CASE AUTH/3534/7/21

ASTELLAS v JANSSEN

Promotion of Zytiga on a website

Astellas Pharma Limited complained about the promotion of Zytiga (abiraterone acetate) on a webpage entitled 'Zytiga Quality of Life' within the Oncology section of Janssen's Medical Cloud website. The website promoted the quality of life (QoL) improvements that Zytiga (abiraterone) could provide making reference to 3 individual clinical trials. Claims of superiority over enzalutamide as well as placebo were made.

The page in question referred to claims regarding abiraterone plus prednisolone (AAP) in the treatment of metastatic castrate-resistant prostate cancer (mCRPC) versus placebo or Astellas' product, Xtandi (enzalutamide) (ENZ).

The detailed response from Janssen is given below.

1 Main webpage heading claim:

'ZYTIGA COULD SIGNIFICANTLY IMPROVE HRQoL [health related quality of life] FOR YOUR PATIENTS WITH mCRPC [metastatic castrate-resistant prostate cancer]'

Astellas alleged that the claim that Zytiga could 'significantly improve HRQoL' *was* all-encompassing, inaccurate, exaggerated and misleading.
Astellas noted that the claim was supported by four references which referred to three separate trials, which did not adequately reflect the totality of QoL evidence relating to abiraterone plus prednisolone and enzalutamide. Therefore, Astellas alleged that the references did not adequately support the claim that abiraterone plus prednisolone 'could significantly improve HRQoL'. There was no evidence presented in the remainder of the material that supported the claim that abiraterone plus prednisolone significantly improved HRQoL overall; it merely 'cherry-picked' data positive to abiraterone plus prednisolone from various sources that related to specific sub-elements of quality of life assessment.

The Panel noted that Astellas did not deny that abiraterone plus prednisolone had demonstrated superior QoL metrics than placebo plus prednisolone in this clinical setting but alleged that this was not the same as claiming that abiraterone plus prednisolone 'improves' QoL; Astellas argued that the data suggested better preservation of QoL over time in patients with metastatic prostate cancer compared to placebo plus prednisone. The Panel noted Janssen's submission that the studies were not designed to demonstrate preservation of QoL. In each statistical section of the 4 publications, the criteria as to how improvement would be defined was given.

The Panel noted Janssen's submission that there was no one single definition of HRQoL, but the Centre for Communicable Disease defined it very broadly as 'Health-related

quality of life (HRQOL) is an individual's or a group's perceived physical and mental health over time'.

The Panel noted Janssen's submission that the four references used in the Zytiga QoL page demonstrated how Zytiga could achieve this by showing improvements in Physical Health (Functional Wellbeing (FWB) and Physical Well Being (PWB)) in Khalaf *et al* and fatigue, in Sternberg *et al* and Thiery-Vuillemin *et al*. For Mental Health the positive beneficial impact was demonstrated by a smaller percentage of patients showing a worsening of cognitive impairment over time in Thiery-Vuillemin *et al* and depression in Khalaf *et al*. Janssen further listed some of the positive results for abiraterone v placebo or enzalutamide which were mentioned in abstracts but were not included on the website.

HRQoL appeared to the Panel to be a broad term that could be supported by a number of patient reported outcomes. The Panel noted that there appeared to be data to show HRQoL related patient reported outcomes could be significantly improved with Zytiga compared to placebo and enzalutamide as submitted by Janssen. The Panel noted Astellas' allegation that there was data from studies which had not been included and thus Janssen had 'cherry picked' the data. The Panel noted Janssen response to this general allegation. Both views were set out in detail in the General comments section below.

Taking all the comments and responses into consideration, the Panel decided that, on balance, Astellas had not proven that the claim at issue was all-encompassing, inaccurate, exaggerated and misleading as alleged. On the evidence before it, based on Astellas' narrow allegation, the Panel ruled no breach of the Code.

The Panel noted that Astellas made reference to the quality of life claim in its allegations regarding other claims in the material. Following its decisions set out below the Panel did not consider that the rulings in Points 2 and 3 below impacted on its ruling in Point 1.

2 First main sub heading claim:

> **'SIGNIFICANTLY FEWER PATIENTS REPORTED WORSENING OF FATIGUE WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE'**

Supported by two minor subheading claims:

> **'Percentage of patients reporting clinically meaningful worsening of fatigue during the first 12 months of treatment, as assessed by BFI-SF [Brief Fatigue Inventory – Short Form].'**
>
> **'Proportion of patients with clinically significant fatigue at baseline reporting an improvement in fatigue intensity.'**

Astellas stated that the claim 'Percentage of patients reporting clinically meaningful worsening of fatigue during the first 12 months of treatment, as assessed by BFI-SF,' was referenced to Thiery-Vuillemin A *et al* 2020 which reported a real-world data study reporting patient reported outcome (PRO) data derived from patient-completed questionnaires. Although the authors concluded that the original sample size was

'adequate', the numbers involved had not been clearly represented for readers to make their own conclusions on this point. The study noted that the questionnaire completion rate decreased over time. In the abiraterone plus prednisolone group, 105 patients were initially enrolled but by the end of the trial 74 patients were left, of which, only 55 completed the required questionnaires. In the enzalutamide group, 106 patients were recruited, reducing to 68 patients still enrolled in the last study period, of which only 49 completed the required questionnaires. This meant that only half of the initial trial population completed the questionnaires in the last period of the study, which Astellas stated called into question the strength of any claims drawn from the study. This aspect of the study was not made clear to readers of the webpage. Moreover, this small observational, non-randomised study claimed significant differences in the domains of fatigue and perceived cognitive function but with no significant impact on global health status/quality of life. The majority of individual patient reported outcome items did not show significant differences and/or favoured enzalutamide (Thiery-Vuillemin A *et al* supplementary table 5) further undermining the overarching claim of 'HRQoL improvement'.

The claim 'Proportion of patients with clinically significant fatigue at baseline reporting an improvement in fatigue intensity' was referenced to Sternberg *et al* 2013.

Astellas stated that the footnote to the associated figure stated: 'COU-AA-301: a phase III, randomised, double-blind, placebo-controlled study conducted in patients with mCRPC in the post-chemotherapy setting' with no mention of the fact that these patient reported outcome (PRO) data were collected as part of an exploratory analysis. Indeed, the study authors specifically stated that 'Patient reported outcomes were therefore included as exploratory end points in this phase III trial'. Astellas referred to the international regulatory guidelines which stated that exploratory trials could not form the basis of formal proof and should be considered as supportive data only. Astellas recognised that the material in question was not for regulatory submission, but the same principle should apply to the use of data to support promotional claims of superiority.

In addition, this claim was a sub heading under the larger heading 'SIGNIFICANTLY FEWER PATIENTS REPORTED WORSENING OF FATIGUE WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE' which could be interpreted by a reader that all data within this section related to enzalutamide as the comparator. However, the figure below the 'Proportion of patients with clinically significant fatigue at baseline reporting an improvement in fatigue intensity' sub-heading referred to the comparison of abiraterone plus prednisolone versus placebo. This was only apparent in the figure where the x-axis of the graph was labelled accordingly. The potential for confusion was increased by the use of the same colour shading for the placebo and enzalutamide bars in the two graphs used consecutively.

Furthermore, the web page did not allow the reader to review a whole figure on one screen without scrolling or changing the zoom settings on the browser; Astellas alleged that this increased the risk of salient information being missed and, in this instance, could mislead the reader, to the actual comparison being made.

With regards to the claim 'Percentage of patients with clinically significant worsening of fatigue during the first 12 months of treatment as assessed by BFI-SF, the Panel noted Janssen's submission that Thiery-Vuillemin *et al* 2020 was described as a large,

multinational study. Janssen denied that no improvement in Quality of Life was seen, as QLQ-C30 Functional scales, QLQ-C30-Symptom scales, BPI-SF, BFI-SF and FACT-Cog were a breadth of validated tools used to measure a variety of different elements of quality of life; not a single domain was significantly in favour for enzalutamide and as per Thiery-Vuillemin *et al*, there were statistically significant differences (p<0.05) in favour of abiraterone over enzalutamide for 18 PRO items. The Panel noted that Thiery-Vuillemin *et al* stated that key PRO items (cognitive impairments and fatigue) were significantly (p<0.05) in favour of abiraterone versus enzalutamide during the study. Fatigue and asthenia (adverse events) were lower with abiraterone than with enzalutamide (5% vs 15% and 10% vs 11%, respectively).

The Panel noted that Thiery-Vuillemin *et al* stated that only the lowest percentage per PRO item (worse-case scenario, all items must be answered to consider a PRO complete) was presented for all patients and for those 'still in study'. The overall median completion rate for the 12-month period was 81% for patients still in the study, based on all 28 PRO questions and all periods, and for both treatments.

The Panel noted Janssen's submission that Astellas failed to take into the account the statistical section of the publication which stated that all analysis were based on an 'Intention-To-Treat' population (211) basis with additional confirmatory sensitivity analysis being undertaken to confirm Thiery-Vuillemin *et al*'s findings. The Panel further noted Janssen's submission that the authors did not cite the questionnaire completion rate as a limitation of the trial. The Panel noted that the authors stated 'the study also has several strengths: it has a large sample size, despite a decline in questionnaire response over 12-mo'.

The Panel noted that beneath the claim at issue, the webpage displayed a bar chart with 'Zytiga plus low-dose prednisolone (n=105)' corresponding to 53% and 'Enzulatimide (n=106)' corresponding to 79%; there appeared to be a statistically significant difference between the two groups (p=0.008).

The Panel considered that whilst the intended audience would likely be aware that given the nature of the disease there would be a reduction in the number of patients completing the questionnaires, it was not clear from the bar chart that the patient numbers given were in relation to the original sample size rather than the number of patients that completed the Brief Fatigue Inventory – Short Form. The Panel therefore ruled a breach of the Code as alleged.

In the Panel's view, whilst it would have been helpful to have stated the final number of patients that completed the questionnaire, to portray the completion rate to readers, the bar chart nonetheless included the original sample size; the Panel noted that the analyses were based on all treated patients (ITT population). Noting its comments above, the Panel did not consider that the material called into question the strength of the claims as alleged. The Panel thus ruled no breach of the Code.

The Panel noted that beneath the second supporting claim 'Proportion of patients with clinically significant fatigue at baseline showing improvement in fatigue intensity' was another bar chart illustrating the difference between the abiraterone and placebo subgroups (58.1% vs 40.3%; p=0.0001). The Panel noted that the chart was referenced to Sternberg *et al* with the associated footnote: 'COU-AA-301: a phase III, randomised,

double-blind, placebo-controlled study conducted in patients with mCRPC in the post-chemotherapy setting'.

The Panel noted Astellas' allegation that there was no mention of the fact that the patient reported outcome (PRO) data had been collected as part of an exploratory analysis. The Panel noted Janssen's submission that this was the pivotal phase III study on which the market authorisation was granted and not an 'exploratory study' but a Phase 3 confirmatory study with an exploratory end point. In the Panel's view, Astellas' allegation was in relation to disclosing that the PRO data formed part of an exploratory analysis; it appeared that Janssen interpreted the allegation as the study being an exploratory trial. Sternberg *et al* stated that it was the first phase III clinical trial in the setting of advanced prostate cancer to specifically evaluate fatigue outcomes, using an established instrument that has been validated for the assessment of cancer-related fatigue.and patient reported outcomes were included as exploratory endpoints in this phase III trial.

The Panel considered that, in omitting a statement that indicated that the data was derived from exploratory end points, the claim was not sufficiently complete to enable the recipient to form their own opinion and ruled a breach of the Code.

The Panel noted the two titles for the bar charts were smaller and directly beneath the larger subheading claim 'SIGNIFICANTLY FEWER PATIENTS REPORTED WORSENING OF FATIGUE WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE'; one bar chart illustrated a comparison between abiraterone (green) and enzalutamide (grey), whilst the second bar chart illustrated a comparison between abiraterone (green) and placebo (grey). In the Panel's view, both bar charts and their titles would be interpreted as supporting the subheading claim that compared Zytiga and enzalutamide which was not so. The Panel considered that this misleading impression that both bar charts supported the same overarching claim was compounded by the same colour (grey) being used for two different comparator arms, enzalutamide and placebo. The Panel considered that the immediate and overall impression to a busy health professional would likely be that both bar charts were supportive of the claim and both bar charts compared abiraterone and enzalutamide which was not so. The Panel, therefore, ruled breaches of the Code.

