CASE AUTH/3592/12/21 *NO BREACH OF THE CODE*

BAYER v JANSSEN

Promotional material for Erleada (apalutamide)

CASE SUMMARY

This inter-company dialogue case was in relation to a promotional on-demand video recording for Erleada (apalutamide) tablets.

The Panel ruled no breach of the following Clause(s) of the 2021 Code in relation to the Erleada video, on the basis that it did not consider that:

> **Bayer had established that Janssen had promoted apalutamide off licence; nor on the evidence before it that Bayer had established that Janssen had limited the discussion to selected adverse events (AEs); nor that the narrative of the speaker in relation to the frequency of capturing adverse events was purely speculative and incapable of substantiation or that because the ARAMIS trial protocol stipulated that all AEs experienced during the trial could be reported at any time point by the subjects that the speaker's narrative in relation to the frequency of capturing adverse was factually inaccurate ; nor that in the particular circumstances of this case, the presentation of the adverse events of the three trials side-by-side was a misleading comparison and disparaged another pharmaceutical company's product.**

No Breach of Clause 11.2	**Requirement not to promote a medicine for an unlicensed indication**
No Breach of Clause 6.1	**Requirement that claims must not be misleading**
No Breach of Clause 6.2	**Requirement that claims must be capable of substantiation**
No Breach of Clause 6.3	**Requirement that all artwork must conform to the letter and spirt of the Code**
No Breach of Clause 6.4	**Requirement that claims must reflect the available evidence regarding possible adverse reactions**
No Breach of Clause 6.6	**Requirement that another company's medicines must not be disparaged**
No Breach of Clause 14.1	**Requirement that misleading comparisons must not be made**
No Breach of Clause 5.1	**Requirement to maintain high standards**
No Breach of Clause 2	**Requirement that activities or material must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**

This summary is not intended to be read in isolation.

For full details, please see the full case report below.

FULL CASE REPORT

Bayer plc complained about a promotional on-demand video recording for Erleada (apalutamide) tablets entitled *'Castration-resistant prostate cancer: The evidence supporting the benefits of earlier treatment'* (CP-277649, November 2021) presented by a named presenter and currently hosted on the Janssen UK Medical Cloud.

BAYER'S INITIAL COMMENTS

Bayer alleged that the video included several factual inaccuracies and disparaging cross-trial comparisons that it requested Janssen addressed through inter-company dialogue which had been ongoing since 14 October 2021. The 29-minute recording, which was aimed at a UK audience, appeared to have been presented as part of a live promotional webinar held on 26 April 2021 and could be accessed via thejanssenmedicalcloud.co.uk website.

Bayer submitted that the initial inter-company dialogue centred around five areas of which two had been resolved. Bayer had unfortunately been unable to reach an agreement with Janssen on three of the critical issues in relation to the Janssen promotional recording in question. Bayer was disappointed that an agreement could not be reached with Janssen through inter-company dialogue alone and informed Janssen that the complaint had now been escalated to the PMCPA for review.

In its complaint, Bayer addressed the issues that were still outstanding in the order that they appeared within Janssen's promotional video and highlighted the clauses of the 2021 Code that Bayer believed had been breached.

Bayer provided all inter-company dialogue documentation between it and Janssen in relation to this complaint.

JANSSEN'S INITIAL COMMENTS

Janssen acknowledged that the inter-company dialogue centred on five areas, two of which had been resolved. Janssen was disappointed that Bayer did not provide a written response to its last letter of 25 November before referral to the PMCPA, thus preventing an agreement being achieved through inter-company dialogue alone. Bayer had also failed to provide a critical reference to support point (1) of claim (3) (highlighted below) further impeding inter-company discussion and progress around this topic.

Janssen did not agree that the item breached the Code and responded to the three unresolved areas referenced by Bayer in its letter of complaint.

1 The promotion of Apalutamide in the micro-metastatic state of castration-resistant prostate cancer (CRPC) and therefore off-licence promotion

COMPLAINT

Bayer stated that at approximately 7.50 minutes of the presentation, named presenter referred to the three second-generation androgen receptor inhibitor (ARI) pivotal phase III trials, namely

SPARTAN, PROSPER and ARAMIS, and categorised the patient populations treated with apalutamide, enzalutamide and darolutamide respectively as being in the micro-metastatic state of CRPC. By using this terminology, Janssen was implying that it was permissible and within licence to treat patients with apalutamide if metastases were present on any imaging modality in the CRPC setting. By definition, if a patient was diagnosed with metastases by any imaging modality, they had metastatic disease and therefore were not suitable for either apalutamide or darolutamide. Apalutamide did not currently have a licence within the metastatic CRPC setting. This was therefore off-licence promotion of apalutamide in breach of Clause 11.2.

In relation to off-licence promotion, Bayer noted that in its response Janssen stated:

> *'[N*amed presenter*] is asserting that the patients enrolled into the 3 different pivotal registration studies for patients with nmCRPC were likely to be in the micro-metastatic state for although the key exclusion criterium for each study was the presence of metastases (as detected by conventional radiology), the key inclusion criterium was a PSADT of <10 months. Such a rapid doubling time in PSA value would indicate the presence of undetectable microscopic collections of tumour cells as borne out by the median time for the development of metastases (again as detected by conventional imaging) being in the region of 11 months for all three medicines. The licensed indication for the three nmCRPC indications reflects the clinical state of this patient population, with the wording being "in adult men who are at high risk of developing metastases.'*

Bayer noted that Janssen had rightly pointed out in its response, the key exclusion criterium for all three pivotal studies in non-metastatic castration-resistant prostate cancer (nmCRPC) was the presence of metastases as detected by conventional imaging, and therefore queried how, Janssen was able to justify the assertion that a rapid doubling time in prostate-specific antigen (PSA) values would indicate the presence *'of undetectable microscopic collections of tumour cells'* when it was possible to detect these on novel imaging as the data suggested that 55% (Fendler *et al*, Clin Cancer Res; 25(24) December 15, 2019) of patients had distant metastasis on PMSA-PET imaging despite negative findings on conventional imaging? Detection of metastasis on any imaging modality equated to a metastatic state and was therefore not within licence as the licence clearly stated:

> 'Erleada is indicated:
>
> - in adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease (see section 5.1).'

Bayer submitted that based on the indication pharmaceutical companies referred to the trial design and data of its products to support its messaging. However, to dismiss findings on an established and widely-used imaging modality to increase the patient population eligible to receive treatments promoted, needed to be questioned.

Bayer had been unable to reach an agreement with Janssen on this point and upheld its view that detection of metastasis on any imaging modality equated to a metastatic state and therefore was not within licence.

Bayer requested that the off-licence promotion of apalutamide within this section of the presentation be removed as highlighted above and that the PMCPA considered a breach of Clause 11.2.

RESPONSE

Janssen submitted that apalutamide was indicated in adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who were at high risk of developing metastatic disease.

The presentation in question made it clear that metastasis in nmCRPC was defined based on conventional imaging.

It was in health professionals' interests to learn from experts what the key drivers were for this disease and its physiological progression triggers.

In oncology, nmCRPC was defined by the absence of visible lesions (cell aggregates) on conventional imaging (Smith *et al*; Fizazi *et al*, Hussain *et al*).

Oncologists, on occasion, might use additional, non-conventional imaging methods (eg PSMA PET scanning) at their discretion. These imaging methods, however, were not used to inform treatment outcomes in nmCRPC as:

a) They could give false positives (eg they detect normal/healthy tissue and cells which were not metastatic) (Hofman *et al*, Gualberto *et al*, Sasikumar *et al*).
b) They were yet not validated in any clinical trials in the nmCRPC setting (Sundahl *et al*).
c) They are still largely used in an experimental setting (Hofman *et al,* Sundahl *et al,* Hyvakka *et al*).

With regard to the complaint, firstly, Bayer made the assertion *that 'by definition, if a patient is diagnosed with metastases by <u>any</u> imaging modality, they have metastatic disease and therefore not suitable for either apalutamide or darolutamide'*. No supporting reference was provided to substantiate this claim.

As stated in Janssen's previous response of 25 November to Bayer, the key patient exclusion criterium for all three pivotal studies for apalutamide, darolutamide and enzalutamide in nmCRPC was the presence of metastases **<u>as detected by conventional imaging</u>**, and the marketing authorisations for all three products in high risk nmCRPC were granted on this basis (Smith MR *et al.* Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med* 2018;378:1408–18; Fizazi K *et al.* Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2019;380:1235–46 and Hussain M *et al.* Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2018;378:2465–74). All three registrational trials identified nmCRPC patients by an increasing PSA concentration and no distant metastases on **<u>conventional imaging</u>**.

This was fully aligned with Bayer's published position as in the publication for the ARAMIS study, the pivotal registration for darolutamide in the nmCRPC indication. [Named Professor] and the ARAMIS study investigators (who were supported and funded by Bayer and Bayer Berlin) defined nmCRPC as follows:

> *'Nonmetastatic, castration-resistant prostate cancer is defined by rising levels of serum prostate-specific antigen (PSA) and an absence of detectable metastases* ***on conventional imaging*** *in patients receiving androgen-deprivation therapy. Patients with nonmetastatic, castration-resistant prostate cancer are at risk for progression to metastatic disease.'* (Fizazi K *et al.* Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2019;380:1235–46).

