasis Free Survival • Overall Survival • Second Progression Free Survival • Progression Free Survival • Time to Symptomatic Progression • Time to Metastasis • Health-related quality of life measures	Comments noted. 'Time to PSA progression' has been added to the scope. The remaining measures are covered in the outcomes included in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		• PSA response • Time to PSA progression	
	NCRI-ACP-RCP-RCR	Yes	Comment noted. No action required.
	Prostate Cancer UK	The key outcome measure will be metastases free survival. Given the early stage of this cancer, overall survival data has yet to mature and will take a long time to do so. Research finds metastases free survival to be a strong surrogate of overall survival in prostate cancer (http://ascopubs.org/doi/10.1200/JCO.2017.73.9987). Metastases free survival is particularly important at this stage of the disease. Non-metastatic disease is largely unsymptomatic and delaying progression will delay the point at which men will start suffering with the symptoms of advanced prostate cancer.	Comments noted. No action required.
Economic analysis	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	A cost-utility analysis incorporating a lifetime horizon is appropriate to reflect the differences in outcomes and costs between apalutamide and ADT. The cost-utility analyses will reflect the current NHS management of patients with non-metastatic castration-resistant prostate cancer and will also include current treatments received when the disease progresses to metastatic castration-resistant prostate cancer.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		NICE has made recommendations for treatment of metastatic castration-resistant prostate cancer therefore the cost-utility analyses will reflect this guidance when defining the prostate cancer treatment pathway.	
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
	Prostate Cancer UK	Yes	Comment noted. No action required.
Equality and Diversity	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	There are no known equality issues.	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No changes suggested	Comment noted. No action required.
	Prostate Cancer UK	N/A	Comment noted. No action required.
Innovation	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	There are currently no licensed treatments for this stage of prostate cancer but three treatments (apalutamide, enzalutamide and darolutamide) are	Comments noted. The appraisal committee will discuss the potentially

Section	Consultee/ Commentator	Comments [sic]	Action
		likely to be licensed within the next two years.	innovative nature of this technology. No action required.
	Janssen-Cilag	There is an unmet need in the treatment of adult men with non-metastatic castration-resistant prostate cancer as there are currently no licensed medications available that have been demonstrated to impact survival. Current NHS clinical management involves ADT, however a subset of patients become resistant to ADT and are at a higher risk of developing metastases as indicated by rising prostate specific antigen (PSA) levels. Metastatic disease is a turning point in the prostate cancer pathway, associated with impactful symptoms and high mortality. There is therefore a need for innovative treatments that delay or prevent the progression to metastatic disease whilst minimising any adverse impact on patient's quality of life. Apalutamide is a once-daily, orally administered treatment with no routine monitoring requirements. It selectively blocks the receptor responsible for the growth of prostate cancer cells and thereby has an immediate, meaningful and durable impact on PSA levels. This impact results in a significant improvement in the time to develop metastases when compared to ADT alone (Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. The New England Journal Of Medicine. 2018).	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	NCRI-ACP-RCP-RCR	Yes Delay in progression/ metastasis and subsequent treatment for men with	Comments noted. The appraisal committee will

Section	Consultee/ Commentator	Comments [sic]	Action
		prostate cancer could be a step change delaying or avoiding treatment for metastatic disease. Published data on the phase 3 study are available (NEJM)	discuss the potentially innovative nature of this technology. No action required.
	Prostate Cancer UK	The technology is innovative because it delivers to an unmet need. The QALY calculation does not include the reduction in anxiety that men will experience from being able to take an active treatment rather than waiting for their cancer to progress to metastatic prostate cancer before further treatment options become available to them. Cryotherapy should not be considered as related NICE interventional procedures guidance since cryotherapy and HIFU are only available in clinical trial settings. Evidence for the efficacy of the other interventional procedures is in the hormone sensitive rather than castrate resistant setting and so will not be relevant here.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
Other considerations	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Prostate Cancer UK	The extent to which delays to cancer progression deliver an improved quality of life – comparing the quality of life among men with castrate-resistant localised and locally advanced prostate cancer to the quality of life experienced by men with castrate-resistant metastatic prostate cancer	Comments noted. No action required.
Questions for	Astellas Pharma	No comment	Comment noted. No