In relation to Astellas' allegation that that there was a risk of salient information being missed as the webpage did not allow the reader to review a whole figure on one screen without scrolling or changing the zoom settings, the Panel noted that readers would be well used to scrolling up and down to obtain all the information. There was no separation or use of footnotes such that the reader would have to scroll over other information to see the relevant information. The Panel noted its ruling of a breach of the Code above and did not consider that otherwise the area occupied by the text and charts on the screen was such that it could mislead the reader to the actual comparison being made as alleged and as such, no breach of the Code was ruled.

3 i) Second main sub heading claim:

'FEWER PATIENTS REPORTED WORSENING OF THEIR PERCEIVED COGNITIVE IMPAIRMENT WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE'

Supported by one minor subheading claim:

> **'AQUARiUS**
>
> **Patients (%) reporting clinically meaningful worsening of perceived cognitive impairment'**

Astellas stated that the claims above referenced Thiery-Vuillemin A *et al* 2020 and its concerns echoed those outlined above ie that that data had been cherry picked without context and presented in a misleading way. Astellas additionally highlighted that this cognitive function claim did not reference the analysis reported in Khalef *et al* 2019 (outlined below and used by Janssen to support the HRQoL claim) which did not demonstrate any differences in cognitive function between abiraterone plus prednisolone and enzalutamide. The claim implied by the graph entitled 'Patients (%) reporting clinically meaningful worsening of perceived cognitive impairment' did not consider the balance of available data to fully inform the reader.

Moreover, the AQUARiUS study authors concluded: 'Overall, these data confirm previously published interim analyses from this study and support the positive impact of abiraterone and enzalutamide treatment on HRQoL under real-world conditions'. Astellas stated that the AQUARiUS study also showed that the results achieved in the pivotal studies substantiated the balance of available evidence for both abiraterone plus prednisolone and enzalutamide in supporting patient QoL without claiming superiority of one over the other.

The Panel noted that the graph presented beneath the claims was entitled 'Patients (%) reporting clinically meaningful worsening of perceived cognitive impairment'. The graph compared the percentages of patients in the abiraterone and enzalutamide arms over months 1, 2, 3, 4–6 and 12. The graph was referenced to two papers (Thiery *et al* 2018 and Thiery *et al* 2020) and included odds ratios and p values for each time period.

With regard to the sub heading claim, 'FEWER PATIENTS REPORTED WORSENING OF THEIR PERCEIVED COGNITIVE IMPAIRMENT WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE', the Panel noted Janssen's submission that there were several positive findings from this study, which Janssen had chosen not to use in the promotional item at issue and that the reason why the perceived cognitive benefit was chosen as opposed to all the other benefits that were seen for abiraterone compared to enzalutamide, was that the cognitive function benefit was maintained throughout the 12-month period. The Panel further noted Janssen's submission that the claim could also be supported by Das *et al*, Parimi *et al*, Shore *et al*, Kvorning *et al* and Raju *et al.* The Panel further noted Janssen's submission that Astellas had failed to mention that Khalaf *et al* stated that 'this MoCA cognitive assessment had not been validated in this clinical setting and that a more rigorous neuropsychiatric evaluation would be necessary to fully characterise any cognitive effects observed with therapy'.

On the evidence before it, the Panel did not consider that Astellas had established that Janssen had cherry picked data, nor that the exclusion of MoCA cognitive assessment outcomes from Khalaf *et al*, which was stated to not have been validated in this clinical setting, meant that the data had been misleadingly presented and no breach of the Code was ruled.

Whilst Astellas alleged that the claim implied by the graph entitled 'Patients (%) reporting clinically meaningful worsening of perceived cognitive impairment' did not consider the balance of available data to fully inform the reader, the Panel did not consider that there was an allegation in relation to the presentation of the graph itself. The Panel thus ruled no breach of the Code.

In relation to the excerpt of the AQUARiUS study highlighted by Astellas, the Panel noted that the conclusion of the study (Thiery-Vuillemin) stated:

> **'This 12-mo study showed that patients with mCRPC who were treated with abiraterone acetate experienced significantly less fatigue and cognitive impairments than enzalutamide-treated patients. This difference occurred early after treatment initiation. In a real-world setting, it suggests an advantage of abiraterone over enzalutamide on fatigue and cognitive function. This difference should be considered when choosing treatment'.**

followed by:

> **'These results are also in line with other published data [20]. The safety outcomes were consistent with the known safety profile of each drug, but abiraterone was associated with fewer fatigue, asthenia and neurological AEs than enzalutamide. Overall, these data confirm previously published interim analyses from this study [9,10], and support the positive impact of abiraterone and enzalutamide treatment on HRQoL under real-world conditions. AQUARiUS also shows that the results achieved in the pivotal studies for each drug can be translated into clinical practise'.**

Whilst the Panel noted that the authors made reference to the positive effects of both abiraterone and enzalutamide, it noted that cognitive impairments appeared to have been experienced in significantly fewer patients in the abiraterone arm compared to the enzalutamide arm, as reflected in the subheading claim at issue. The Panel therefore did not consider that Astellas had established that the claim, which compared abiraterone and enzalutamide, was misleading as alleged and thus ruled no breach of the Code.

3ii) Third main sub heading

> **'PATIENTS REPORTED IMPROVED HRQoL‡ WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE'**
>
> **Supported by minor subheadings**
>
> **'Patients reported less clinically significant worsening with ZYTIGA plus low- dose prednisolone vs. enzalutamide (all patients) for PWB [physical well-being] and FWB [functional well-being]'**
>
> **'Post-hoc analysis: Change in PHQ-9 [Patient Health Questionnaire-9] scores from baseline significantly favoured ZYTIGA over enzalutamide at Weeks 4, 8 and 12'**

Astellas stated that the Khalaf study was clearly not robust enough to support a promotional superiority claim for abiraterone over enzalutamide. Indeed, the authors

stated that 'For all comparisons we used a significance α level of $p \leq 0.05$ without correction for multiple testing, as our statistical analyses were not prespecified and are considered exploratory'. In the abstract to the manuscript the authors further noted: 'these analyses were not prespecified, and results should be considered to be hypothesis generating'. This was not clear in the promotional material and in fact Janssen went as far to claim 'clinical significance'; based on these data; therefore, Astellas alleged this to be misleading.

The main heading, in this section, 'PATIENTS REPORTED IMPROVED HRQoL‡ WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE' included the term 'HRQoL' which was generally understood to cover a full spectrum of factors that were disease specific, as demonstrated by the use of a validated quality of life instrument, the FACT-P [Functional Assessment of Cancer Therapy-Prostate] questionnaire. Khalaf *et al* reported that significant FACT-P differences between the treatments were only noted in the >75 year age group, a fact that Janssen did not make clear in the promotional material. In addition, Janssen's materials only highlighted functional wellbeing (FWB) and physical wellbeing (PWB) sub-scales of the FACT-P analysis, whereas there were four sub- scales (plus 'additional concerns') in this instrument. This selective use of data clearly did not warrant an all-encompassing HRQoL superiority claim.

Astellas alleged that the figure supporting the claim 'Patients reported less clinically significant worsening with ZYTIGA plus low-dose prednisolone vs. enzalutamide (all patients) for PWB and FWB' depicted an adapted graph that had clearly been cut and presented to show positive data for abiraterone plus prednisolone only. The original graph depicted a total of 9 outcome measures across a variety of QoL questionnaires (including total FACT- P which represented global QoL outcomes) but the adapted figure only presented the 2 significant results. Although this reflected the associated sub-heading, the adapted figure obscured the full data that would have provided the reader a more comprehensive view of the overarching web page claim for HRQoL improvement.

Astellas alleged that this was another clear example of 'cherry-picked' data that was misleading and not reflective of all available evidence. Moreover, the study authors, Khalaf *et al* also conceded that:

> **'The limitations of our study included the relatively small number of patients, which resulted in large confidence intervals at individual time points for FACT-P assessments, as well as the open-label design… . these analyses were not prespecified, and results should be considered to be hypothesis generating'.**

Astellas alleged that the nature and extent of these limitations were not clearly represented in the Janssen material, and thus did not allow readers to obtain a properly informed view of the data presented, in order for them to reach their own conclusions (and the 'clinically significant' claim misled as to the nature of the data).

Astellas referred to the second minor sub-heading within this section 'Post-hoc analysis: Change in PHQ-9 scores from baseline significantly favoured ZYTIGA over enzalutamide at Weeks 4, 8 and 12' highlighted a graph from Khalaf *et al* that showed a change in PHQ-9 scores. Astellas alleged that this promotional claim implied that enzalutamide might cause depression/depressive episodes which was inconsistent with the product's SPC

(which did not list depression or depressive episodes as an adverse reaction to enzalutamide). This information, in isolation, misrepresented the benefit-risk evaluation for enzalutamide in this setting and was thus, both inaccurate and misleading and also disparaged Astellas' product. Khalaf *et al* also stated that 'no pre-planned formal psychiatric assessments were mandated to validate PHQ-9 results' highlighting the authors identification of the significant limitation to the interpretation of the results, which was not reflected in the material.

Astellas stated that it did not accept that by merely avoiding the use of the word 'depression' or any other similar term in the material, a clinician would not link depression to enzalutamide when presented with data from the PHQ-9 questionnaire. The promotion of a graph that showed PHQ-9 outcomes was a clear signpost to the insinuation that enzalutamide caused depressive symptoms and/or depression despite the absence of any evidence of this from a number of randomised placebo controlled Phase III clinical trials, that presented a much more robust evidence base than a single post-hoc exploratory analysis from a small open-label Phase II clinical trial.

The Panel noted that Astellas alleged that the Khalaf *et al* study, the cited reference to the above claims, was not robust enough to support a promotional superiority claim for abiraterone over enzalutamide and that to go as far to claim clinical significance based on these data was misleading
The Panel noted that according to Khalaf *et al*, FACT-P was a validated patient self-administered questionnaire comprising 39 questions and consisted of four quality-of-life domains (physical [PWB], functional [FWB], emotional [EWB], and social [SWB] well-being. Khalaf *et al* stated that evaluation of HRQoL, depression, and cognitive function was a secondary objective.

The Panel noted Janssen's submission that PHQ-9 and Montreal Cognitive Assessment (MoCA) were post hoc analyses and had always been clearly labelled as such on the website. The Panel further noted that reference to Khalaf *et al*, beneath a chart that supported the claim, was accompanied by the statement 'this analysis was not prespecified, and results should [not] be considered to be hypothesis generating'. The Panel noted that the statement appeared to form part of a footnote in smaller font size than the rest of the page. Whilst it had been corrected as part of the inter-company dialogue, the Panel considered that the corrected statement below the bar chart was not sufficiently clear for readers to be able to make an informed comparison between the products. Therefore, a breach of the Code was ruled.

With regard to the heading *'PATIENTS REPORTED IMPROVED HRQoL‡ WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE',* the Panel noted Astellas' allegation that the material did not make clear that significant FACT-P differences were only noted in the >75 year age group. In addition, Astellas' alleged that Janssen's materials only highlighted functional wellbeing (FWB) and physical wellbeing (PWB) sub-scales of the FACT-P analysis, whereas there were four sub-scales (plus 'additional concerns') in this instrument. Astellas alleged that this selective use of data clearly did not warrant an all-encompassing HRQoL superiority claim.

The Panel noted Janssen's submisison that the conclusion from the study stated:

> **'Our study demonstrated improved PROs in patients with mCRPC treated with first line abiraterone compared with enzalutamide, based on FACT-P, HRQoL scores and PHQ-9 depression scores'.**

The Panel noted Janssen's submission that even though it could have included a promotional claim relating to the 50% of patients aged 75 and over, for the many HRQoL domains across which significant differences were demonstrated, it decided not to include it and simply added, directly above the bar chart "For all other measures, no statistically significant difference was seen".