This paper was published in September 2020 and since this time the definition of nmCRPC had not changed, so Bayer's assertion that patients should be classified according to the results seen on novel imaging techniques was incorrect and was also not in line with standard UK Practice, as defined by *NICE Guideline 131: Prostate Cancer: Diagnosis and Management*, which was based on conventional imaging.

Janssen noted that at 7.12 the named presenter stated: *'but I think one of the biggest... evidence is coming from the non-metastatic CRPC setting, and this we need to clarify, is on conventional imaging'.* The title of the accompanying slide which was shown at the same time had written on at the top *'Non metastatic CRPC: on conventional imaging'.* At 7.45, the named presenter described nmCRPC *'as going a step backwards in the micrometastatic state of CRPC'*, therefore clearly distinct from metastatic castrate resistant prostate cancer (mCRPC), and the two different disease states were shown on slides 4 and 5, with the latter also showing which medicines were licensed for use in mCRPC, with apalutamide not being one of them.

Janssen noted that secondly, Bayer questioned how Janssen was able to '*justify the assertion that a rapid doubling time in PSA values would indicate the presence of "undetectable microscopic collections of tumour cells" when we are able to detect these on novel imaging as the data suggest that 55% of patients have distant metastasis on PSMA-PET imaging despite negative findings on conventional imaging'* (Gualberto R *et al*. Schwannoma: A rare cause of false-positive 68Ga-PSMA PET/CT uptake in the evaluation of metastatic prostate cancer. *Urology Case Reports.* 2022; 41: 101974). As Bayer pointed out in its letter of 11 November, *'we, as a pharmaceutical community, need to ensure we provide the clinical community with balanced and unambiguous information to allow the individual healthcare professional to make informed decisions about patient care'*. With this in mind, the presentation highlighted that recent data on novel next generation imaging modalities indicated that it was likely that the nmCRPC patient population in the three clinical trials discussed had micro metastatic disease on entry to the trials despite the absence of metastases on conventional imaging (Fendler *et al* 2019). Janssen believed that as companies, it had an ethical responsibility to highlight this to treating physicians and the medical community. Janssen noted that the author also stated in this very publication that '*Prostate-specific membrane antigen ligand positron emission tomography (PSMA-PET) detects prostate cancer with superior sensitivity to conventional imaging, but its performance in nmCRPC remains largely unknown'* (Fendler *et al*. Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res* 2019; 25(24): 7448-7454).

Janssen noted that thirdly, Bayer asserted that *'Detection of metastasis on any imaging modality equates to a metastatic state'* without any substantiating references. This statement was at odds with clinical guidelines and each of the three companies' studies.

The phase three trial outcomes leading to the market authorisations of apalutamide, darolutamide and enzalutamide remained valid based only on the entry criteria of conventional

imaging, and the use of the products under licence likewise should therefore only be based on conventional imaging. The role of positron emission tomography (PET), such as prostate specific membrane antigen (PSMA)-PET remained unclear, as no pivotal phase 3 prospective randomised clinical trials had been published in which they had been used to inform treatment decisions. Janssen submitted that it should not therefore exclude patients from receiving potential benefits from licensed products using novel next generation imaging modalities that redefined the populations that were used within the clinical trials on which the marketing authorisations were based. Three sets of guidelines from European Society for Medical Oncology (ESMO) (2020), European Association of Urology (EAU) (2021) and American Society of Clinical Oncology (ASCO) (2019) supported this view:

> ESMO guidelines (2020) stated (Parker C *et al*. Prostate cancer: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020; 31(9): 1119-1134): '*Whole-body MRI, choline-positron emission tomography-computed tomography (PET-CT) and prostate-specific membrane antigen (PSMA)-PET-CT have better sensitivity and specificity than CT or bone scan but have not been shown to improve clinical outcomes. The evidence regarding PET and whole-body MRI in this setting is not adequate to make a recommendation concerning their use'.*
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> EAU guidelines (2021) stated (Mottet, N., *et al*. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer – 2021 update. Part 6: Treatment. *Eur Urol*, 2021): '*With more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more patients are diagnosed with early mCRPC. It remains unclear if the use of PSMA PET/CT in this setting improves outcome'.*
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> ASCO guidelines (2019) stated (American Society of Clinical Oncology (2019). Optimum imaging strategies for advanced prostate cancer: *ASCO Guideline*. https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/2019-Optimum-Imaging-Prostate-Summary-Table.pdf): '*For men with nonmetastatic castration-resistant prostate cancer (CRPC), NGI [Next Generation Imaging] can be offered only if a change in the clinical care is contemplated. Assuming patients have received or are ineligible for local salvage treatment options, NGI may clarify the presence or absence of metastatic disease, but the data on detection capabilities of NGI in this setting and impact on management are limited'.*

Janssen submitted that it did not advocate or support the use of apalutamide in metastatic prostate cancer diagnosed as defined by conventional imaging. Janssen did advocate and support that 'we, as a pharmaceutical community, need to ensure we provide the clinical community with balanced and unambiguous information to allow the individual healthcare professional to make informed decisions about patient care'. This was what the named presenter was doing in this presentation by voicing the established view that nmCRPC was likely to be associated with micro-metastatic disease (not detectable by conventional imaging), and that the use of any novel or next-generation imaging modalities rather than the conventional imaging used in the three clinical trials was not yet supported by randomised clinical data, a view also supported by the three recognised recent European and American guidelines.

In addition, as Janssen noted in its second response to Bayer; Bayer appeared to share Janssen's view as they clearly supported and illustrated the prostate cancer community's view both in their definition of nmCRPC and what constituted conventional imaging in its own promotional materials:

a) ‘Bayer European Prostate Cancer Preceptorship, PP-NUB-GB-0134’,

At 4.19 on a slide titled ‘Definition of MO CRPR (nmCRPC) it stated, *inter alia*, no detectable metastasis on conventional imaging (CT scan, MRI or bone scan).

At 9:38 on a slide titled ‘In the clinic: Identifying men with nmCRPC it stated, *inter alia*, conventional imaging bone scan and CT scan, no metastasis.

b) In a separate meeting (PP-NUB-GB-0322, July 2021), Bayer again used the definition of nmCRPC as adopted by Janssen and pointed out that next-generation imaging should not be used. The slide titled ‘Imaging modalities in patients with nmCRPC’, it stated ‘Various imaging techniques are used to stage prostate cancer and detect metastasis andtumour recurrence. However, the definition of nmCRPC is traditionally based on conventional imaging rather than next-generation imaging. The ARAMIS, PROSPER and SPARTAN trials used conventional imaging (bone scan, CT and MRI) to determine diagnosis of nmCRPC. Subsequent approvals of second generation ARIs in nmCRPC were based on these studies and their use of conventional imaging. The UK Blueteq criteria only specifies the use of conventional imaging in the diagnosis and monitoring of patients with nmCRPC. The potential role of more sensitive imaging modalities, including PSMA-PET, is unclear as there are currently no longitudinal studies investigating clinical outcomes in patients with nmCRPC’.

In additional material, as Janssen also noted in its second response to Bayer, Bayer clearly supported and illustrated the prostate cancer community’s view on the inappropriateness of the use of novel new generation imaging that had not been clinically validated in nmCRPC in other examples of its own promotional materials:

a) PP-NUB-GB-0316, July 2021

i) At 22.35 a named Professor provided the definition of nmCRPC as per EAU targeting UK health professionals: ‘*So, for all castrate-resistant prostate cancer, because it’s what we have data on, the guidelines suggest bone scan and CT scan as the standard imaging. Because it is what was used in order to recruit patients into all the studies we’ve looked at. And if we change what we use for imaging, we’re aware that we will change what we find. But then the question is, does the data really apply to what you found? And it isn’t quite clear at the moment how that bit will work. So, <u>at the moment, the guidelines are clear that it’s conventional imaging in this group allows us to determine which patients are suitable for treatment, and which treatments</u>*’. A second named Professor continued ‘*Thank you. I think that’s pretty clear, isn’t it*?’

ii) Further on at 23:40 a third named Professor targeting UK health professionals in the same promotional material endorsed that definition highlighting ‘*I would actually echo what [name] just said, and I think that I mean, a test that helps to inform what we should do, and maybe really leads to a change in treatment decision, that to me is a useful test. For patients with potential nmCRPC, my treatment of choice is ADT plus a new hormonal agent according to the three studies that you showed (SPARTAN, PROSPER, ARAMIS) so, intensified therapy. If I find a metastasis, what am I going to do? I’m going to put that*

patient on ADT plus probably a new hormonal agent. So, intensified therapy. So, my treatment for these patients will be exactly the same because we know that intensified therapy, at that point, is beneficial. We have three large phase 3 trials that show us the very same message. So we have a clear evidence trail that we can follow here. And the molecular imaging or test doesn't change anything. And I think, in the face of these three trials that we have, thinking about local therapy and someone having maybe one spot on PSMA imaging, but having a castrate-resistant setting, not biochemical recurrence, where it's a whole different story, but a progressive castration-resistant setting. Then I would say there is so much lack of data and so much good data on the other hand, to me, conventional imaging in this setting is completely fine and the correct thing to do.'.

b) 'Imaging and monitoring nmCRPC' PP-NUB-GB-0209, April 2021

*A*t 1.27 the second named Professor above stated '*I use standard imaging techniques with the CT scan, because we know a lot of these patients, once they do progress, it's not just bone disease we should be looking for, it's visceral disease and nodal disease, in particular. So, cross-sectional imaging and a bone scan. And this is obviously with conventional imaging. The next-generation imaging, we really don't know how best to interpret this at the moment. And if we go back over the last 17 years since the TAX 327 study, the first study in metastatic castrate resistant prostate cancer, showing the improvements with docetaxel, all of the studies since then across the field of prostate cancer been done with standard imaging. And that's how we can interpret the survival data. With next-generation imaging, with PSMA-PET, and with whole-body MRI, we really are not quite certain yet how best to utilise this information. I have access to standard imaging at my centre, with a CT scan for cross-sectional imaging, and with a bone scan that's freely accessible. I think these are the standard imaging techniques we would use for these patients to look for metastases. And these are the imaging modalities where, across the whole spectrum of prostate cancer, we've seen the improvements in survival based on the imaging in these protocols. MRI I wouldn't do, because I'm not really interested in the local disease, within the prostate, that may have already been previously treated with radiotherapy, in the main, in my practice, or with prostatectomy. But I am interested in looking for nodal disease and for other areas of metastatic disease, and that can be easily seen with a CT, usually with contrast, and a bone scan. I think this is a disease entity where the more you look for it, the more you find it*'.