Section	Consultee/ Commentator	Comments [sic]	Action
consultation			action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	Have all relevant comparators for apalutamide been included in the scope? **Yes, androgen deprivation therapy is an appropriate comparator.** **Enzalutamide is currently unlicensed in the UK for this indication and is scheduled for appraisal by NICE. As such it cannot currently be considered a standard or alternative treatment in the NHS and is therefore not a relevant comparator for this appraisal.**	Comments noted. To ensure the timeliness of the scope in the event of any possible scenarios such as delays in the submission, the scope has been kept broad and comparators in relevant appraisals have been included "(subject to ongoing NICE appraisal)". No action required.
		Which treatments are considered to be established clinical practice in the NHS for non-metastatic, hormone-relapsed prostate cancer? **Androgen deprivation therapy**	Comment noted. No action required.
		Are radical prostatectomy or radical radiotherapy relevant comparators? **No, radical prostatectomy or radical radiotherapy are treatment options for localised prostate cancer. The indication under review is at a later time in the non-metastatic pathway and refers to a population that already received treatment including radical therapy.**	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are the outcomes listed appropriate? **Janssen has provided more detail on outcomes in the comments above.** Are there any subgroups of people in whom apalutamide is expected to be more clinically effective and cost effective or other groups that should be examined separately? **There are no groups within the treatment population under consideration that should be considered separately.** Where do you consider apalutamide will fit into the existing NICE pathway, Prostate cancer? **Apalutamide is relevant after patients have had a biochemical recurrence following treatment for localised or locally advanced prostate cancer.** 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 proposed remit and scope may need changing in order to meet these aims. In particular, please, tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which apalutamide will be licensed; • could lead to recommendations that have a different impact on people	Please see relevant section. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		protected by the equality legislation than on the wider population, e.g. 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. **No comment** Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. **No comment** Do you consider apalutamide to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? **Yes, see innovation comments above.** Do you consider that the use of apalutamide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? **No** Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.	Comment noted. No action required. Please see relevant section. Comment noted. No action required.

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		No comment To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. **No** NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). **Janssen considers the STA process to be appropriate to appraise apalutamide.** NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. • Would it be appropriate to use the cost comparison methodology for this topic? **No, the efficacy of apalutamide differs to the standard of care (ADT)**	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? **No, the efficacy of apalutamide differs to the standard of care (ADT)** • Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? **Yes** • Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? **No**	
	NCRI-ACP-RCP-RCR	To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly Yes: Currently patients may be managed by urology, oncology or primary care.	Comments noted. No action required.
	Prostate Cancer UK	**Which treatments are considered to be established clinical practice in the NHS for non-metastatic, hormone-relapsed prostate cancer?** Currently, men who are castrate resistant but with no visible metastases have no treatment options. They must wait for their cancer to metastasise,	Comments noted. No action required.

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		receiving periodic tests to diagnose metastasis, before treatment options become available to them. These men will have exhausted or ruled out radical treatment options including radical prostatectomy, radiotherapy and brachytherapy. These men and their carers will experience anxiety at the lack of treatment options, particularly if the man's PSA is rising rapidly. **Is radical prostatectomy a relevant comparator?** Unless radical treatment is ruled out, apalutamide should be taken following, not instead of, radical treatment including prostatectomy. As there is potential for prostate cancer to have disseminated, we do not believe that radical prostatectomy is a relevant comparator to apalutamide. **Are there any subgroups of people for whom apalutamide is expected to be more clinically effective and cost effective?** As the clinical trial for apalutamide (SPARTAN) and the licence will likely reflect, this treatment will be more effective in patients that the trial defines as having 'high risk' non-metastatic castrate-resistant prostate cancer. High risk is defined as a prostate-specific antigen doubling time of 10 months or less during continuous androgen-deprivation therapy. Further analysis of the data from the SPARTAN trial may find stratified patient groups are more or less likely to benefit from the treatment. Patients in the SPARTAN trial were stratified according to PSA doubling time (>6 months vs. <6 months), use of bone sparing agents, classification of local or regional nodal disease (N0 vs. N1) at the time of trial entry, and previous prostate cancer treatment (radical treatment, Gondotropin or antiandrogen).	Comments noted. No action required. Comments noted. Subgroups have not been defined in the scope but the company can choose to submit evidence for specific subgroups. No action required.

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		Where will apalutamide fit into the existing NICE pathway This will fit into high-risk localised or locally advanced prostate cancer once men become castrate-resistant and after hormone therapy and /or radical prostatectomy or radical radiotherapy has been performed or considered. **Barriers to adoption** Administration of this treatment is simple, there should not be any barriers to adoption of this technology in practice.	Comments noted. No action required. Comments noted. No action required.
Additional comments on the draft scope	Astellas Pharma	Astellas Pharma Ltd considers it would not be appropriate to use the cost comparison methodology for this topic. Astellas Pharma Ltd considers a cost-utility approach more appropriate for this appraisal as this methodology allows for a better assessment of uncertainty regarding the expected costs and effects of the use of apalutamide in clinical practice.	Comments noted. No action required.
	Bayer	No further comments.	Comment noted. No action required.
	Janssen-Cilag	As noted in the background of the scope, patients with non-metastatic castration-resistant are monitored for evidence of disease metastases, at which point other treatments are considered. In recent years, NICE approved several treatments for metastatic castration-resistant disease (eg.,TA387, TA377, TA259). In order to model the disease pathway accurately over a lifetime horizon for the economic analysis, Janssen will compare the use of apalutamide versus ADT in the non-metastatic castration-resistant setting followed by the NICE	Comments noted. No action required.

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		approved treatments for metastatic castration-resistant disease.	
	NCRI-ACP-RCP-RCR	Advances in imaging / other technology for improved staging (ie better diagnosis of men with metastatic disease not currently detected by current CT and nuclear medicine bone scans) are likely to be developed/ enter practice in the near future.	Comments noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health and Social Care
Ipsen Ltd