The Panel noted that Khalaf *et al* stated that it

> **'showed that abiraterone was associated with superior HRQoL over time compared with enzalutamide' and that 'the difference between arms was seen across many HRQoL domains and was of clinically significant magnitude for patients aged ≥ 75 yr'.**

Whilst the Panel considered that it would have been useful to have highlighted that clinical significance was only seen for patients aged 75 or over, the Panel nonetheless noted that the claim '*PATIENTS REPORTED IMPROVED HRQoL‡ WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE'* was supported by a graph that focussed on FWB and PWB for all patients the graph appeared to reflect the cited data. The Panel, noting its comments above, did not consider that the claims were such that they misled readers and thus ruled no breaches of the Code.

'*Patients reported less clinically significant worsening with ZYTIGA plus low-dose prednisolone vs. enzalutamide (all patients) for PWB and FWB'*

The Panel noted Astellas' concern that the figure supporting the claim depicted an adapted graph that had clearly been cut and presented to show positive data for abiraterone plus prednisolone only. The original graph depicted a total of 9 outcome measures across a variety of QoL questionnaires (including total FACT- P which represented global QoL outcomes) but the adapted figure only presented the 2 significant results which although reflected the associated sub-heading, obscured the full data that would have provided the reader a more comprehensive view of the overarching webpage claim for HRQoL improvement and was misleading and not reflective of all available evidence.

The Panel noted Janssen's submission that Astellas was correct in that the adapted bar chart only showed the results for PWB (Physical Well Being) and FWB (Functional Well Being) with the clear accompanying statement that *"For all other measures, no statistically significant difference was seen".* Therefore, the reader was provided with relevant and accurate information about the results to allow them to interpret the data, which Janssen considered was adequate to support the claim. The bar chart simply displayed the results relating to the above claim.

The Panel noted that according to Khalaf *et al*, the proportion of patients with clinically significant worsening was higher in the enzalutamide arm for the PWB domain (37% vs 21%; p=0.013) and the FWB domain (39% vs 23% p=0.015). The Panel considered that the chart illustrating the PWB and FWB data and the claim 'Patients reported less clinically

significant worsening with ZYTIGA plus low-dose prednisolone vs. enzalutamide (all patients) for PWB and FWB' appeared to be reflective of the cited data. The Panel considered that in the circumstances it was not misleading to not present other HRQoL measures on the chart or in the claim. It was stated that no statistically significant differences were seen, (although this was not actually so). Readers would not be misled about the data that was presented. No breaches of the Code were ruled.

'*Post-hoc analysis: Change in PHQ-9 scores from baseline significantly favoured ZYTIGA over enzalutamide at Weeks 4, 8 and 12*'

The Panel noted Astellas' allegation that this promotional claim implied that enzalutamide might cause depression/depressive episodes which was inconsistent with the product's SPC (which did not list depression or depressive episodes as an adverse reaction to enzalutamide). This information, in isolation, misrepresented the benefit-risk evaluation for enzalutamide in this setting and was thus, both inaccurate and misleading. Astellas further alleged that this section disparaged its product. Of note, Khalaf *et al* also stated that 'no pre-planned formal psychiatric assessments were mandated to validate PHQ-9 results' highlighting the authors identification of the significant limitation to the interpretation of these results, which was not reflected in the material.

Astellas did not consider that by avoiding the use of the word 'depression' or any other similar term in the material, a clinician would not link depression to enzalutamide when presented with data from the PHQ-9 questionnaire. The promotion of a graph that showed PHQ-9 outcomes was a clear sign-post to the insinuation that enzalutamide caused depressive symptoms and/or depression despite the absence of any evidence of this from a number of randomised placebo controlled Phase III clinical trials, that presented a much more robust evidence base than a single post-hoc exploratory analysis from a small open-label Phase II clinical trial.

The Panel noted Janssen's submission that the figure shown on the Janssen website was adapted from Figure 3 of the Khalaf publication and had all the statistical considerations included on it that were cited on the paper for weeks, 4, 8 and 12. Similarly all the caveats as per the publication were given ie, this was a post hoc analysis, the results were not prespecified and that they should be considered to be hypothesis generating.

With regard to Janssen's submission that it had simply reproduced the table in the Khalaf publication and made no mention of the word depression in the promotional item, the Panel noted that this was not so. A footnote on the item in question described PHQ-9 as consisting of nine diagnostic criteria for depressive episode from the Diagnostic and Statistical Manual of Mental Disorders.

The Panel noted Janssen's submission that the head-to-head comparative study of abiraterone acetate vs enzalutamide (Parimi *et al* 2016) showed that significantly more patients in the enzalutamide arm had a worsening of depression severity score 19% v 4% (P=0.03); the conclusions included: 'In this preliminary analysis, there were more pts with a worsening severity of reported depression symptoms and a trend towards an increase in cognitive impairment with ENZA as compared to ABI. These data help to characterize and define the incidence of these symptoms'. The Panel noted that the reference provided for Parimi *et al* 2016 was that of a poster when the study, NCT02125357, was

ongoing; it appeared to the Panel that the poster illustrated a preliminary analysis of the data which was later presented in Khalaf *et al* 2019.

The Panel noted Janssen's submission that depression was listed as a recognised Adverse Event for Enzalutamide (7 cases) on the MHRA Website for Drug Analysis Profiles and on the Cancer McMillan Webpage depression was listed as an acknowledged side effect for enzalutamide, stating that patients may feel low or depressed whilst on this treatment. The Panel noted that the Cancer McMillan Webpage stated below the heading 'Mood changes' that 'You may have some mood changes during this treatment. You may feel low or depressed. Let your doctor or nurse know if you notice any changes'. In relation to enzalutamide common side effects, the Panel, however, noted that it could not find a reference to 7 cases of depression within the MHRA Website for Drug Analysis Profile for enzalutamide as provided by Janssen.

The Panel noted that PHQ-9 was a self-administered questionnaire consisting of the nine diagnostic criteria for depressive episode and had been validated and shown to perform well in patients with a diagnosis of cancer. The Panel noted that below the claim 'Post-hoc analysis: Change in PHQ-9 scores from baseline significantly favoured ZYTIGA over enzalutamide at Weeks 4, 8 and 12' which was referenced to Khalaf *et al* 2019 was a graphical illustration, accompanied by the statement 'this analysis was not prespecified, and results should [not] be considered to be hypothesis generating'. In the Panel's view, PHQ-9 was a depressive scale and one of many HRQoL measures that would help inform health professionals' understanding. The Panel considered that the claim and illustration implied that there was some unfavourable data in relation to depression for patients taking enzalutamide, when compared to abiraterone. The Panel noted its comments above regarding the nature of the data submitted by Janssen to support the differences between the medicines in relation to depression severity. It considered however that the material in question was a misleading comparison which disparaged Astellas' product, particularly as there was no mention of the absence of a reference to depression in the enzalutamide SPC and did not reflect the available evidence. The Panel thus ruled breaches of the Code.

Astellas Pharma Limited complained about the promotion of Zytiga (abiraterone acetate) on Janssen's Medical Cloud website.

Astellas made some general comments to which Janssen responded and these are set out bellow followed by each individual allegation, response and Panel ruling.

GENERAL COMMENTS FROM ASTELLAS

Astellas Pharma stated that it worked to both the letter and spirit of Code and aimed to settle inter-company complaints via inter-company dialogue. Astellas started inter-company dialogue with Janssen in February 2021 and despite correspondence and a call with Janssen, the inter-company dialogue proved unsuccessful in relation to the substantive points raised by Astellas. Therefore, Astellas submitted a complaint regarding the Janssen Medical Cloud website, specifically relating to the Quality of Life page within the Zytiga (abiraterone acetate) pages of the Oncology section: https://www.janssenmedicalcloud.co.uk/oncology/prostate-cancer/zytiga/quality-of-life.

Astellas alleged that the promotional webpage was in breach of Clauses 3.2, 7.2, 7.3, 7.8, 7.9, 8.1 and 9.1 of the 2019 Code.

Details of the complaint

Overall impression

Astellas stated that the webpage in question was found within the Oncology section of the 'Janssen Medical Cloud' website and was entitled 'Zytiga Quality of Life'. This website could be accessed by any viewers who nominated themselves as a 'healthcare professional'. The page in question referred specifically to the claims regarding abiraterone plus prednisolone (AAP) in the treatment of metastatic castrate-resistant prostate cancer (mCRPC) versus placebo (PBO) or Astellas' product, Xtandi (enzalutamide) (ENZ).

The website promoted the quality of life (QoL) improvements that Zytiga (abiraterone) could provide making reference to 3 individual clinical trials. Claims of superiority over enzalutamide as well as placebo were made.

Astellas alleged that the overall layout of the pages was unclear, with misleading signposting to placebo and enzalutamide data as a result of a lack of clear headings (detailed below). It was difficult to review all the figures related to a claim without scrolling down or adjusting the browser zoom settings, putting undue onus on the reader to undertake an informed review of the evidence presented. For example, where statements were referenced to a footnote, these could only be seen by scrolling down and searching the small print.

Astellas alleged that the data presented had been carefully selected to support the claims, providing positive information for abiraterone plus prednisolone without sufficient representation of the entirety of the data, which readers would require to make a fully informed opinion on the data presented. The references did not adequately reflect the totality of QoL evidence relating to abiraterone plus prednisolone or enzalutamide. Indeed, reporting of a study of health related quality of life (HRQoL) with enzalutamide in mCRPC, Loriot *et al* 2015, stated in the discussion section:

> 'The significant benefit in overall survival by abiraterone acetate plus prednisone versus prednisone plus placebo was accompanied by a reduction in risk of degradation in FACT-P total score (HR 0·79 [95% CI 0·67–0·93]; p=0·005) and PCS score (HR 0·72 [0·61–0·84]; p<0·0001), whereas the HRs in our study for FACT-P total score and PCS score were 0·62 (0·54–0·72) and 0·69 (0·60– 0·78), respectively, with enzalutamide versus placebo.'

Furthermore, Basch 2015 providing a review of enzalutamide mCRPC data stated: 'both of these drugs add several months of survival, with superior physical functioning and overall quality of life compared with placebo'.

Moreover, the description of the studies provided on the Janssen website was very sparse, which Astellas stated precluded readers from being able to gain an informed opinion as to the validity of the promotional claim, especially in regard to the multiple limitations of the study methodologies, as outlined in the references provided.

Finally, with regards to supporting the overarching claim of QoL 'improvement', Astellas did not deny abiraterone plus prednisolone had demonstrated superior QoL metrics than placebo plus prednisolone in this clinical setting, but this was not the same as claiming that abiraterone plus prednisolone 'improves' QoL; Astellas would argue rather it suggested better preservation of QoL over time in these patients with metastatic prostate cancer compared to placebo plus prednisone.

Astellas strongly asserted the promotional webpage clearly disregarded the requirement of providing a clear and balanced view of the totality of information available. Both enzalutamide and abiraterone plus prednisolone had demonstrated QoL benefits in multiple pivotal trials and QoL analyses.

Thus, Astellas alleged that the Janssen webpage breached Clauses 3.2, 7.2, 7.3, 7.8, 7.9, 8.1 and 9.1 of the 2019 Code.

Astellas' detailed allegations are set out below after Janssen's general response.

GENERAL COMMENTS FROM THE RESPONDENT

Janssen denied all breaches of Code, and specifically with respect to Clauses 3.2, 7.2, 7.3, 7.8, 7.9, 8.1 and 9.1 as alleged by Astellas. In addition, Janssen raised concerns regarding the way in which Astellas had conducted itself during the inter-company dialogue.

Janssen submitted that Astellas' actions and documentation did not support Astellas' assertion that it fully complied with inter-company dialogue procedures.

For the initial complaint, Astellas' letter (12 February 2021) was sent to Janssen's general Medical Information Box at 17.04. Although it was addressed to the medical director, Astellas had made no attempt to contact in advance, 'to alert the respondent company to a complaint and to outline the basis of that complaint'. This first letter was only 3 pages long and alleged that the promotional item was in breach of Clauses 7.2, 7.3, 7.9, 8.1 and 9.1.