Janssen therefore denied a breach of Clause 11.2.

PANEL RULING

The Panel noted that Bayer stated that the presenter categorised the patient populations treated with apalutamide, enzalutamide and darolutamide in the three pivotal phase III trials (SPARTAN (Smith *et al*), PROSPER (Hussain *et al*) and ARAMIS (Fizazi *et al*) as being in the micro-metastatic state of CRPC and alleged that by using this terminology, Janssen was implying that it was permissible to treat patients with apalutamide if metastases were present on any imaging modality in the CRPC setting which constituted off licence promotion. Bayer stated that by

definition, if a patient was diagnosed with metastases by any imaging modality, they had metastatic disease and therefore were not suitable for apalutamide which did not currently have a licence within the metastatic CRPC setting.

The Panel noted that the screenshot provided by Bayer included a picture of the presenter on the left-hand side with his name and place of work below. On the right-hand side was the title 'AR-targeted therapy works!' followed by three boxes titled 'Apalutamide', 'Enzalutamide', and 'Darolutamide' with a snapshot of the publication of each of the medicines pivotal phase III trials, (SPARTAN (Smith *et al*), PROSPER (Hussain *et al*) and ARAMIS (Fizazi *et al*) respectively) in the New England Journal of Medicine below. The screenshot included a banner across the bottom of the screen stating 'going a step backwards in the micro-metastatic state of CRPC,' which appeared, to the Panel, were captions/subtitles which transcribed the speaker's narrative.

The Panel noted that the narrative of this slide, according to the transcript of the video provided by Janssen, stated '..but I think one of the biggest evidences coming from the non-metastatic CRPC setting, and this we need to clarify, is on conventional imaging. So these are patients with non-metastatic CRPC and we all agree this is probably very low-volume metastatic CRPC given the fact that PSA is rapidly rising. And in these patients, when we introduced AR-targeted therapy that worked in the metastatic setting with visible metastases, going a step backwards in the micro-metastatic state of CRPC, this therapeutic modality works extremely well ..'.

The Panel noted the next slide was titled 'Primary endpoint: Metastasis-free survival in nmCRPC patients with PSADT ≤ 10 months' and included graphs showing the metastasis-free survival (%) by month of the comparator arm vs placebo in the SPARTAN, PROSPER, and ARAMIS trials. The narrative for this slide was '… and these three papers support, so it's not one or two, it's actually three studies that show that treating these patients makes a significant difference in terms of metastases-free survival – it was about 2 years with apalutamide and about 22 and 24 months with enzalutamide and darolutamide. So very comparable in terms of delaying the appearance of metastases in higher risk non-metastatic CRPC'.

The Panel noted that according to its SPC, Erleada (apalutamide) was indicated, *inter alia*, in adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease (see section 5.1).

The Panel noted that both Bayer and Janssen acknowledged that the key exclusion criterium for all three pivotal studies (SPARTAN, PROSPER and ARAMIS) in non-metastatic castration-resistant prostate cancer (nmCRPC) was the presence of metastases as detected by conventional imaging. The Panel further noted Janssen's submission that the marketing authorisations for all three products in high risk nmCRPC were granted on that basis. According to Janssen, all three registrational trials identified nmCRPC patients by an increasing PSA concentration and no distant metastases on conventional imaging and the presentation highlighted that recent data on novel next generation imaging modalities indicated that it was likely that the nmCRPC patient population in the three clinical trials discussed had micro-metastatic disease on entry to the trials despite the absence of metastases on conventional imaging. The Panel noted Janssen's submission that it should not therefore exclude patients from receiving potential benefits from licensed products using novel next generation imaging modalities that redefined the populations that were used within the clinical trials on which the marketing authorisations were based.

The Panel noted Janssens's submission that in oncology, nmCRPC is defined by the absence of visible lesions (cell aggregates) on conventional imaging and cited the publications of the above three pivotal studies, namely Smith *et al*, Fizazi *et al*, and Hussain *et al*.

The Panel noted Janssen's submission that Bayer appeared to share this view as Bayer supported and illustrated the prostate cancer community's view both in their definition of nmCRPC and what constituted conventional imaging in its own promotional materials. The Panel noted that examples of Bayer's materials provided by Janssen included the definition of nmCRPC as being no detectable metastasis on conventional imaging (CT scan, MRI, or bone scan). A screenshot provided by, and which was according to Janssen from a Bayer presentation dated July 2021, stated:

> 'Various imaging techniques are used to stage prostate cancer and detect metastasis and tumour recurrence. However, the definition of nmCRPC is traditionally based on conventional imaging rather than next-generation imaging. The ARAMIS, PROSPER and SPARTAN trials used conventional imaging (bone scan, CT and MRI) to determine diagnosis of nmCRPC. Subsequent approvals of second generation ARIs in nmCRPC were based on these studies and their use of conventional imaging. The UK Blueteq criteria only specifies the use of conventional imaging in the diagnosis and monitoring of patients with nmCRPC. The potential role of more sensitive imaging modalities, including PSMA-PET, is unclear as there are currently no longitudinal studies investigating clinical outcomes in patients with nmCRPC'.

In a further extract of a Bayer presentation provided by Janssen, the presenter stated:

> 'So, for all castrate-resistant prostate cancer, because it's what we have data on, the guidelines suggest bone scan and CT scan as the standard imaging. Because it is what was used in order to recruit patients into all the studies we've looked at. And if we change what we use for imaging, we're aware that we will change what we find. But then the question is, does the data really apply to what you found? And it isn't quite clear at the moment how that bit will work. So, <u>at the moment, the guidelines are clear that it's conventional imaging in this group allows us to determine which patients are suitable for treatment, and which treatments</u>'.

The Panel further noted that Fendler *et al* provided by both Janssen and Bayer stated that nonmetastatic castration-resistant prostate cancer (nmCRPC) is characterised by a rising prostate-specific antigen (PSA) level, castrate testosterone levels, and no evidence of distant metastases by conventional bone scan and cross-sectional imaging of the chest, abdomen, and pelvis.

The Panel noted Janssen's submission that at 7.45, the named presenter described nmCRPC *'as going a step backwards in the micrometastatic state of CRPC'*, therefore clearly distinct from metastatic castrate resistant prostate cancer (mCRPC), and the two different disease states were shown on slides 4 and 5, with the latter also showing which medicines were licensed for use in mCRPC, with apalutamide not being one of them. The Panel noted Janssen's submission that it did not advocate or support the use of apalutamide in metastatic prostate cancer diagnosed as defined by conventional imaging.

Whilst the Panel noted that no evidence was provided to support Janssen's submission that the established view was that nmCRPC was likely to be associated with micro-metastatic disease

(not detectable by conventional imaging), the Panel noted that metastasis in nmCRPC appeared to be defined based on conventional imaging. The complainant had the burden of proving his/her complaint on the balance of probabilities, and noting the above, the Panel did not consider that Bayer had established that Janssen had promoted apalutamide off licence as alleged and **no breach of Clause 11.2** was ruled.

2 Incomplete and disparaging safety information/adverse events (AEs) of the nmCRPC trials

COMPLAINT

Bayer stated that firstly, at approximately 16.07 minutes within the presentation, the named presenter stated *'When we are looking at the strength of capturing adverse events you definitely don't want to be looking only at the treated arms, but you need to be looking at the placebo arms of the trials. And when we look at the adverse events side by side of the three trials, and this is not intended to be head-head comparisons, there are some things that are clearly different'.* Bayer submitted that the information presented in this segment of the presentation on the AEs reported within the trials was an incomplete and unbalanced comparison of the safety data from the trials; limiting the discussion to selected AEs with a failure to discuss the Grade 3, 4 and 5 adverse events which related to severe, life-threatening and death-related AEs respectively. By excluding this data, the physicians presented with this, received an incomplete picture of the safety profiles of these medicines, which was misleading. Bayer alleged breaches of Clauses 6.1, 6.3, 6.4 and 14.1.