Janssen sent a reply on 26 February 2021, within the customary 10 working days. On 12 March, Astellas sent a second letter to Janssen stating that it disagreed with all the points that Janssen had made without given any reasons which was not in accordance with the guidance given which stated 'The complainant should provide written comments to the respondent stating clearly its position with respect to all points originally raised'. In addition, Astellas cited a case where Janssen in the Netherlands had been found in breach for the inappropriate use of one of the studies referred to in the UK Zytiga QOL webpage and which in Astellas' view had clear similarities to the current complaint in the UK. When asked for copies of the Dutch promotional item and an English translation of the ruling, neither were provided and there was no subsequent mention of this case in subsequent inter-company dialogue.

Astellas then sent a third letter on 12 April which included additional complaints and alleged breaches of the Code. Whereas the initial letter of complaint had been 3 pages long, this third letter was 9 pages long and alleged breaches of Clauses 3.1, 7.2, 7.3, 7.4, 7.9, 8.1 and 9.1.

Inter-company dialogue by telephone conference (TC) was held on 12 May 2021 where two agreements were reached as documented in the Astellas written minutes for this call. These were that Janssen would remove a 'not' relating to Khalaf *et al* and change the 5mgs OD to

5mgs bd or 10mgs OD. This was duly done and communicated to Astellas. As Astellas had marked these two actions as being complete, Janssen believed that on these two points, inter-company dialogue had been successful. Janssen was therefore disappointed that Astellas had raised these as new potential breaches which was not in accordance with the procedure which stated that 'that companies should not resurrect any issue later as part of a complaint to the PMCPA without first attempting further inter-company dialogue'.

This had not happened.

In summary, Janssen refuted any and all breaches of the Code alleged by Astellas, who had made multiple complaints against the Zytiga Quality of Life page which had constantly changed over time . Astellas had even questioned the suitability of Zytiga being granted a licence in the UK (Astellas letter to Janssen 12 April 2021). In its letter to the PMCPA, Astellas introduced 7 new complaints and resurrected 2 previous complaints which Janssen believed had been resolved at the inter-company dialogue level. Such actions were not in line with the spirit of inter-company dialogue and served to undermine the process of self-regulation of the pharmaceutical industry as a whole.

Overview of the promotional item

a) Design and layout

The promotional item at issue related to a single webpage on the Janssen Medical Cloud which was clearly marked as intended for UK Health Professionals only. The webpage provided a summary of the consistent trends, of the positive Quality of Life benefits that had been seen in men with metastatic Castrate Resistant Prostate Cancer (mCRPC) prescribed Zytiga (abiraterone acetate).

Janssen stated that the webpage had the title claim 'Zytiga could significantly improve HRQoL for your patients with mCRPC', below which were 4 bar charts and 1 box plot that had been adapted from 3 different studies, for which there were 3 publications and 1 poster. In addition to the main claim, there were 4 other claims, written in CAPITALS and 5 headings for the charts, written in **bold**. Each chart had either contained within it or directly below it, relevant information concerning the nature of the study including: its design, dose of medicine, results, (with limitations where appropriate) patient numbers, p values and odds ratio (where appropriate) so that the reader could make an informed decision concerning the validity and applicability of these results to routine medical practice.

In summary, the item was a simple and succinct summary of the data about Zytiga's health related quality of life (HRQoL) benefits in this group of patients. For patients with metastatic hormone-sensitive prostate cancer (mHSPC), there was a separate webpage, which was not the subject of this complaint.

b) Supporting references and study designs

The main claim for the item was 'Zytiga could significantly improve HRQoL for your patients with mCRPC', which was supported by 4 references from 3 individual studies, which all stated that an improvement in HRQoL were seen in patients on Zytiga. A summary of the study designs and HRQoL findings were provided below.

Janssen stated that Sternberg *et al* 2013 was a phase III, randomised, double-blind, placebo-controlled study, in mCRPC men who had failed previous docetaxel therapy (n= 797), where fatigue was measured using the Brief Fatigue Inventory (BFI) questionnaire as a prespecified exploratory end point. This was the pivotal registration study on which the 'Accelerated Approval was granted in the USA and which the authors describe as being the 'First phase III study to look at a HRQoL end point*'*. The conclusion was that 'Abiraterone acetate and prednisone was associated with Clinically meaningful improvements in fatigue compared with prednisolone alone'. The comparator was placebo.

Janssen stated that Khalaf *et al* 2019 was a phase II, multicentre, randomised study of abiraterone acetate 1000mg and prednisone 5 mg daily versus enzalutamide 160 mg daily, for first-line treatment of mCRPC, (n= 202) where HRQoL, depression (PHQ-9) and cognitive function were prespecified, secondary objectives. Astellas and Janssen both provided a Grant-in-Aid' for this study. The conclusion for this study stated that 'Our study demonstrated improved PROs [patient reported outcomes] in patients with mCRPC treated with first-line abiraterone compared with those treated with enzalutamide, based on FACT-P, HRQoL scores and PHQ-9 depression scores'. The comparator was enzalutamide.

Janssen stated that Thiery-Vuillemin *et al* 2020 was a phase IV, 12 month, two-cohort, prospective, observational, non randomised multicentre study in mCRPC patients (n=211) conducted by office or hospital-based urology and/or oncology specialists in Denmark, France and the UK where a variety of different QOL measures were evaluated and where the authors stated that 'few studies have studied the impact on these two treatments in the real-life setting*'.* The conclusion for this study being *'*In a real-world setting, this 12-month analysis suggests an advantage of abiraterone acetate plus prednisone over enzalutamide on fatigue and cognitive function; this finding occurred early after treatment initiation. This difference should be considered when choosing treatment'. The comparator was enzalutamide.

Janssen stated that these studies included a total of 1210 men with mCRPC, were of differing clinical trial design, undertaken in both the hospital and community setting, in men with both first line and post-docetaxel mCRPC and used a variety of different validated Quality of Life measurements. NICE guidance PMG4 stated that experimental studies (such as controlled trials), and observational studies (such as before-and-after studies) could be used to consider the effectiveness of interventions. (NICE 2018).

The studies were all published in highly prestigious, peer-reviewed journals, namely Steinberg, in The Annals of Oncology (Impact Factor 32.9) and Khalaf and Thiery-Vuillemin in European Oncology, which was the official publication for the European Urology Association, (Impact Factor 17.5) with the interim results for the Thiery-Vuillemin study being presented in poster form at ASCO in 2018. All publications included detailed statistical sections and had named statisticians included as authors in the publications, which was important to note as several of Astellas' complaints related to statistical considerations.

For two of the studies (Thiery-Vuillemin and Khalaf) the comparator medicine was enzalutamide. For the third study, (Sternberg) it was placebo.

c) <u>Study results shown on the Zytiga Quality of Life Webpage</u>

Janssen stated that only those results which were specifically mentioned in the abstracts of the 3 publications were shown on the webpage at issue, as these were the ones which the authors

considered to be the main and most relevant findings of the study. No other results, including additional other beneficial ones for abiraterone acetate (see below in section 2c) were included in the promotional item.

d) Additional Head-to-Head Comparative studies for abiraterone v enzalutamide to assess HRQoL which were NOT shown on the Zytiga Quality of Life Webpage

A literature search undertaken on 6 August 2021 revealed that there were 7 head-to-head comparative clinical trials where the HRQoL benefits of abiraterone acetate had been compared to enzalutamide. For those four clinical trials which had NOT been used in this promotional item, Janssen submitted that the results all favoured abiraterone over enzalutamide with the conclusions being as follows:

> Shore *et al*. 2019 **Conclusions: '**Although baseline values were similar, more fatigue and neurocognitive differences were seen with enzalutamide compared to abiraterone acetate plus prednisolone'.
>
> Das P *et al*. 2018 **Conclusions:** 'Our data suggest that there are marked differences between AA + P vs ENZA and their effects on physical and emotional wellbeing. Patients reported more depression symptoms and a clear trend towards an increase in cognitive impairment with ENZ as compared to AA+P'.
>
> Parimi *et al*. 2016 **Conclusions:** *'*In this preliminary analysis, there were more pts with a worsening severity of reported depression symptoms and a trend towards an increase in cognitive impairment with ENZA as compared to ABI. These data help to characterize and define the incidence of these symptoms'.
>
> Kvorning TK *et al*. **Conclusions:** *'*Abiraterone and prednisone should be considered the first choice for patients with mCRPC where fatigue is a concern'*.*

Similar to the findings of the comparative clinical trials, the one retrospective clinical audit which the literature search revealed by Raju R *et al* showed that fatigue was the main reason for dose reductions or delays in the enzalutamide group.

Janssen pointed out that Astellas failed to mention any of these 4 additional head-to-head studies, whose results were consistent with those presented on the Janssen website.

Thus, Janssen submitted that any accusation that Janssen had 'cherry-picked' the results, both in terms of the study results taken from the publications used in the promotional item or from the available database for comparative abiraterone v enzalutamide was unfounded. Indeed, the reverse was the case; Janssen had failed to include ALL the positive HRQoL benefits for abiraterone versus enzalutamide on its website.

Overall impression

Janssen's response to Astellas' general accusations about the promotional item which were then repeated later in Astellas' letter of complaint were as follows:

a) Alleged unclear layout, misleading signposting

Astellas raised a new and very non-specific complaint against the website as a whole. Janssen stated that this first new complaint, now raised with the PMCPA, was not discussed during inter-company dialogue (ICD) was that 'the overall layout of the pages is unclear with misleading signposting to PBO and ENZ data as a result lack of clear headings'.

Janssen refuted this allegation as the webpage contained 4 headline claims (written in CAPITALS) and 5 individual titles located directly above each chart, (written in **bold**). All the claims and chart titles were referenced, and the charts included the required 'Adapted from with the relevant publication' cited. In addition, the study details were located immediately below each bar chart, so that it was very clear from where the claim and the data originated.

The promotional item included 5 different charts, two of them taken from the Thiery-Vuillemin study, two from the Khalaf study and one from the Sternberg study. This was clearly marked, with all the necessary study details (see point d above) being repeated under each chart as appropriate.

b) Alleged difficult to review

The second new complaint which Astellas raised in its letter to the PMCPA and which was never discussed during inter-company dialogue was that 'It is difficult to review all the figures, relating to a claim without scrolling down or adjusting the browser zoom settings, putting undue onus on the reader to undertake an informed review of the evidence presented. For example, where statements are referenced to a footnote, these can only be seen by scrolling down and searching the small print'.

Janssen denied that this was the case, as the headings were clearly laid out with a descriptor of the main aspects of the study given underneath. The footnote at the bottom of the page gave details of the definitions, acronyms, and abbreviations used. Janssen submitted that there was no need to adjust browser settings to find this additional information as the font size of the footnote was like that used inside the graph. Importantly, the footnotes were not used to qualify any of the claims and had no impact on the impression given by the study results.

c) Alleged careful selection of data

Astellas stated that 'The data presented has been carefully selected to support the claims, providing positive information for AAP without sufficient representation of the entirety of the data which readers would requires to make a fully informed opinion of the data presented'.

Janssen stated that the above accusation was incorrect. A wide range of HRQoL assessments which included fatigue, cognitive impairment, functional and physical well-being, PHQ-9 had been presented to provide a holistic representation of the HRQoL data available. All the data shown on the website were taken from the abstract sections of the 4 main publications and therefore being deemed by the authors to be the most important and relevant findings of the three studies. Indeed, some of the positive results for abiraterone v placebo or enzalutamide which were mentioned in the abstracts had **NOT** been included on the website. These were as follows: For Sternberg *et al* 2013

> 'Improvement in fatigue interference 55% v 38% (p=0.0075)' and 'Accelerated improvement in fatigue intensity' (median 59 days v 194 days (p= 0.0155). For Khalaf *et al* 'We showed that abiraterone was associated with superior HRQoL over time compared

> with enzalutamide. The difference between arms was seen across many HRQoL domains and was of clinically significant magnitude for patients aged >75 years'.

For Thiery-Vuillemin *et al 2020:*

> 'there were statistically significant differences ($p<0.05$) in favour of abiraterone over enzalutamide for 18 PRO items, as highlighted in Supplementary Table 3 (absolute data). With a more conservative approach (at least three periods [≥50%] needed to be significant in consecutive periods), nine of these PRO items were statistically significantly in favour of abiraterone over enzalutamide; these were mainly related to cognition, fatigue appetite loss, and nausea.'

And

> 'There were four other items with statistically significant clinically meaningful worsening (CMW) in favour of abiraterone; these were 'emotional functioning, 'social functioning', 'physical functioning', and 'pain right now'.

d) Alleged total QoL data not adequately reflected for abiraterone v enzalutamide

Astellas alleged that 'The references do not adequately reflect the totality of QoL evidence relating to AAP or ENZ*'.* In terms of trying to justify this accusation Astellas referred the Panel to a single sentence in the Discussion section of Loriot *et al* 2015, (a 13-page publication) which showed the clinical trial results of enzalutamide v placebo. In this one sentence, the authors provided some results for abiraterone and then claimed that the results for enzalutamide were superior. In making this comparison however, there had been no formal statistical indirect treatment comparison and, the values used for abiraterone were also only interim findings as the reference used was Rathkopf *et al* (entitled 'Updated **interim** Efficacy analysis and long-term efficacy of arbiraterone acetate in metastatic cancer patients without prior chemotherapy'). Furthermore, the authors themselves stated that 'Formal indirect treatment comparisons between the performance of abiraterone acetate plus prednisolone and enzalutamide are challenging for several reasons not least because of the markedly different exposures in the control groups'. Thus, there were 3 reasons why any comparison of abiraterone and enzalutamide in the discussion section of this publication was without any merit.

Astellas referred the PMCPA to a 2-page review article by Basch to substantiate its claim that Janssen had been cherry-picking the data. However, this article failed to provide any HRQoL outcome data for abiraterone, thus negating any meaningful comparisons between the two medicines. So, whereas Astellas alleged that 'the data presented has been carefully selected to support the claims', Janssen submitted that Astellas chose to cherry-pick a conclusion from Basch's brief review, which indeed was not reflective of conclusions across other analyses eg a review by Batra A *et al*. 2020 concluded that 'self-reported depression measures favoured abiraterone over enzalutamide and both abiraterone and enzalutamide over placebo'.

Janssen stated that as already mentioned, an important omission by Astellas was its failure to mention, 4 other Head-to-Head comparative studies referred in section d above where the HRQoL benefits of abiraterone had been compared to those of enzalutamide and found to be superior.

e) Allegedly sparse description of studies

Astellas stated that 'the description of the studies provided in the Janssen Website is very sparse which precludes the readers from being able to gain an informed opinion as to the validity of the promotional claim, especially in regard to the multiple limitations of the study methodologies as outlined by the authors of all the references provided'.

Janssen denied this. For each headline located above the 5 charts, the reference was given, as was the information regarding study, design, patient numbers, comparator medicines, statistical analysis and HRQoL parameter, and statistical analysis used. Where there was NO differences between abiraterone and enzalutamide, this was clearly stated (Figure 4 Khalaf *et al*) and when the results were a post hoc analysis which were not prespecified and therefore should be considered as 'Hypothesis generating' this too was clearly stated.

f) Allegedly Preservation v Improvement

Astellas stated that 'it does not deny that AAP has demonstrated superior QoL metrics than PBO + prednisolone in this clinical setting, but this is not the same as claiming that AAP "improves QoL"; we would argue rather that it suggests better preservation of QoL over time in these patients with metastatic prostate cancer compared to PBO + prednisone".

Janssen stated that the studies were not designed to demonstrate preservation of QoL. In each statistical section of the 4 publications, the criteria as to how improvement would be defined was given. Indeed whereas 'preservation' was a word that did not feature in any of the publications 'improvement' did in all of them and on multiple occassions as follows:

> Sternberg *et al* stated 'The results demonstrate that abiraterone acetate and prednisone provide substantial and **meaningful improvements** in self-reported fatigue outcomes in patients with mCRPC after docetaxel therapy compared with prednisone alone. Treatment with abiraterone-prednisone led to significant increases in the proportion of patients **exhibiting improvements in fatigue intensity and fatigue interference**; the higher proportion with improved fatigue interference is particularly notable given that this represents a functional measure that until now has never been reported for an Oncology agent'.
>
> Khalaf *et al* stated 'Our study **demonstrated improved PROs** in patients with mCRPC treated with first line abiraterone compared with those treated with enzalutamide, based on FACT-P, HRQoL scores and PHQ-9 depression scores'.
>
> The NICE Final Appraisal Determination document for abiraterone for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy noted that 'the committee concluded that abiraterone was likely to be effective and increase quality of life' (NICE TA387). In the main body of the document, NICE also stated in their Single Technology Appraisal for Zytiga in men with previous chemotherapy (NICE TA259) that *'*subjects receiving abiraterone acetate + prednisone were more likely to experience better quality of life whilst experiencing improvement in survival compared to prednisone. They are more likely to experience reduced pain, improved functional status and decreased fatigue and have more time before their pain, functional status and fatigue worsens'.

When writing to Janssen, the Authority asked it to consider the requirements of Clauses 3.2, 7.2, 7.3, 7.8, 7.9, 8.1 and 9.1 of the Code as cited by Astellas.

PANEL'S GENERAL COMMENTS

The Panel noted that Janssen had raised concerns regarding inter-company dialogue. The Constitution and Procedure detailed the requirements for inter-company dialogue at Paragraph 5.3. The Case Preparation Manager considered both parties' comments about inter-company dialogue very carefully and decided that inter-company dialogue had taken place and was unsuccessful in relation to all matters apart from in relation to what Janssen described as 'the erroneous mention of the 5mg dose of prednisone' which the case preparation manager decided was resolved during inter-company dialogue. Janssen was informed of the case preparation manager's decisions in July 2022.

The Panel noted Janssen's submission that the webpage was a simple and succinct summary of the data about Zytiga's health related quality of life (HRQoL) benefits in the mCRPC group of patients.

The Panel noted that the webpage in question was found within the Oncology section of the 'Janssen Medical Cloud' website and was entitled 'Zytiga Quality of Life'. It included the headline claim 'Zytiga could significantly improve HRQoL for your patients with mCRPC', below which were 4 bar charts and 1 box plot that had been adapted from 3 different studies, for which there were 3 publications and 1 poster. The Panel noted Janssen's submission that all of these publications included detailed statistical sections and had named statisticians included as authors in the publications; two of the studies (Thiery-Vuillemin *et al* and Khalaf *et al*) included enzalutamide as the comparator medicine whereas for the third study (Sternberg *et al*), placebo was the comparator. According to Janssen, these studies included a total of 1210 men with mCRPC, were of differing clinical trial design, undertaken in both the hospital and community setting, in men with both first line and post-docetaxel mCRPC and used a variety of different validated Quality of Life measurements.

DETAILED COMPLAINT AND CONSIDERATION BY THE PANEL

1 Main webpage heading claim

> **'ZYTIGA COULD SIGNIFICANTLY IMPROVE HRQoL** [health related quality of life] **FOR YOUR PATIENTS WITH mCRPC** [metastatic castrate-resistant prostate cancer]**'**

COMPLAINT

Astellas alleged that the claim that Zytiga could 'significantly improve HRQoL' *wa*s all-encompassing, inaccurate, exaggerated and misleading.

Astellas noted that the claim was supported by four references which referred to three separate trials, which did not adequately reflect the totality of QoL evidence relating to abiraterone plus prednisolone and enzalutamide. Therefore, Astellas alleged that the references did not adequately support the claim that abiraterone plus prednisolone 'could significantly improve HRQoL'. There was no evidence presented in the remainder of the material that supported the claim that abiraterone plus prednisolone significantly improved HRQoL overall; it merely 'cherry-picked' data positive to abiraterone plus prednisolone from various sources that related to specific sub-elements of quality of life assessment.

Astellas alleged a breach of Clause 7.2.

RESPONSE

Janssen submitted that the claim was appropriate, accurate, based on the body of data and capable of substantiation and refuted the accusation for the reasons given below.

There was no one single definition of HRQoL, but the Centre for Communicable Disease defined it very broadly as 'Health-related quality of life (HRQOL) is an individual's or a group's perceived physical and mental health over time'.

The four references used in the Zytiga QoL page demonstrated how Zytiga could achieve this by showing improvements in Physical Health (Functional Wellbeing (FWB) and Physical Well Being (PWB)) in Khalaf *et al* and fatigue, in Sternberg *et al* and Thiery-Vuillemin *et al*. For Mental Health the positive beneficial impact was demonstrated by a smaller percentage of patients showing a worsening of cognitive impairment over time in Thiery-Vuillemin *et al* and depression in Khalaf *et al*.

Khalaf *et al*, for which Astellas provided a Grant in aid also, stated 'We showed that abiraterone was associated with superior HRQol over time compared with enzalutamide'.

The NICE Single Technology Appraisal for Zytiga for men with mCRPC following previous chemotherapy stated that Zytiga provided an improvement in HRQoL on 7 occasions (Pages 15,18,27,75 (3 times) and 77). NICE also reviewed the Phase 3 study results (Sternberg *et al*) and concluded (page 15):

> 'Subjects receiving AAP were more likely to experience better quality of life whilst experiencing improvement in survival compared to PP. They are more likely to experience reduced pain, improved functional status and decreased fatigue…'

Janssen submitted that even Loriot *et al* publication, which Astellas referred to in its letter of complaint to the PMCPA, stated that 'abiraterone acetate plus prednisolone was associated **with tangible improvements in most HRQoL domains and disease-related symptoms versus control in patients** with metastatic castration-resistant prostate cancer after chemotherapy.

Janssen submitted that finally, in terms of Code of Practice considerations for promotional material, the use of the word 'could' in the claim was important, as Janssen acknowledged that whereas the results were statistically significant for the group, not all patients would benefit from Zytiga, all the time. This was brought to Astellas' attention in the inter-company dialogue.

Janssen therefore denied that the above claim was 'all-encompassing, inaccurate, exaggerated and misleading' and in breach of Clause 7.2 as alleged.

PANEL RULING

The Panel noted that Astellas did not deny that abiraterone plus prednisolone had demonstrated superior QoL metrics than placebo plus prednisolone in this clinical setting but alleged that this was not the same as claiming that abiraterone plus prednisolone 'improves' QoL; Astellas argued that the data suggested better preservation of QoL over time in patients with metastatic

prostate cancer compared to placebo plus prednisone. The Panel noted Janssen's submission that the studies were not designed to demonstrate preservation of QoL. In each statistical section of the 4 publications, the criteria as to how improvement would be defined was given.

The Panel then considered Astellas' allegation that Janssen's claim 'Zytiga could significantly improve HRQoL for your patients with mCRPC' was all-encompassing, inaccurate, exaggerated and misleading. According to Astellas, the references did not adequately reflect the totality of the QoL evidence nor support the claim that abiraterone 'could significantly improve HRQoL'; there was no evidence presented in the material that supported the claim that abiraterone plus prednisolone significantly improved HRQoL overall; it merely 'cherry-picked' data positive to abiraterone plus prednisolone from various sources that related to specific sub-elements of quality of life assessment.

The Panel noted Janssen's submission that there was no one single definition of HRQoL, but the Centre for Communicable Disease defined it very broadly as 'Health-related quality of life (HRQOL) is an individual's or a group's perceived physical and mental health over time'.

The Panel noted Janssen's submission that the four references used in the Zytiga QoL page demonstrated how Zytiga could achieve this by showing improvements in Physical Health (Functional Wellbeing (FWB) and Physical Well Being (PWB)) in Khalaf *et al* and fatigue, in Sternberg *et al* and Thiery-Vuillemin *et al*. For Mental Health the positive beneficial impact was demonstrated by a smaller percentage of patients showing a worsening of cognitive impairment over time in Thiery-Vuillemin *et al* and depression in Khalaf *et al*. Janssen further listed some of the positive results for abiraterone v placebo or enzalutamide which were mentioned in abstracts but were not included on the website.