Bayer submitted that secondly, at approximately 16.16 minutes within the recording, the named presenter attempted to compare how frequently patients were monitored for capturing AEs and explained that in the SPARTAN trial for apalutamide, it was every 4 weeks compared to every 16 weeks in the PROSPER trial (enzalutamide) and the ARAMIS trial (darolutamide). The presenter stated *'Clearly, when we are asking patients to remember a possible adverse event, it is much easier to remember what happened in the last 4 weeks than in the last 4 months what happened and this is clearly highlighted when you look at the placebo arms of these trials. If you look at the placebo arm in the apalutamide study and you would assume placebo arms can be compared, the placebo arm in the SPARTAN study was 93% complained of an adverse event, whereas in PROSPER and ARAMIS it was 77%. So clearly the frequency and the intensity of which you look for adverse events will be very significantly different, depending on how frequently you look for these adverse events because you would not expect a placebo itself to have adverse events. And so clearly you would have to look at the delta between the placebo arm and the treated arm to get a sense of how much your treated arm might be overriding the adverse events related to ageing, ADT and the disease itself. And when you look at fatigue again you see 21% in the placebo arm versus 14 or 8% in the ARAMIS arm so clearly there are differences that need to be captured'*. Bayer alleged that this was purely speculative in nature and this claim was unsubstantiated in breach of Clause 6.2. It was also factually inaccurate in breach of Clause 6.1 because, as stipulated in the ARAMIS trial protocol, all AEs experienced during the trial could be reported at any time point by the subjects to the clinical research associate (CRA) or other contract research organisation (CRO) personnel by telephone or email as well as during visits to the study centre at day 1, day 15, day 29, week 16 and every 16 weeks thereafter.

Bayer stated that at approximately 18.04 minutes the named presenter presented a side-by-side trial comparison of the relative risk (RR) of AEs when compared with placebo. The SPARTAN,

PROSPER and ARAMIS trials were not head-to-head trials and therefore could not be directly compared. Janssen used a disclaimer that had been placed in bold red text at the bottom of the slides presented in this segment stating that *'These are not head to head comparison studies – data presented side by side for illustration purposes only'*. The disclaimer, however, became meaningless when the speaker invited direct comparison between the studies as illustrated above.

Bayer stated that it was therefore a misleading comparison between the three trials once again and in this regard, alleged a breach of Clauses 6.1, 6.6 and 14.1.

Bayer noted that in response to its complaint on this point Janssen stated:

> *'[Named presenter] has over 20 years' experience as clinical trial investigator. These are his words, based on his experience. What he says is very rational and does not necessitate the provision of a reference. Indeed, it could be considered rather disparaging to question his experience and expertise and Janssen would ask Bayer to be considerate of clause 6.7 (8.2) The health Professions and the clinical and scientific opinions of health Professionals must not be disparaged and would ask Bayer to provide suitable references to demonstrate otherwise. If Bayer however, were to have information to show that this was incorrect then Janssen would ask them to supply the relevant reference for consideration.'*

Bayer stated that it had highlighted to Janssen in its response that a pharmaceutical company was responsible for all materials that were presented by thought leaders (TLs) that were contracted to do so in a promotional capacity on said pharmaceutical company's behalf. Bayer stated that Janssen therefore had a duty to ensure that TLs contracted by its establishment therefore complied with the provisions of the ABPI Code. The ABPI Code made it clear that such materials must be certified and furthermore an appropriate certified briefing was provided to the TL to ensure this provision of the Code was made.

Furthermore, Bayer upheld its initial view and had provided the examples in its initial complaint of the factually inaccurate, purely speculative and disparaging nature of the adverse events presented in this Janssen promotional recording of the three second-generation ARI trials in breach of Clauses 6.1, 6.2, 6.6 and 14.1 of the Code. Bayer did not agree that the inter-company dialogue on this point could be closed.

In summary to this section of the complaint, Bayer requested that the PMCPA considered breaches of Clauses 6.1, 6.2, 6.3, 6.4, 6.6 and 14.1 of the ABPI Code.

OBJ

RESPONSE

Janssen agreed that a pharmaceutical company was responsible for all materials that were presented by thought leaders that were contracted to do so in a promotional capacity on its behalf. Janssen noted also that the SPC for apalutamide stated that *'Treatment with apalutamide should be initiated and supervised by specialist physicians experienced in the medical treatment of prostate cancer'* and that the audience for this video would be expected to be specialists in prostate cancer. Janssen also reiterated that it agreed with Bayer that *'we, as a pharmaceutical community, need to ensure we provide the clinical community with balanced and unambiguous information to allow the individual healthcare professional to make informed decisions about patient care'*.

Whilst this item was clearly promotional, the presentation was focused on presenting the benefits of early treatment in patients with nmCRPC, including the use of each of the licensed, second-generation androgen receptor (AR) inhibitors, and this was the primary reason for illustrating the results from all three trials on the same slides.

The presentation did not invite, at any point, head-to-head comparisons. That was stated by the named presenter verbally on numerous occasions and was also simultaneously captured by constant-flow subtitles.

The presentation throughout highlighted the pitfalls of making cross-trial comparisons, and any differentiation across trials related to differences in important aspects of trial design chosen to illustrate and highlight these pitfalls. There was no intent at any point to differentiate products based on outcomes of the active arms from the three different trials. In this section of the presentation the named presenter highlighted the importance of trial design in the interpretation of clinical trial safety outcomes, and again verbally stated *'this is not intended to be head-to-head comparisons*', and then highlighted trial design differences using placebo arm outcomes as an illustration of why trial outcomes should not be compared. He gave (while stating *'we have to be very careful'*) an example of a method potentially useful in mitigating the difficulties inherent in comparisons, accepting that instinctively some clinicians made them anyway. The focus here was on the differences in trial design not in the difference between the outcomes of the active arms of the trials, and then only as an illustration of why clinicians should not make comparisons across trials.

Janssen noted that Bayer stated:

> *'Firstly, at approximately 16.07 minutes within the presentation, [Named presenter] states that "When we are looking at the strength of capturing adverse events you definitely don't want to be looking only at the treated arms, but you need to be looking at the placebo arms of the trials. And when we look at the adverse events side by side of the three trials, and this is not intended to be head-head comparisons, there are some things that are clearly different."*
>
> *The information presented in this segment of the presentation on the Aes reported within the trials is an incomplete and unbalanced comparison of the safety data from the trials; limiting the discussion to selected AE's with a failure to discuss the Grade 3, 4 and 5 adverse events which relate to severe, life-threatening and death related Aes respectively. By excluding this data, the physician presented with this, receives an incomplete picture of the safety profiles of these drugs, which is misleading. We request that PMCPA considers breaches of clauses 6.1, 6.3, 6.4 and 14.1.'*

As stated above, this was not intended to be a comparison of treatment outcomes. The named presenter had provided a complete and broad overview of AE information for the AR inhibitors under the following headings: any AEs (which already include all Grade 3, 4 and 5 AEs); Any serious AEs (which include anyway grades 4 and 5 – requiring hospitalisation or resulting in death, persistent or significant injury, or are life threatening), AEs (all grades) before presenting AEs (all grades) for 5 specific AEs all of which were identified and published in their respective registrational trials as adverse events of special interest (AESI). The European Medicines Agency (European Medicines Agency (EMA). Scientific guideline for development of safety update report. 2008, https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-2-f-

development-safety-update-report-step-3_en.pdf) adhered to the Council for International Organizations of Medical Sciences (CIOMS VII) definition of AESI as *'a class of adverse events that may or may not be serious but have special meaning or importance for a particular drug or class of drugs'.* CIOMS VII also advised '*there are some fundamental steps that can be taken to improve the process for detecting signals. These included: prompt medical evaluation of all individual serious cases, regardless of attribution or expectedness, and adverse events of special interest, whether serious or not'* (Council for International Organizations of Medical Sciences (CIOMS); 2005. https://cioms.ch/wp-content/uploads/2017/01/Mgment_Safety_Info.pdf Accessed 18/11/2021). These adverse events of special interest for apalutamide, as would be expected, were consistent with those listed in the apalutamide SPC Section 4.4 (Special warnings and precautions) to which clinicians should pay particular attention.

Janssen believed that, in the context of the efficacy information provided in the video, this provided an appropriate balance of efficacy and safety information. The safety information slides were presented and discussed for a significant length of time, and discussion of safety data provided a significant proportion of the discussion in the context of the overall video. As throughout the presentation, much of the discussion looked in a balanced way at the licensed second-generation AR inhibitors as a class as part of the overall discussion on the benefits of early treatment. While Janssen recognised the video as promotional and it was classified as such and certified appropriately, Janssen aimed, in all its materials, to not only be accurate, balanced, fair, and objective, but also to ensure that it did so in the context of the broad scientific and therapeutic environment and scientific opinion.

Janssen therefore denied a breach of Clauses 6.1, 6.3, 6.4 and 14.1.

Janssen noted that Bayer stated:

> *'Secondly, at approximately 16.16 minutes within the recording, [Named presenter] attempts to compare how frequently patients were monitored for capturing AEs and explains that in the SPARTAN trial for apalutamide, it was every 4 weeks compared to every 16 weeks in the PROSPER trial (enzalutamide) and the ARAMIS trial (darolutamide). He states ''Clearly, when we are asking patients to remember a possible adverse event, it is much easier to remember what happened in the last 4 weeks than in the last 4 months what happened and this is clearly highlighted when you look at the placebo arms of these trials. If you look at the placebo arm in the apalutamide study and you would assume placebo arms can be compared, the placebo arm in the SPARTAN study was 93% complained of an adverse event, whereas in PROSPER and ARAMIS it was 77%. So clearly the frequency and the intensity of which you look for adverse events will be very significantly different, depending on how frequently you look for these adverse events because you would not expect a placebo itself to have adverse events. And so clearly you would have to look at the delta between the placebo arm and the treated arm to get a sense of how much your treated arm might be overriding the adverse events related to ageing, ADT and the disease itself. And when you look at fatigue again you see 21% in the placebo arm versus 14 or 8% in the ARAMIS arm so clearly there are differences that need to be captured.'' This is purely speculative in nature and this claim is unsubstantiated and therefore in breach of clause 6.2. This is also factually inaccurate and therefore also in breach of clause 6.1 because as stipulated in the ARAMIS trial protocol, all AEs experienced during the trial could be reported at any time point by the subjects to*

the CRA or other CRO personnel by telephone or email as well as during visits to the study centre at day 1, day 15, day 29, week 16, and every 16 weeks thereafter.'