HRQoL appeared to the Panel to be a broad term that could be supported by a number of patient reported outcomes. The Panel noted that there appeared to be data to show HRQoL related patient reported outcomes could be significantly improved with Zytiga compared to placebo and enzalutamide as submitted by Janssen. The Panel noted Astellas' allegation that there was data from studies which had not been included and thus Janssen had 'cherry picked the data. The Panel noted Janssen response to this general allegation. Both views were set out in detail in the General comments section above.

Taking all the comments and responses into consideration, the Panel decided that, on balance, Astellas had not proven that the claim at issue was all-encompassing, inaccurate, exaggerated and misleading as alleged. On the evidence before it, based on Astellas' narrow allegation, the Panel ruled no breach of Clause 7.2.

The Panel noted that Astellas made reference to the quality of life claim in its allegations regarding other claims in the material. Following its decisions set out below the Panel did not consider that the rulings in Points 2 and 3 below impacted on its ruling in Point 1.

2 First main sub heading claim

'SIGNIFICANTLY FEWER PATIENTS REPORTED WORSENING OF FATIGUE WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE'

Supported by two minor subheading claims:

'Percentage of patients reporting clinically meaningful worsening of fatigue during the first 12 months of treatment, as assessed by BFI-SF [Brief Fatigue Inventory – Short Form]**.'**

'Proportion of patients with clinically significant fatigue at baseline reporting an improvement in fatigue intensity.'

COMPLAINT

Astellas stated that the claim 'Percentage of patients reporting clinically meaningful worsening of fatigue during the first 12 months of treatment, as assessed by BFI-SF**,**' was referenced to Thiery-Vuillemin A *et al*. 2020 which reported a real-world data study reporting patient reported outcome (PRO) data derived from patient-completed questionnaires. Although the authors concluded that the original sample size was 'adequate', the numbers involved had not been clearly represented for readers to make their own conclusions on this point. The study noted that the questionnaire completion rate decreased over time. In the abiraterone plus prednisolone group, 105 patients were initially enrolled but by the end of the trial 74 patients were left, of which, only 55 completed the required questionnaires. In the enzalutamide group, 106 patients were recruited, reducing to 68 patients still enrolled in the last study period, of which only 49 completed the required questionnaires. This meant that only half of the initial trial population completed the questionnaires in the last period of the study, which Astellas stated called into question the strength of any claims drawn from the study. This aspect of the study was not made clear to readers of the webpage. Moreover, this small observational, non-randomised study claimed significant differences in the domains of fatigue and perceived cognitive function but with no significant impact on global health status/quality of life. The majority of individual patient reported outcome items did not show significant differences and/or favoured enzalutamide (Thiery-Vuillemin A *et al* supplementary table 5) further undermining the overarching claim of 'HRQoL improvement'.

The claim 'Proportion of patients with clinically significant fatigue at baseline reporting an improvement in fatigue intensity' was referenced to Sternberg *et al* 2013.

Astellas stated that the footnote to the associated figure stated: 'COU-AA-301: a phase III, randomised, double-blind, placebo-controlled study conducted in patients with mCRPC in the post-chemotherapy setting' with no mention of the fact that these patient reported outcome (PRO) data were collected as part of an exploratory analysis. Indeed, the study authors specifically stated that 'Patient reported outcomes were therefore included as exploratory end points in this phase III trial'. Astellas referred to the international regulatory guidelines (International Conference of Harmonisation (ICH E9)) which stated that exploratory trials could not form the basis of formal proof and should be considered as supportive data only. Astellas recognised that the material in question was not for regulatory submission, but the same principle should apply to the use of data to support promotional claims of superiority.

In addition, this claim was a sub heading under the larger heading 'SIGNIFICANTLY FEWER PATIENTS REPORTED WORSENING OF FATIGUE WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE' which could be interpreted by a reader that all data within this section related to enzalutamide as the comparator. However, the figure below the 'Proportion of patients with clinically significant fatigue at baseline reporting an improvement in fatigue intensity' sub-heading referred to the comparison of abiraterone plus prednisolone versus placebo. This was only apparent in the figure where the x-axis of the graph was labelled

accordingly. The potential for confusion was increased by the use of the same colour shading for the placebo and enzalutamide bars in the two graphs used consecutively.

Furthermore, the web page did not allow the reader to review a whole figure on one screen without scrolling or changing the zoom settings on the browser; Astellas alleged that this increased the risk of salient information being missed and, in this instance, could mislead the reader, to the actual comparison being made.

Astellas alleged a breach of Clauses 7.2, 7.3 and 7.8.

RESPONSE

Janssen stated that Astellas made several criticisms and alleged breaches of Clauses 7.2, 7.3 and 7.8. However, apart from Clause 7.8 (a new allegation which was never discussed at inter-company dialogue), Astellas did not show how these concerns/criticisms translated into clear breaches of Clauses 7.2 and 7.3, as there was no mention of the statements being, inaccurate, unbalanced, unfair, not objective, ambiguous, or misleading. Nonetheless Janssen addressed the concerns raised as follows:

Percentage of patients with clinically significant worsening of fatigue during the first 12 months of treatment as assessed by BFI-SF (Thiery-Vuillemin *et al* 2020).

a) Alleged limited number of patients

Janssen pointed out that Astellas did not question the results but did question the number of patients who had completed the questionnaire over the 12-month period for what was a terminal condition. The authors did not cite the questionnaire completion rate as a limitation of the trial. Instead, the authors mentioned that a conservative approach was taken since 'only the lowest percentage per PRO (worse-case scenario, all items must be answered to consider a PRO complete) was presented for all patients and for those 'still in study'. Janssen submitted that Astellas misquoted Thiery-Vuillemin by alleging that the authors stated that the patient numbers 'were adequate'. Janssen pointed out that the authors actually stated:

> 'the study also has several strengths: it has a large sample size, despite a decline in questionnaire response over 12-mo'. There were 7 opportunities for data collection since 'collection of PRO data began before baseline visit'

and

> 'questionnaire data were collected during routine visits and analysed by periods 1, 2, 3, 4-6, 7-9, and 10-12'.

Janssen submitted that Astellas also failed to take into account the statistical section of the publication which stated that all analysis were based on an 'Intention-To-Treat' basis with additional confirmatory sensitivity analysis being undertaken to confirm the findings.

b) Alleged patient numbers had not been clearly represented

Janssen submitted that Astellas was incorrect in stating that 'the numbers involved have not been clearly represented for readers to make their own conclusion'. The numbers (105 and 106) were clearly stated on the respective bar chart. (Figure 1 Thiery-Vuillemin)

c) Alleged 'Small study'

Astellas described this study as being 'small' study whereas the authors described it as having a large sample size, as already referred to above. Janssen noted this was a large, multinational study, involving 211 patients, which was conducted at 26 different sites in France, Denmark and the UK.

d) Alleged 'No significant impact on global health status/quality of Life'

Astellas stated that 'there was no significant impact on global health status/quality of life'.

Janssen submitted that the study did not look at 'Global Health Status' as this was the remit of the World Health Organisation and was a not term that was used in Health-Related Quality of Life studies. In terms of Quality of Life, Astellas was incorrect in making the assertion that no improvement in Quality of Life was seen, as QLQ-C30 Functional scales, QLQ-C30-Symptom scales, BP [pain] I-SF, BFI-SF and FACT-Cog were a breadth of tools used to measure a variety of different elements of quality of life. All of which were validated questionnaires.

e) Alleged majority of PROs were all in enzalutamide's favour

Astellas stated that 'The majority of individual PRO items did not show significant differences and/or favoured ENZ (Thiery-Vuillemin A *et al* … 2020 … (3) 380-387 supp table 5)'.

Janssen submitted that this assertion was incorrect. Actually, it was the other way round as 'supplementary table 5' succinctly showed that the vast majority of results were significantly in abiraterone's favour (dark green) or showed a trend in favour of abiraterone (light green). Not a single domain was significantly in favour for enzalutamide. Supplementary table 3 for the Thiery-Vuillemin publication presented the absolute data and highlighted that there were statistically significant differences ($p<0.05$) in favour of abiraterone over enzalutamide for 18 PRO items.

Also, Thiery-Vuillemin *et al* stated on multiple occasions that abiraterone was superior to enzalutamide, with the authors key results and conclusion being:

> 'Key PRO items (cognitive impairments and fatigue) were significantly ($p<0.05$) in favour of abiraterone versus enzalutamide during the study'.
>
> 'This 12-mo study showed that patient with mCRPC who were treated with abiraterone experienced significantly less fatigue and cognitive impairments than enzalutamide-treated patients. This difference occurred early after treatment initiation. In a real-world setting, it suggests an advantage of abiraterone over enzalutamide on fatigue and cognitive function. This difference should be considered when choosing treatment. These results are also in line with other published data'.

Proportion of patients with clinically significant fatigue at baseline showing improvement in fatigue intensity (Sternberg)

Janssen stated that Astellas' view that this was an 'exploratory' study was incorrect. This was the pivotal phase III study on which the market authorisation was granted. Sternberg *et al* even stated that 'our study is the first phase III trial in advanced prostate cancer to systematically assess fatigue outcomes using a validated fatigue specific instrument'. Full details of the prospective, predefined fatigue analysis were given over 3 pages (1018-1020) in the Sternberg publication which also showed in the actual questionnaire used in the study.

Janssen submitted that the ICH-E9 Guidelines for Exploratory Trials referred to by Astellas did not apply, as this was not an 'exploratory study', it was a Phase 3 confirmatory study with an exploratory end point. There was a big difference between the two, not least as the Code allowed for promotional material to include data from exploratory end points, providing the primary end point was positive, which they were in the Sternberg study.

'Significantly fewer patients reported worsening of fatigue with Zytiga plus low dose prednisolone v enzalutamide'

Janssen referred to Astellas' allegation that this claim was misleading as there were the two sets of results positioned below it, both of which could be construed as relating to enzalutamide. Janssen submitted that this claim, only had one reference positioned against it and the two bar charts located directly below it were clearly labelled with their own titles and clinical trial descriptors accompanying them. There could be no doubt that they were from two separate studies.

Janssen stated that in the bar charts, Zytiga was always coloured green and the comparator medicine grey; it was clearly labelled as to whether this was placebo or enzalutamide. It was interesting to note that Astellas described this same graph as being 'Clearly labelled'.

Janssen would like the Panel to note that neither the issue of the colour of the comparator, nor the 'unclear labelling' were brought up in inter-company dialogue, so this was the third instance where a new complaint had been raised with the PMCPA.

Similarly, the issue concerning difficuly with browsers and scrolling down had not been mentioned in any of the previous correspondence or discussion over the last 6 months. So any alleged breach of Clause 7.8, which Janssen denied, had not been a part of inter-company dialogue and was a fourth new complaint which was being raised with the PMCPA.

With respect to the above, Janssen denied that the above claims were inaccurate, unbalanced, unfair, not objective, ambiguous, misleading, were not based on an up-to-date evaluation of the data and that the artwork did not confirm to the letter and spirit of the Code and so therefore refuted any alleged breaches of Clauses 7.2, 7.3 and 7.8.

PANEL RULING

With regards to the claim 'Percentage of patients with clinically significant worsening of fatigue during the first 12 months of treatment as assessed by BFI-SF, the Panel noted Janssen's submission that Thiery-Vuillemin *et al* 2020 was described as a large, multinational study, involving 211 patients, which was conducted at 26 different sites in France, Denmark and the UK. Janssen denied that no improvement in Quality of Life was seen, as QLQ-C30 Functional scales, QLQ-C30-Symptom scales, BPI-SF, BFI-SF and FACT-Cog were a breadth of validated

tools used to measure a variety of different elements of quality of life; not a single domain was significantly in favour for enzalutamide and as per Thiery-Vuillemin *et al*, there were statistically significant differences ($p<0.05$) in favour of abiraterone over enzalutamide for 18 PRO items. The Panel noted that Thiery-Vuillemin *et al* stated that key PRO items (cognitive impairments and fatigue) were significantly ($p<0.05$) in favour of abiraterone versus enzalutamide during the study. Fatigue and asthenia (adverse events) were lower with abiraterone than with enzalutamide (5% vs 15% and 10% vs 11%, respectively).