Janssen submitted that studies in which adverse effects were carefully sought would report a higher frequency than studies in which they were sought less carefully (Loke Y.K *et al.* Systematic reviews of adverse effects: framework for a structured approach. *BMC Med Res Methodol*. 2007; 7:32). With regard to slide H, the ARAMIS publication for darolutamide stated that, *'data were collected at 16-week intervals during the double-blind treatment period, at the start of the open-label treatment period, and every 16 weeks thereafter*' (Fizazi K *et al.* Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2019;380:1235–46) and the SPARTAN protocol (ClinicalTrials.gov [Internet]. National Library of Medicine (US). Identifier NCT01946204, A Study of Apalutamide (ARN-509) in Men With Non-Metastatic Castration-Resistant Prostate Cancer (SPARTAN). Protocol ARN-509-003 Amendment 8. March 2017.Available from: https://clinicaltrials.gov/ProvidedDocs/04/NCT01946204/Prot_000.pdf. Accessed 14/01/2022) stated '*patients will be assessed for AEs at each monthly clinic visit while on the study'*. The named presenter was not speculating, he was stating the frequency of monitoring for each trial as it was defined in the public domain for both trials, before explaining *'clearly, the frequency and intensity of which you look for adverse events will be very significantly different, depending on how frequently you look for these adverse events*' in line with Wernicke *et al* in their comparison of spontaneously reported and solicited collection methods which concluded *'as expected, adverse events collected by solicitation leads to higher reporting rates',* and supported by a range of established experts in published literature reviews and books on pharmacovigilance (Wernicke JF *et al*. Detecting Treatment Emergent Adverse Events in Clinical Trials. A comparison of spontaneously reported and solicited collection methods. *Drug Safety.* 2005; 28(11): 1057-1063; 19. Molokhia M *et al*. Improving reporting of adverse drug reactions: Systematic review. *Clin Epidemiol*. 2009; 1: 75-92; 20. Allen EN *et al*. Eliciting adverse effects data from participants in clinical trials. *Cochrane Database of Systematic Reviews*. 2018; 1: 1465-1858 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.MR000039.pub2/full. Accessed 04 January 2022; Talbot J, Keisu M and Stahle L. *Clinical Trials - Collecting Safety Data and Establishing the Adverse Drug reactions Profile.* 215-291. In (Eds.) Talbot J. and Aronson K*. Stephens' Detection and Evaluation of Adverse Drug Reactions: Principles and Practice.* Sixth Edition. 2012. John Wiley & Sons Ltd and Herson J. *Safety Monitoring*. 293-318. In (Ed.) Gould L. *Statistical Methods for Evaluating Safety in Medical Product Development.* 2015. John Wiley & Sons Ltd).

Janssen, again, emphasised that in this section of the presentation the named presenter highlighted the importance of the trial design in the interpretation of clinical trial outcomes, and highlighted the potential pitfalls in making cross trial comparisons. The focus was on the difference in trial design not in the difference between the outcomes of the active arms of the trials, and therefore advocated within-trial relative risk calculations in assessing outcomes, while emphasising why cross-trial comparisons should not be made. The named presenter was highlighting the established and published view that solicited collection methods for adverse events as part of the trial design was expected to lead to a higher adverse event rate compared to spontaneous reporting (Loke Y.K *et al.* Systematic reviews of adverse effects: framework for a structured approach. *BMC Med Res Methodol*. 2007; 7:32; Wernicke JF *et al*. Detecting Treatment Emergent Adverse Events in Clinical Trials. A comparison of spontaneously reported and solicited collection methods. *Drug Safety.* 2005; 28(11): 1057-1063; Molokhia M *et al*. Improving reporting of adverse drug reactions: Systematic review. *Clin Epidemiol*. 2009; 1: 75-

92; Allen EN *et al*. Eliciting adverse effects data from participants in clinical trials. *Cochrane Database of Systematic Reviews*. 2018; 1: 1465-1858 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.MR000039.pub2/full. Accessed 04 January 2022; Talbot J, Keisu M and Stahle L. *Clinical Trials - Collecting Safety Data and Establishing the Adverse Drug reactions Profile.* 215-291. In (Eds.) Talbot J. and Aronson K. *Stephens' Detection and Evaluation of Adverse Drug Reactions: Principles and Practice.* Sixth Edition. 2012. John Wiley & Sons Ltd and Herson J. *Safety Monitoring*. 293-318. In (Ed.) Gould L. *Statistical Methods for Evaluating Safety in Medical Product Development.* 2015. John Wiley & Sons Ltd). The named presenter also pointed out that the use of relative risk was a method that removed one source of bias if clinicians were tempted to compare across trials by accounting for differences in the placebo arms. However, the named presenter was very careful throughout the presentation to repeatedly say that Janssen should not be making cross-trial comparisons and was illustrating why by giving this example. The monitoring schedules in the trials were not speculative and were clearly defined in the trial protocols and publications (Fizazi K *et al.* Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2019;380:1235–46 and ClinicalTrials.gov [Internet]. National Library of Medicine (US). Identifier NCT01946204, A Study of Apalutamide (ARN-509) in Men With Non-Metastatic Castration-Resistant Prostate Cancer (SPARTAN). Protocol ARN-509-003 Amendment 8. March 2017.Available from: https://clinicaltrials.gov/ProvidedDocs/04/NCT01946204/Prot_000.pdf. Accessed 14/01/2022).

Janssen therefore denied breaches of Clauses 6.1 and 6.2.

Janssen noted that Bayer stated that:

> *'At approximately 18.04 minutes [Named presenter] presents a side-by-side trial comparison of the relative risk (RR) of AEs when compared with placebo. The SPARTAN, PROSPER and ARAMIS trials were not head-to-head trials and therefore cannot be directly compared. Janssen used a disclaimer that has been placed in bold red text at the bottom of the slides presented in this segment stating that "These are not head-to-head comparison studies – data presented side by side for illustration purposes only". The disclaimer, however, becomes meaningless when the speaker invites direct comparison between the studies as illustrated above.*
>
> *This is therefore a misleading comparison between the three trials once again and in this regard, a breach of clauses 6.1, 6.6 and 14.1.'*

For the reasons discussed above, Janssen denied a misleading comparison between the trials being presented. While the named presenter mentioned two outcomes with regard to rash for apalutamide and darolutamide at this point in the video, he was using it as an illustration of how the use of relative risk was a better alternative to the use of absolute numbers for the presentation of safety data, and there was no associated claim with regard to outcomes for the different products. As stated above, the emphasis was on similarities in results rather than any differences in outcomes between products, and he was not inviting direct comparisons of the outcomes of the active arms. There was no claim made that could be considered disparaging regarding Bayer's products. The named presenter also clearly stated we *'don't want to be looking at the treated arms, but you need to be looking at the placebo arms of the trials'* and *'this is not intended to be head-to-head comparisons'.*

Janssen therefore denied breaches of Clause 6.1, 6.6 and 14.1.

In summary, Janssen disagreed that either incomplete or disparaging safety information had been provided. The safety information was balanced when compared to the efficacy data presented, and was focused on the most important safety concerns with an overview focused on adverse events of special interest that were included in Section 4.4 (Special warnings and precautions) of the SPC, while also presenting a clear emphasis on the pitfalls of cross-trial comparison based on publicly available factual information regarding differences in trial design, with no disparaging claims made with regard to Bayer's products.

Janssen therefore denied breaches of Clauses 6.1, 6.2, 6.3, 6.4, 6.6 and 14.1 of the ABPI Code.

PANEL RULING

The Panel noted Bayer's allegation that the information presented in this segment on the adverse events reported within the trials was an incomplete and unbalanced comparison of the safety data from the trials; the discussion was limited to selected adverse events with a failure to discuss the Grade 3, 4 and 5 adverse events which related to severe, life-threatening and death-related adverse events respectively.

The Panel noted that the slide at issue was titled 'Adverse events of interest in nmCRPC trials' and included a table that compared the active and placebo arms in the SPARTAN, PROSPER and ARAMIS trials, side by side. The table included the rows: Monitoring schedule; Median duration of trial regimen (months); Any AEs n (%); Any serious AEs n (%); and AEs (all grades), % and listed fatigue, hypertension, rash, falls, fractures, and mental impairment disorders. The adverse event monitoring schedule was every 4 weeks for SPARTAN and every 16 weeks for PROSPER and ARAMIS. The Panel noted a bold red footnote at the bottom of the slide stated 'These are not head-to-head comparison studies – data presented for illustrative purposes only'.

The Panel noted Janssen's submission that the speaker had provided a complete and broad overview of adverse event information for the AR inhibitors under the headings: any AEs (which already included all Grade 3, 4 and 5 AEs); Any serious AEs (which included grades 4 and 5 – requiring hospitalisation or resulting in death, persistent or significant injury, or were life threatening), before presenting AEs (all grades) for 5 specific AEs all of which were identified and published in their respective registrational trials as adverse events of special interest (AESI) which according to Janssen was defined by the Council for International Organizations of Medical Sciences (CIOMS VII) as *'*a class of adverse events that may or may not be serious but have special meaning or importance for a particular drug or class of drugs'. The Panel noted Bayer's submission that the adverse events of special interest for apalutamide were consistent with those to which clinicians should pay particular attention as listed in Section 4.4 (Special warnings and precautions) of the apalutamide SPC.

The Panel, therefore, on the evidence before it, did not consider that Bayer had established that Janssen had limited the discussion to selected AEs with a failure to discuss the Grade 3, 4 and 5 adverse events resulting in an incomplete and unbalanced comparison of the safety data from the trials as alleged. Therefore, based on the narrow allegation, the Panel ruled **no breach of Clauses 6.1, 6.3, 6.4 and 14.1**.

The Panel noted Bayer's further concern that the presenter attempted to compare how frequently patients were monitored for capturing AEs in SPARTAN trial for apalutamide (every 4

weeks) compared to every 16 weeks in the PROSPER trial (enzalutamide) and the ARAMIS trial (darolutamide) stating that the frequency and intensity of adverse events would be significantly different depending on how frequently you looked for these adverse events so you would have to look at the delta between the placebo arm and the treated arm to get a sense of how much your treated arm might be overriding the adverse events related to ageing, ADT and the disease itself. The Panel noted Bayer's allegation that this was purely speculative in nature, factually inaccurate and unsubstantiated because as stipulated in the ARAMIS trial protocol, all AEs experienced during the trial could be reported at any time point by the subjects to the clinical research associate (CRA) or other contract research organisation (CRO) personnel by telephone or email as well as during visits to the study centre at day 1, day 15, day 29, week 16 and every 16 weeks thereafter.

The Panel noted that in relation to the slides at issue, the presenter stated '..when we're looking at the strength of capturing adverse events, you definitely don't want to be looking only at the treated arms, but you need to be looking at the placebo arms of the trials. And when we look at the adverse events side by side of the three trials, and this is not intended to be head-to-head comparisons, there are some things that are clearly very different. First, when we look at how frequently patients were monitored for capturing adverse events in the apalutamide study of SPARTAN, it was every 4 weeks compared to every 16 weeks in the other two trials. And, clearly, when we're asking patients to remember a possible adverse event, it's much easier to remember in the last 4 weeks than in the last 4 months what happened. And this is clearly highlighted when you look at the placebo arms of these trials. If you look at the placebo arm in the apalutamide study – and you would assume placebo arms can be compared – the placebo arm in the SPARTAN was 93% complained of an adverse event, whereas in PROSPER and ARAMIS, it was 77%. So, clearly, the frequency and the intensity of which you look for adverse events will be very significantly different, depending on how frequently you look for these adverse events, because you would not expect a placebo itself to have adverse events. And so, clearly, you need to look at delta between the placebo arm and the treated arm to get a sense of how much your treatment arm might be overriding the adverse events related to ageing, ADT and the disease itself'.

The Panel noted Janssen's submission that the presenter was highlighting the established and published view that solicited collection methods for adverse events, as part of the trial design, was expected to lead to a higher adverse event rate compared to spontaneous reporting. The Panel further noted Janssen's submission that studies in which adverse effects were carefully sought would report a higher frequency than studies in which they were sought less carefully and the speaker's view in this regard was in line with Wernicke *et al* in their comparison of spontaneously reported and solicited collection methods and was supported by a range of established experts in published literature reviews and books on pharmacovigilance. Janssen cited a further five publications in this regard namely Loke Y.K *et al*, Molokhia M *et al,* Allen EN *et al*, Talbot J *et al*, and Herson J. The Panel noted than Wernicke *at al* concluded that 'As expected, adverse events collected by solicitation leads to higher reporting rates'.

The Panel, noting Janssen's submission and citations, did not consider that Bayer had established that the narrative of the speaker in relation to the frequency of capturing adverse events was purely speculative and incapable of substantiation as alleged and on the evidence before it, **no breach of Clause 6.2** was ruled. Nor did the Panel consider that Bayer had established that because the ARAMIS trial protocol stipulated that all AEs experienced during the trial could be reported at any time point by the subjects by telephone, email or during visits, that the speaker's narrative in relation to the frequency of capturing adverse was factually

inaccurate as alleged. Based on the narrow allegation, the Panel ruled **no breach of Clause 6.1** in this regard.

The Panel noted that Bayer was further concerned that the next slide, titled 'Relative risk of AEs compared with placebo at approximately 18.04 minutes, presented a side-by-side trial comparison of the relative risk (RR) of AEs when compared with placebo. Bayer was concerned that the SPARTAN, PROSPER and ARAMIS trials were not head-to-head trials and therefore could not be directly compared. Janssen used a disclaimer that had been placed in bold red text at the bottom of the slides presented in this segment stating that 'These are not head to head comparison studies – data presented side by side for illustration purposes only'. The disclaimer, however, became meaningless according to Bayer when the speaker invited direct comparison between the studies as illustrated above.

The Panel noted the narrative for the slide at issue was 'And when you look at fatigue again, you see 21% in the placebo arm versus 14 or 8% in the ARAMIS arm – so, clearly, there are differences that need to be captured. And one of the ways that I found might be the simplest to try, and we have to be very careful to look at comparisons, is to put relative risk ratios. And so when we look at SPARTAN for example, any AE, the relevant risk is 1.04 between the placebo and the treated arm. And you see the differences across the board. So, really, the differences are really not as significant as one would expect. And even with something like a rash, where there is a rash reported clearly with apalutamide, it's a four-fold increased risk compared to the placebo, but even with darolutamide, it was a three-fold increased risk but the absolute numbers are small but the relative risk is in the same range'.

The Panel noted Janssen's submission that the presentation did not at any point invite head-to-head comparisons. The Panel noted Janssen's submission that this was stated by the presenter verbally on numerous occasions and was also simultaneously captured by constant-flow subtitles. According to Janssen, the presentation highlighted the pitfalls of making cross-trial comparisons throughout, and any differentiation across trials related to differences in important aspects of trial design chosen to illustrate and highlight these pitfalls. The Panel noted Janssen's submission that there was no intent at any point to differentiate products based on outcomes of the active arms from the three different trials. In this section the speaker highlighted the importance of trial design in the interpretation of clinical trial safety outcomes, and again stated *'this is not intended to be head-to-head comparisons*', and then highlighted trial design differences using placebo arm outcomes as an illustration of why trial outcomes should not be compared. He gave (while stating *'we have to be very careful'*) an example of a method potentially useful in mitigating the difficulties inherent in comparisons, accepting that instinctively some clinicians make them anyway.

The Panel noted that the bottom of the slides stated 'These are not head-to-head comparison studies – data presented for illustrative purposes only' in small bold red font.

The Panel noted Janssen's submission that the emphasis was on similarities in results rather than any differences in outcomes between products, and the presenter was not inviting direct comparisons of the outcomes of the active arms.

In the Panel's view, the presenter drew out differences between the active arm and placebo, and not between the three androgen receptor inhibitors (ARIs). It noted that this was not the subject of the allegation. The Panel did not consider that in the particular circumstances of the case, the presenter's presentation of the adverse events of the three trials side-by-side was a

misleading comparison as alleged nor did it disparage another pharmaceutical company's product. The Panel therefore, based on the complainant's narrow allegation, ruled **no breach of Clauses 6.1, 6.6 and 14.1**.

3 Off-licence promotion: The use of Apalutamide in patients with metastatic CRPC as detected on novel-Imaging

COMPLAINT

Bayer stated that at approximately 20.0 minutes into the presentation, the named presenter suggested if metastases on novel imaging such as a prostate-specific membrane antigen positron emission tomography (PSMA-PET) scan was detected but not visible on conventional imaging, treatment should not change and advocated that the physician progressed with treatment irrespective of this. The named presenter stated, '*It shouldn't change because the level 1 evidence is with systemic therapy'.*

In addition, at approximately 21.15 minutes into the presentation, the named presenter added *'And just to stress how frequently this novel imaging would be positive, this was a German-led study that we collaborated with looking at patients almost identical to the trial patients in the SPARTAN and the other trials, and 98% of patients would have something visible on the PSMA-PET, if we did PSMA in these kinds of patients'.*

At approximately 21.39 minutes of the recording, the named presenter appeared to be promoting the survey results from clinicians who attended the Advanced Prostate Cancer Consensus Conference (APCCC) Consensus 2019 meeting who were asked *'If patients were high-risk, non-metastatic CRPC on conventional imaging and appeared to have metastases on advanced imaging, would that change your management?'.* The named presenter explained, *'Almost 90% said no, they would treat as non-metastatic CRPC with agents like apalutamide or enzalutamide and not change their strategy of therapy if for some reason, advanced imaging was used'.*

The above three statements made by the presenter supported the use of products licensed for nmCRPC in patients in whom metastases had been detected using novel imaging. This was not appropriate to present at a promotional meeting or use on a promotional website as this advocated the off-licence use of apalutamide as metastases had been detected on imaging. The disease therefore could no longer be classified as non-metastatic disease. This was inconsistent with the licensed indication for apalutamide in breach of Clause 11.2 of the Code.