The Panel noted that Thiery-Vuillemin *et al* stated that only the lowest percentage per PRO item (worse-case scenario, all items must be answered to consider a PRO complete) was presented for all patients and for those 'still in study'. The overall median completion rate for the 12-mo period was 81% for patients still in the study (this rate was based on all 28 PRO questions and all periods, and for both treatments).

The Panel noted Janssen's submission that Astellas failed to take into the account the statistical section of the publication which stated that all analysis were based on an 'Intention-To-Treat' population (211) basis with additional confirmatory sensitivity analysis being undertaken to confirm Thiery-Vuillemin *et al*'s findings. The Panel further noted Janssen's submission that the authors did not cite the questionnaire completion rate as a limitation of the trial. The Panel noted that the authors stated 'the study also has several strengths: it has a large sample size, despite a decline in questionnaire response over 12-mo'.

The Panel noted that beneath the claim at issue, the webpage displayed a bar chart with 'Zytiga plus low-dose prednisolone (n=105)' corresponding to 53% and 'Enzulatimide (n=106)' corresponding to 79%; there appeared to be a statistically significant difference between the two groups ($p=0.008$).

The Panel considered that whilst the intended audience would likely be aware that given the nature of the disease there would be a reduction in the number of patients completing the questionnaires, it was not clear from the bar chart that the patient numbers given were in relation to the original sample size rather than the number of patients that completed the Brief Fatigue Inventory – Short Form. The Panel therefore ruled a breach of Clause 7.2 as alleged

In the Panel's view, whilst it would have been helpful to have stated the final number of patients that completed the questionnaire, to portray the completion rate to readers, the bar chart nonetheless included the original sample size; the Panel noted that the analyses were based on all treated patients (ITT population). Noting its comments above, the Panel did not consider that the material called into question the strength of the claims as alleged. The Panel thus ruled no breach of Clause 7.2

The Panel noted that beneath the second supporting claim 'Proportion of patients with clinically significant fatigue at baseline showing improvement in fatigue intensity' was another bar chart illustrating the difference between the abiraterone and placebo subgroups (58.1% vs 40.3%; $p=0.0001$). The Panel noted that the chart was referenced to Sternberg *et al* with the associated footnote: 'COU-AA-301: a phase III, randomised, double-blind, placebo-controlled study conducted in patients with mCRPC in the post-chemotherapy setting'.

The Panel noted Astellas' allegation that there was no mention of the fact that the patient reported outcome (PRO) data had been collected as part of an exploratory analysis. The Panel noted Janssen's submission that this was the pivotal phase III study on which the market

authorisation was granted and not an 'exploratory study' but a Phase 3 confirmatory study with an exploratory end point. In the Panel's view, Astellas' allegation was in relation to disclosing that the PRO data formed part of an exploratory analysis; it appeared that Janssen interpreted the allegation as the study being an exploratory trial. Sternberg *et al* stated that it was the first phase III clinical trial in the setting of advanced prostate cancer to specifically evaluate fatigue outcomes, using an established instrument that has been validated for the assessment of cancer-related fatigue. It further stated that abiraterone acetate had a much better safety profile than cytotoxic chemotherapy, while early evidence from phase I–II studies suggested that it might produce symptomatic improvement. Patient reported outcomes were therefore included as exploratory endpoints in this phase III trial. Clinically meaningful changes in eligible patients were prespecified before conducting all analyses. A patient was considered to have 'fatigue intensity improvement' if their fatigue intensity score decreased by ≥ 2points from baseline at two or more consecutive assessments. In analyzing patient-reported outcomes, missing data had the potential to bias the overall results, and sensitivity analyses compensating for missing data were of great benefit. Therefore, two different types of models were developed as post-hoc sensitivity analyses, ie (i) repeated measure mixed effects models and (ii) joint mixed effects and log time-to-dropout models. These models were based on previously published methods, and their purpose was to estimate mean fatigue scores over time using different approaches to account for missing data. The model estimates therefore minimized potential attrition bias due to missing data/study dropout.

The Panel considered that, in omitting a statement that indicated that the data was derived from exploratory end points, the claim was not sufficiently complete to enable the recipient to form their own opinion and ruled a breach of Clause 7.2.

The Panel noted that Clause 7.3 stated, *inter alia*, that comparisons were permitted in promotional material provided they were not misleading. Clause 7.8 stated, *inter alia*, that all artwork including illustrations, graphs and tables must conform to the letter and spirit of the Code and, when taken from published studies, a reference must be given. Graphs and tables must be presented in such a way as to give a clear, fair, balanced view of the matters with which they deal, and must not be included unless they are relevant to the claims or comparisons being made.

The Panel noted the two titles for the bar charts were smaller and directly beneath the larger subheading claim 'SIGNIFICANTLY FEWER PATIENTS REPORTED WORSENING OF FATIGUE WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE'; one bar chart illustrated a comparison between abiraterone (green) and enzalutamide (grey), whilst the second bar chart illustrated a comparison between abiraterone (green) and placebo (grey). In the Panel's view, both bar charts and their titles would be interpreted as supporting the subheading claim that compared Zytiga and enzalutamide which was not so. The Panel considered that this misleading impression that both bar charts supported the same overarching claim was compounded by the same colour (grey) being used for two different comparator arms, enzalutamide and placebo. The Panel considered that the immediate and overall impression to a busy health professional would likely be that both bar charts were supportive of the claim and both bar charts compared abiraterone and enzalutamide which was not so. The Panel, therefore, ruled a breach of Clauses 7.3 and 7.8.

In relation to Astellas' allegation that that there was a risk of salient information being missed as the webpage did not allow the reader to review a whole figure on one screen without scrolling or changing the zoom settings, the Panel noted that readers would be well used to scrolling up and

down to obtain all the information. There was no separation or use of footnotes such that the reader would have to scroll over other information to see the relevant information. The Panel noted its ruling of a breach of Clause 7.3 above and did not consider that otherwise the area occupied by the text and charts on the screen was such that it could mislead the reader to the actual comparison being made as alleged and as such, no breach of Clause 7.2 was ruled.

3i) Second main sub heading claim

'FEWER PATIENTS REPORTED WORSENING OF THEIR PERCEIVED COGNITIVE IMPAIRMENT WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE'

Supported by one minor subheading claim:

'AQUARiUS

Patients (%) reporting clinically meaningful worsening of perceived cognitive impairment'

COMPLAINT

Astellas stated that the claims above referenced Thiery-Vuillemin A *et al* 2020. Astellas' concerns regarding this claim echoed those outlined above ie that that data had been cherry picked without context and presented in a misleading way. Astellas additionally highlighted that this cognitive function claim did not reference the analysis reported in Khalef *et al* 2019 (outlined below and used by Janssen to support the HRQoL claim) which did not demonstrate any differences in cognitive function between abiraterone plus prednisolone and enzalutamide. The claim implied by the graph entitled 'Patients (%) reporting clinically meaningful worsening of perceived cognitive impairment' did not consider the balance of available data to fully inform the reader.

Moreover, the AQUARiUS study authors concluded: 'Overall, these data confirm previously published interim analyses from this study and support the positive impact of abiraterone and enzalutamide treatment on HRQoL under real-world conditions'. Astellas stated that the AQUARiUS study also showed that the results achieved in the pivotal studies substantiated the balance of available evidence for both abiraterone plus prednisolone and enzalutamide in supporting patient QoL without claiming superiority of one over the other.

RESPONSE

Fewer patients reported worsening of their perceived cognitive impairment with Zytiga plus low dose prednisolone vs enzalutamide (Thiery-Vuillemin).

a) Alleged cherry-picking of data

Janssen stated in response to Astellas' allegation that it was 'Cherry picking' the data from this study that there were several positive findings from this study, which Janssen chose not to use in the promotional item. For example, Thiery-Vuillemin *et al* stated:

> 'Statistically significant improvements in favour of abiraterone over enzalutamide were observed for perceived cognitive function, comments from other (FACT-Cog and cognitive functioning (QLQ-C30) which were evident at period 1. Similar findings were observed for worst level of fatigue, usual level of fatigue, fatigue right now (BFI-SF and fatigue (QLQ-C30).'

Janssen submitted that the reason why the perceived cognitive benefit was chosen as opposed to all the other benefits that were seen for abiraterone compared to enzalutamide, was that the benefit in cognitive function benefit was maintained throughout the 12-month period. Janssen submitted that Astellas' view that Janssen 'does not consider the balance of available data to fully inform the reader', was incorrect as in Janssen's view this claim could also be supported by Das *et al*, Parimi *et al*, Shore *et al*, Kvorning *et al* and Raju *et al*, studies referred to in the overview of the promotional item section d above.

Janssen, noted that for this particular claim, no specific breach of the Code had been cited by Astellas.

b) Khalaf findings for MoCA (Montreal Cognitive Assessment)

In response to Astellas' assertion that the above cognitive function claim did not reference the analysis in Khalaf *et al,* which did not show any differences in cognitive function between abiraterone and enzalutamide using the MoCA questionnaire, Janssen submitted that Astellas failed to mention that Khalaf *et al* also stated that this MoCA cognitive assessment had not been validated in this clinical setting and that a more rigorous neuropsychiatric evaluation would be necessary to fully characterise any cognitive effects observed with therapy.

Janssen stated that in summarising the conclusions from the AQUARiUS study (Thiery-Vuillemin), Astellas failed to mention that the authors stated that:

> 'This study showed that abiraterone was consistently associated with less cognitive impairments and fatigue than enzalutamide over the 12-month period and that these differences were observed early after treatment initiation'.

Janssen referred the Panel to the positive cognitive benefits which had been seen in the Shore, Das and Parimi studies as mentioned above (general section).

c) Conclusions from the AQUARiUS study

Astellas stated that 'The AQUARiUS study (Thiery-Vuillemin) also shows that the results achieved in pivotal studies substantiates the balance of evidence available for both AAP and ENZ supporting patient QoL without claiming superiority of one over the other'.

Janssen submitted that the conclusion of Thiery-Vuillemin *et al* was completely different to what was alleged by Astellas as Thiery-Vuillemin *et al* stated the following:

> 'This 12-mo study showed that patients with mCRPC who were treated with abiraterone acetate experienced significantly less fatigue and cognitive impairments than enzalutamide- treated patients. This difference occurred early after treatment initiation. In a real-world setting, it suggests an advantage of abiraterone over enzalutamide on fatigue and cognitive function. This difference should be considered when choosing treatment'.

PANEL RULING

The Panel noted that the graph presented beneath the claims was entitled 'Patients (%) reporting clinically meaningful worsening of perceived cognitive impairment'. The graph compared the percentages of patients in the abiraterone and enzalutamide arms over months 1, 2, 3, 4–6 and 12. The graph was referenced to two papers (Thiery *et al* 2018 and Thiery *et al* 2020) and included odds ratios and p values for each time period.

With regard to the sub heading claim, 'FEWER PATIENTS REPORTED WORSENING OF THEIR PERCEIVED COGNITIVE IMPAIRMENT WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE', the Panel noted that no specific breach of the Code had been cited but instead Astellas had alleged that its concerns in relation to this claim echoed its concerns above ie that data had been cherry picked without context and presented in a misleading way. Accordingly, the Panel considered the matter in relation to Clauses 7.2, 7.3 and 7.8.

The Panel noted Janssen's submission that there were several positive findings from this study, which Janssen had chosen not to use in the promotional item at issue and that the reason why the perceived cognitive benefit was chosen as opposed to all the other benefits that were seen for abiraterone compared to enzalutamide, was that the cognitive function benefit was maintained throughout the 12-month period. The Panel further noted Janssen's submission that the claim could also be supported by Das *et al*, Parimi *et al*, Shore *et al*, Kvorning *et al* and Raju *et al.* The Panel further noted Janssen's submission that Astellas had failed to mention that Khalaf *et al* stated that 'this MoCA cognitive assessment had not been validated in this clinical setting and that a more rigorous neuropsychiatric evaluation would be necessary to fully characterise any cognitive effects observed with therapy'.