Bayer noted that in respect of off-licence promotion, Janssen stated in its response:

> '*The introduction of novel imaging techniques such as PSMA-PET scans are much more sensitive than conventional imaging in being able to detect metastases in patients with prostate cancer. Slide 24 shows the impact of such novel imaging approaches and it could well be that in the future the management of prostate cancer changes. But this has not happened yet, with such imaging modalities still being considered experimental and their value in staging patients unknown. There are also a limited number of such scans available in the UK and in Europe, the exception being Germany. [Named presenter] states at 21.0 that "We should not redefine nmCRPC based on the introduction of novel imaging, the definition was based on conventional imaging". This is in accordance with current UK practice. Bayer have also failed to accurately reflect the question that was*

asked of the delegates shown on Slide 26 which was "What systemic treatment approach do you recommend for the majority of your CRPC patients with PSADT ≤ 10 months, who are non-metastatic on conventional imaging and have metastases on advanced imaging?" Nearly eighty nine percent agreed that they would "treat nmCRPC with agents such as apalutamide or enzalutamide" hence confirming current medical opinion that patients with metastatic disease seen on advanced imaging, should maintain their classification as being nmCRPC and treated with those agents licensed for nmCRPC, such as apalutamide and enzalutamide.'

Bayer noted that Janssen had suggested in its response that PSMA-PET was considered an experimental imaging modality and its value in staging nmCRPC patients was unknown and therefore any metastases detected on this modality should be disregarded. Janssen had also suggested that in instances where metastases had been detected on PSMA-PET, patients should still receive treatments such as apalutamide as though these patients were non-metastatic. Bayer disagreed with this. PSMA-PET was fast becoming more and more widely available to stage prostate cancer, contrary to Janssen's view and was Food and Drug Administration (FDA) approved as well as reimbursed by NHS England for prostate cancer diagnosis and staging currently in two scenarios in the UK:

a) In primary disease when considering radical treatment and staging of:
    - high risk clinically relevant Stage T3 or more
    - PSA >20ng/ml
    - Gleason score > 8
    - Suitable for curative treatment (radiotherapy (RT) or prostatectomy) after conventional imaging.

b) Suspected recurrence in patients with rapidly rising PSA and negative or equivocal conventional imaging where results would directly influence patient management.

Bayer states that, therefore, PSMA-PET was a legitimate, approved and recognised imaging modality in the staging of prostate cancer and could not be dismissed as experimental. Furthermore, the response from Janssen stating '*that patients with metastatic disease seen on advanced imaging should maintain their classification as being nmCRPC and treated with those agents licensed for nmCRPC, such as apalutamide and enzalutamide'* was therefore off-label and in breach of Clause 11.2 of the Code. Bayer did not agree that the inter-company dialogue on this point could be closed.

Bayer alleged a breach of Clause 11.2**.**

RESPONSE

Janssen submitted that in oncology, nmCRPC was defined as the lack of visible lesions (cell aggregates) on conventional imaging. This was reflected in how all three clinical trials (SPARTAN, PROSPER, ARAMIS) distinguished the non-metastatic state of CRPC from metastatic CRPC by using conventional imaging.

Other non-conventional imaging methods could be used, on occasion and for various legitimate reasons by health professionals but these imaging methods were not used to inform treatment outcomes in nmCRPC as:

a) They could give false positives (eg they detect normal/ healthy tissue and cells which were not metastatic) (Hofman *et al*. Prostate-Specific Membrane Antigen PET:Clinical Utility in Prostate Cancer, Normal Patterns, Pearls, and Pitfalls. *Radiographics*. 2018; 38(1): 200-217; Gualberto R *et al*. Schwannoma: A rare cause of false-positive 68Ga-PSMA PET/CT uptake in the evaluation of metastatic prostate cancer. *Urology Case Reports.* 2022; 41: 101974 and Sasikumar A *et al*. 68Ga-PSMA PET/CT False-Positive Tracer Uptake in Paget Disease. *Clinical Nuclear Medicine*. 2016; 41(10): 454-455).
b) They were yet not validated in any clinical trials in the nmCRPC setting (Sundahl *et al*. When What You See Is Not Always What You Get: Raising the Bar of Evidence for New Diagnostic Imaging Modalities. *European Urology.* 2021; 79(5): 565-567).
c) They were still largely used in an experimental setting (Hofman *et al*. Prostate-Specific Membrane Antigen PET:Clinical Utility in Prostate Cancer, Normal Patterns, Pearls, and Pitfalls. *Radiographics*. 2018; 38(1): 200-217; Sundahl *et al*. When What You See Is Not Always What You Get: Raising the Bar of Evidence for New Diagnostic Imaging Modalities. *European Urology.* 2021; 79(5): 565-567 and Hyvakka A *et al*. More Than Meets the Eye: Scientific Rationale behind Molecular Imaging and Therapeutic Targeting of Prostate-Specific Membrane Antigen (PSMA) in Metastatic Prostate Cancer and Beyond. *Cancers*. 2021; 13(9): 2244).

Janssen noted that with regard to the complaint, firstly, Bayer referenced the following statements: 'approximately 20 minutes into the presentation', 'approximately 21.15 minutes into the presentation' and 'at approximately 21.39 minutes of the recording':

'*It shouldn't change because the level 1 evidence is with systemic therapy.'*

'And just to stress how frequently this novel imaging would be positive, this was a German-led study that we collaborated with looking at patients almost identical to the trial patients in the SPARTAN and the other trials, and 98% of patients would have something visible on the PSMA-PET, if we did PSMA in these kinds of patients.'

'If patients were high-risk, non-metastatic CRPC on conventional imaging and appeared to have metastases on advanced imaging, would that change your management?' 'Almost 90% said no, they would treat as non-metastatic CRPC with agents like apalutamide or enzalutamide and not change their strategy of therapy if for some reason, advanced imaging was used.'

Janssen noted that Bayer further stated that:

'The above three statements made by the speaker support the use of products licensed for nmCRPC in patients in whom metastases have been detected using novel imaging. This is not appropriate to present at a promotional meeting or use on a promotional website as this advocates the off-licence use of apalutamide as metastases have been detected on imaging. The disease therefore can no longer be classified as non-metastatic disease. This is inconsistent with the licensed indication for apalutamide and is therefore a breach of 11.2 of the Code of Practice.'

Janssen submitted that an assessment of whether these statements were consistent with the licensed indication depended on the interpretation of the definitions of 'metastatic' and 'non-metastatic' CRPC, and Janssen strongly believed that the interpretation was determined by the

medical community's assessment of these terms in the context of the clinical trials used for marketing authorisation as explained in section one above (Smith MR *et al.* Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med* 2018;378:1408–18; Fizazi K *et al.* Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2019;380:1235–46 and Hussain M *et al.* Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2018;378:2465–74).

Janssen believed that the named presenter's interpretation in the video and the data that he presented throughout supported the established view within the prostate cancer community that micro-metastatic disease was potentially associated with the disease state of nmCRPC, and therefore within the licensed indication for apalutamide (and that for darolutamide) as discussed above, and that this was clearly demarcated (by the very definition of nmCRPC) from metastatic disease as defined by conventional imaging. In this context, the named presenter was actually providing clarity on the license framework of apalutamide.

As stated above, and in Janssen's previous response to Bayer, the key exclusion criterium for all three pivotal studies for apalutamide, darolutamide and enzalutamide in nmCRPC was the presence of metastases as detected by conventional imaging, and the marketing authorisations for all three products in high risk nmCRPC were granted on this basis (Smith MR *et al.* Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med* 2018;378:1408–18; Fizazi K *et al.* Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2019;380:1235–46 and Hussain M *et al.* Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2018;378:2465–74). All three registrational trials identified nmCRPC patients by an increasing PSA concentration and no distant metastases on conventional imaging. As Bayer highlighted, *'we, as a pharmaceutical community, need to ensure we provide the clinical community with balanced and unambiguous information to allow the individual healthcare professional to make informed decisions about patient care'*. The presentation therefore highlighted that recent data on novel next generation imaging modalities confirmed the previously held belief that it was likely that the patient population in the three clinical trials discussed had micro-metastatic disease on entry to the trials despite the absence of metastases on conventional imaging (Fendler *et al*. Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res* 2019; 25(24): 7448-7454), and that this state was associated with non-metastatic castrate resistant prostate cancer (nmCRPC) as it was defined within the licence for apalutamide. Janssen believed that it had an ethical responsibility to highlight this not only in scientific exchanges but also in promotional items.

Janssen also noted that Fendler *et al* also stated in their publication that *'Prostate-specific membrane antigen ligand positron emission tomography (PSMA-PET) detects prostate cancer with superior sensitivity to conventional imaging, but its performance in nmCRPC remains largely unknown*'. A literature search revealed the following recent publications supported Fendler *et al*, Janssen's and the oncology community's view:

> Alipour *et al* (2019) stated '*Despite high sensitivity and specificity, PSMA PET/CT as a single modality for staging advanced prostate cancer is suboptimal, given the low PSMA expression in this subgroup'.*
>
> Hyvakka *et al* (2021) stated '*The expression of PSMA in prostate cancer can be very heterogeneous and some metastases are negative for PSMA.... it is not clear how to manipulate PSMA expression for therapeutic purposes'.*

> Vrachimis (2020) stated '*It is undisputed that PSMA PET/CT provides a more accurate picture of prostate cancer patients and can lead to both upstaging and downstaging, thus affecting therapeutic management. Though it is not clear yet if the more accurate staging will lead to better therapeutic decisions and improve patient outcomes'.*

As discussed in section one above, the three sets of established and respected guidelines from ESMO (2020), EAU (2021) and ASCO (2019) supported this view:

European Society for Medical Oncology (ESMO) guidelines (2020) stated: '*Whole-body MRI, choline-positron emission tomography-computed tomography (PET-CT) and prostate-specific membrane antigen (PSMA)-PET-CT have better sensitivity and specificity than CT or bone scan but have not been shown to improve clinical outcomes. The evidence regarding PET and whole-body MRI in this setting is not adequate to make a recommendation concerning their use'.*

European Association of Urology (EAU) guidelines (2021) stated: '*With more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more patients are diagnosed with early mCRPC. It remains unclear if the use of PSMA PET/CT in this setting improves outcome'.*

American Society of Clinical Oncology (ASCO) guidelines (2019) stated: '*For men with nonmetastatic castration-resistant prostate cancer (CRPC), NGI [Next Generation Imaging] can be offered only if a change in the clinical care is contemplated. Assuming patients have received or are ineligible for local salvage treatment options, NGI may clarify the presence or absence of metastatic disease, but the data on detection capabilities of NGI in this setting and impact on management are limited'.*

Janssen stated that the trial outcomes remained valid based only on the entry criteria of conventional imaging, and the use of the products under licence likewise should be based on the conventional imaging used in the clinical trials leading to market authorisation. The role of positron emission tomography (PET), such as prostate specific membrane antigen (PSMA)-PET, remained unclear as no pivotal phase 3, prospective randomised clinical trials had been published in which they had been used to inform treatment decisions. Janssen submitted that it should not therefore exclude patients from receiving potential benefits from the use of licensed products by using novel next generation imaging modalities that effectively redefine the populations that were used within the clinical trials on which the marketing authorisations were based.

Janssen noted that Bayer stated that:

> *'PSMA-PET is fast becoming more and more widely available to stage prostate cancer, contrary to Janssen's view and is FDA approved as well reimbursed by NHS England for prostate cancer diagnosis and staging currently in two scenarios in the UK:*
>
> *a) In primary disease when considering radical treatment and staging of:*
> - *high risk clinically relevant Stage T3 or more*
> - *PSA >20ng/ml*
> - *Gleason score > 8*
> - *Suitable for curative treatment (RT or prostatectomy) after conventional imaging*

b) Suspected recurrence in patients with rapidly rising PSA and negative or equivocal conventional imaging where results would directly influence patient management.'

Firstly, Janssen was disappointed Bayer failed to provide the supporting reference for this claim as requested in its letter of 25 November, since Janssen was unable to locate such a recommendation from NHS England.

Secondly, a literature search revealed that the centres with access to PSMA-PET were Birmingham, the Royal Marsden, UCLH, University Hospital, Liverpool, Guys and St Thomas', Coventry and Warwick, and the Paul Strickland Centre. Janssen also noted that PSMA-PET was not available in Scotland.

Thirdly, Janssen noted that scenario a) was not relevant in the context of nmCRPC, and that scenario b) which highlighted PSMA-PET use *'where results would directly influence patient management'* was also not applicable as discussed above and in section one. Janssen believed that the data that the named presenter presented and commented on clearly illustrated the majority view of the prostate cancer medical community that this was not a scenario in which PSMA-PET results would or should directly influence patient management, and this was reflected in the most up-to-date clinical guidelines as listed above as well as in the most recent published literature (Smith MR *et al.* Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med* 2018;378:1408–18; Fizazi K *et al.* Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2019;380:1235–46; Hussain M *et al.* Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2018;378:2465–74; National Institute of Clinical Excellence (NICE). 2021. Prostate cancer: diagnosis and management [NICE Guideline 131]. https://www.nice.org.uk/guidance/ng131/resources/prostate-cancer-diagnosis-and-management-pdf-66141714312133. Accessed 24/12/2021; Fendler *et al*. Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res* 2019; 25(24): 7448-7454; Parker C *et al*. Prostate cancer: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020; 31(9): 1119-1134; Mottet, N., *et al*. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer – 2021 update. Part 6: Treatment. *Eur Urol*, 2021 and American Society of Clinical Oncology (2019). Optimum imaging strategies for advanced prostate cancer: *ASCO Guideline*. https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/2019-Optimum-Imaging-Prostate-Summary-Table.pdf).

Janssen submitted that whilst PSMA-PET scanning was FDA-approved in the US, it was still not routinely used in UK practice. Currently, NHS England had reimbursed apalutamide in nmCRPC based on the following criteria stated in the National Cancer Drugs Fund List (NHS England. National Cancer Drugs Fund List. Nov 2021. https://www.england.nhs.uk/wp-content/uploads/2017/04/National-Cancer-Drugs-Fund-list_version1.196_-17112021.pdf Accessed 18/11/2021):

> *'This patient has non-metastatic prostate cancer as defined by recent imaging with conventional imaging with both a whole-body isotope bone scan and a CT/MR scan of the chest, abdomen and pelvis.'*

As Janssen pointed out above in section one and in its second response to Bayer, it noted also how Bayer defined both nmCRPC and conventional imaging in its own promotional materials.

Therefore, the context of nmCRPC was not yet a scenario in which the use of PSMA-PET was supported or reimbursed according to available published literature and guidelines, supporting Janssen's view that PSMA-PET did not currently fall within the definition of conventional imaging. The discussion of the results of Fendler *et al* in the presentation do, however, provide important context to prescribers faced with making management decisions based on the definition of nmCRPC, and the discussion was therefore important and relevant for presentation in promotional material, which should be accurate, balanced, fair, objective and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly.

Janssen therefore denied a breach of Clause 11.2.

PANEL RULING

The Panel noted Bayer's allegation that three statements highlighted by it supported the use of products licensed for nmCRPC in patients in whom metastases had been detected using novel imaging and thus advocated the off-licence use of apalutamide.

The Panel noted Janssen's submission that an assessment of whether these statements were consistent with the licensed indication depended on the interpretation of the definitions of 'metastatic' and 'non-metastatic' CRPC, and it considered that the interpretation was determined by the medical community's assessment of these terms in the context of the clinical trials used for marketing authorisation as explained at Point 1 above.

The Panel noted Janssen's submission that the key exclusion criterium for all three pivotal studies for apalutamide, darolutamide and enzalutamide in nmCRPC was the presence of metastases as detected by conventional imaging, and the marketing authorisations for all three products in high risk nmCRPC were granted on this basis. The Panel further noted Janssen's submission that the trial outcomes remained valid based only on the entry criteria of conventional imaging, and the use of the products under licence likewise should be based on the conventional imaging used in the clinical trials leading to market authorisation. According to Janssen, the role of positron emission tomography (PET), such as prostate specific membrane antigen (PSMA)-PET, remained unclear as no pivotal phase 3, prospective randomised clinical trials had been published in which they had been used to inform treatment decisions; therefore it should not exclude patients from receiving potential benefits from the use of licensed products by using novel next generation imaging modalities that effectively redefine the populations that were used within the clinical trials on which the marketing authorisations were based.

The Panel noted Janssen's submission that whilst PSMA-PET scanning was FDA-approved in the US, it was still not routinely used in UK practice. Currently, NHS England had reimbursed apalutamide in nmCRPC based on the following criteria stated in the National Cancer Drugs Fund List:

> 'This patient has non-metastatic prostate cancer as defined by recent imaging with conventional imaging with both a whole-body isotope bone scan and a CT/MR scan of the chest, abdomen and pelvis.'

The Panel noted Janssen's submission that as pointed out above in section one, Bayer had similarly defined both nmCRPC and conventional imaging in its own promotional materials.

The Panel noted that the complainant bore the burden and proof. Noting the above, the Panel did not consider, on the evidence before it, that Bayer had established that three statements made by the presenter as highlighted by Bayer promoted apalutamide off licence as alleged and **no breach of Clause 11.2** was ruled**.**

4 Summary

COMPLAINT

In summary, Bayer explained why it considered that Janssen was in breach of Clauses 6.1, 6.2, 6.3, 6.4, 6.6, 11.2 and 14.1 on multiple counts highlighted within the body of its complaint and for this reason believed that Janssen had failed to maintain high standards in breach of Clause 5.1.

Due to the serious nature in respect of the off-licence promotion of apalutamide in metastatic CRPC patients which was inconsistent with the particulars stated in the summary of product characteristics (SPC) and the incomplete safety data presented for apalutamide in the SPARTAN trial, Bayer considered that Janssen had brought discredit upon, and reduced confidence in, the pharmaceutical industry and was therefore also in breach of Clause 2 of the 2021 ABPI Code.

RESPONSE

In summary Janssen believed the promotional video provided an appropriate discussion and presentation of published evidence by a respected and highly experienced prostate cancer clinician that puts in context the trial data and up-to-date evidence based on the published literature, and that allowed other specialist physicians experienced in the medical treatment of prostate cancer to make informed prescribing decisions based on a very clear analysis and interpretation of the most recent data.

Janssen therefore denied breaches of Clauses 2, 5.1, 6.1, 6.2, 6.3, 6.4, 6.6, 11.2 and 14.1.

PANEL RULING

The Panel noted its comments and rulings above and consequently ruled **no breach of Clauses 5.1 and 2.**

Complaint received **17 December 2021**

Case completed **3 March 2023**