On the evidence before it, the Panel did not consider that Astellas had established that Janssen had cherry picked data, nor that the exclusion of MoCA cognitive assessment outcomes from Khalaf *et al*, which was stated to not have been validated in this clinical setting, meant that the data had been misleadingly presented in breach of Clause 7.2. No breach of Clause 7.2 was ruled.

Whilst Astellas alleged that the claim implied by the graph entitled 'Patients (%) reporting clinically meaningful worsening of perceived cognitive impairment' did not consider the balance of available data to fully inform the reader, the Panel did not consider that there was an allegation in relation to the presentation of the graph itself. The Panel thus ruled no breach of Clause 7.8.

In relation to the excerpt of the AQUARiUS study highlighted by Astellas, the Panel noted that the conclusion of the study (Thiery-Vuillemin) stated:

> 'This 12-mo study showed that patients with mCRPC who were treated with abiraterone acetate experienced significantly less fatigue and cognitive impairments than enzalutamide-treated patients. This difference occurred early after treatment initiation. In a real-world setting, it suggests an advantage of abiraterone over enzalutamide on fatigue and cognitive function. This difference should be considered when choosing treatment'.

followed by:

> 'These results are also in line with other published data [20]. The safety outcomes were consistent with the known safety profile of each drug, but abiraterone was associated with fewer fatigue, asthenia and neurological AEs than enzalutamide. Overall, these data confirm previously published interim analyses from this study [9,10], and support the positive impact of abiraterone and enzalutamide treatment on HRQoL under real-world conditions. AQUARiUS also shows that the results achieved in the pivotal studies for each drug can be translated into clinical practise'.

Whilst the Panel noted that the authors made reference to the positive effects of both abiraterone and enzalutamide, it noted that cognitive impairments appeared to have been experienced in significantly fewer patients in the abiraterone arm compared to the enzalutamide arm, as reflected in the subheading claim at issue. The Panel therefore did not consider that Astellas had established that the claim, which compared abiraterone and enzalutamide, was misleading as alleged and thus no breach of Clause 7.3 was ruled.

3ii) Third main sub heading

> **'PATIENTS REPORTED IMPROVED HRQoL‡ WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE'**
>
> **Supported by minor subheadings**
>
> **'Patients reported less clinically significant worsening with ZYTIGA plus low- dose prednisolone vs. enzalutamide (all patients) for PWB [physical well-being] and FWB [functional well-being]'**
>
> **'Post-hoc analysis: Change in PHQ-9 [Patient Health Questionnaire-9] scores from baseline significantly favoured ZYTIGA over enzalutamide at Weeks 4, 8 and 12'**

COMPLAINT

Astellas stated that the data used from Khalaf *et al* was not obtained from a prespecified analysis and therefore should only be deemed hypothesis generating. Although this was clearly stated in the paper, this important feature of the analysis was incorrect in the promotional material. Janssen subsequently conceded this error during inter-company dialogue and had since made an amendment to correct this (as of 27 May 2021). Despite this revision, the Khalaf study was clearly not robust enough to support a promotional superiority claim for abiraterone over enzalutamide. Indeed, the authors stated that 'For all comparisons we used a significance α level of $p \leq 0.05$ without correction for multiple testing, as our statistical analyses were not prespecified and are considered exploratory'. In the abstract to the manuscript the authors further noted: 'these analyses were not prespecified, and results should be considered to be hypothesis generating'. This was not clear in the promotional material and in fact Janssen went as far to claim 'clinical significance'; based on these data; therefore, Astellas alleged this to be misleading in breach of Clause 7.3.

Khalaf *et al* also stated that patients were given abiraterone plus 5mg prednisone once daily which was outside the marketing authorisation for abiraterone plus prednisolone in the mCRPC indication. Astellas discovered that the publication had erroneously stated 5mg prednisolone once daily when the trial actually used 5mg prednisolone twice daily (which was within the marketing authorisation, as reflected in the product's summary of product characteristic (SPC)).

Astellas stated that Janssen had faithfully transcribed this error from Khalaf *et al* into its materials, despite the fact it was inconsistent with the SPC and represented an underdosing of a medicine used to reduce the incidence of side effects of abiraterone. This was highlighted during the inter-company dialogue and despite initially rejecting Astellas' position on this issue, in correspondence, Janssen agreed to review and amend this error after it was also pointed out, during a virtual meeting, that the dose was incorrect within the paper itself. Whilst un-amended, this had implications for patient safety (ie potentially encouraging prescribers to use a suboptimal dose of prednisolone whilst administering abiraterone) and was therefore a breach of Clause 3.2.

The main heading, in this section, 'PATIENTS REPORTED IMPROVED HRQoL‡ WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE' included the term 'HRQoL' which was generally understood to cover a full spectrum of factors that were disease specific, as demonstrated by the use of a validated quality of life instrument, the FACT-P [Functional Assessment of Cancer Therapy-Prostate] questionnaire. Khalaf *et al* reported that significant FACT-P differences between the treatments were only noted in the >75 year age group, a fact that Janssen did not make clear in the promotional material. In addition, Janssen's materials only highlighted functional wellbeing (FWB) and physical wellbeing (PWB) sub-scales of the FACT-P analysis, whereas there were four sub- scales (plus 'additional concerns') in this instrument. This selective use of data clearly did not warrant an all-encompassing HRQoL superiority claim.

Astellas alleged breaches of Clauses 7.2, 7.3 and 7.8.

Astellas alleged that the figure supporting the claim **'Patients reported less clinically significant worsening with ZYTIGA plus low-dose prednisolone vs. enzalutamide (all patients) for PWB and FWB'** depicted an adapted graph that had clearly been cut and presented to show positive data for abiraterone plus prednisolone only. The original graph depicted a total of 9 outcome measures across a variety of QoL questionnaires (including total FACT- P which represented global QoL outcomes) but the adapted figure only presented the 2 significant results. Although this reflected the associated sub-heading, the adapted figure obscured the full data that would have provided the reader a more comprehensive view of the overarching web page claim for HRQoL improvement.

Astellas alleged that this was another clear example of 'cherry-picked' data that was misleading and not reflective of all available evidence. Moreover, the study authors, Khalaf *et al* also conceded that:

> 'The limitations of our study included the relatively small number of patients, which resulted in large confidence intervals at individual time points for FACT-P assessments, as well as the open-label design… . these analyses were not prespecified, and results should be considered to be hypothesis generating'.

Astellas alleged that the nature and extent of these limitations were not clearly represented in the Janssen material, and thus did not allow readers to obtain a properly informed view of the data presented, in order for them to reach their own conclusions (and the 'clinically significant' claim misled as to the nature of the data).

Astellas alleged breaches Clauses 7.3 and 7.8.

Astellas referred to the second minor sub-heading within this section 'Post-hoc analysis: Change in PHQ-9 scores from baseline significantly favoured ZYTIGA over enzalutamide at Weeks 4, 8 and 12' highlighted a graph from Khalaf *et al* that showed a change in PHQ-9 scores.

Khalaf *et al* stated 'The PHQ-9 is a self-administered questionnaire consisting of the nine diagnostic criteria for depressive episode from the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)'. Moreover, NICE Clinical guideline CG123 recommended the PHQ-9 as an assessment tool for depression. Astellas alleged that this promotional claim implied that enzalutamide might cause depression/depressive episodes which was inconsistent with the product's SPC (which did not list depression or depressive episodes as an adverse reaction to enzalutamide). This information, in isolation, misrepresented the benefit-risk evaluation for enzalutamide in this setting and was thus, both inaccurate and misleading. Astellas alleged that this section also disparaged Astellas' product. Of note, Khalaf *et al* also stated that 'no pre-planned formal psychiatric assessments were mandated to validate PHQ-9 results' highlighting the authors identification of the significant limitation to the interpretation of the results, which was not reflected in the material.

Astellas stated that it did not accept that by merely avoiding the use of the word 'depression' or any other similar term in the material, a clinician would not link depression to enzalutamide when presented with data from the PHQ-9 questionnaire. The promotion of a graph that showed PHQ-9 outcomes was a clear signpost to the insinuation that enzalutamide caused depressive symptoms and/or depression despite the absence of any evidence of this from a number of randomised placebo controlled Phase III clinical trials, that presented a much more robust evidence base than a single post-hoc exploratory analysis from a small open-label Phase II clinical trial.

Astellas alleged breaches of Clauses 7.3, 7.9 and 8.1.

RESPONSE

a) <u>Alleged lack of prespecified analysis in the Khalaf study</u>

Janssen submitted that Astellas' allegation that 'the data used from the Khalaf study was not obtained from a prespecified analysis and therefore should only be deemed hypothesis generating' and that use of ANY data from this study would be in breach of Clause 7.3 was incorrect. Janssen submitted that ALL the Quality-of-Life end points were prespecified except those for PHQ-9 and Montreal Cognitive Assessment (MoCA) which were post hoc analyses and which had always been clearly labelled as such on the website.

Janssen stated that the statistical section in Khalaf *et al* gave details of the of the Mixed Effect Model for the prespecified repeated measures for the assessment of FACT-P and its various Quality of Life domains. Similarly, the statistical consideration for the post hoc analyses for the PHQ-9 and MoCA analyses were provided. Notwithstanding this, the Code allowed for post hoc analysis to be used in promotional material if the nature of the data was made clear which it was. Janssen therefore denied that this claim was misleading and therefore a breach of Clause 7.3.

b) <u>Agreement made at ICD now being brought up as a new breach of the Code</u>

Janssen submitted that for the PHQ-9 results (figure 5 Khalaf) Janssen had clearly stated in the title that the results were from a post hoc analysis, and that this analysis had not been prespecified. Janssen had unfortunately erroneously included an additional 'Not' so the sentence read 'The analyses were not prespecified so the results should not be hypothesis generating'. At the ICD telephone conversation on 13 May, Janssen freely admitted this error and agreed to remove the word 'not' so the sentence was changed to 'The analyses were not prespecified so the results should be considered hypothesis generating': No further request was made by Astellas regarding this claim and the agreed action point was subsequently noted as 'Completed' in the Astellas minutes of the telephone conversation. Janssen was therefore disappointed to learn that this was now being referred to as a breach of Clause 7.3 as this was counter to the guidance concerning ICD.

c) Agreement made at ICD now being brought up as a new breach of the Code

In response to Astellas' reference to the erroneous mention of the dose of abiraterone acetate prednisone 5mg in the promotional item which was the dose given in the Sternberg publication, Janssen submitted that at the ICD telephone conversation on 13 May 2021, Janssen agreed to check the publication by looking at the original study design on clinical trials.gov. After doing this, Janssen agreed that there had been an error in the publication and accordingly amended the promotional piece to read prednisolone 5mgs bd or 10mgs OD. Janssen was therefore disappointed to learn that Astellas had decided to report this error in the publication and promotional material and cite a breach of Clause 3.2 which had not been cited in previous correspondence. Janssen believed, such an action to be counter to the guidance given for ICD.

In this fifth new allegation, Astellas asserted that the mention of 5mg as a footnote below the figure would encourage physicians to use this dose, even though it was clearly labelled as a phase II study, and there was no encouragement to use this dose. Astellas also alleged that this would have posed a safety issue even though it did not provide any evidence to substantiate this. Janssen stated that the Zytiga EPAR (page 69) specifically referred to omission of prednisolone in certain patients for which careful monitoring was advised.

Janssen therefore denied, that faithfully reproducing the dose of prednisolone as 5mg od as opposed to 5mg bd or 10mg OD was a safety issue and any alleged breach of Clause 3.2.

PATIENTS REPORTED IMPROVED HRQoL WITH ZYTIGA PLUS LOW DOSE PREDNISOLONE VS ENZALUTAMIDE (Figure 4 Khalaf)

In attempting to substantiate the allegation, that this claim was 'a selective use of data which does not warrant an all embracing HRQoL claim' in breach of Clauses 7.2. 7.3 and 7.8, Astellas raised several concerns which Janssen addressed as follows.

a) Alleged FACT-P was the only validated HRQoL validated questionnaire

Astellas stated that the above claim **'**includes the term "HRQOL"' which is generally understood to cover a full spectrum of factors that are disease specific, as demonstrated using a validated Quality of Life instrument, the FACT-P questionnaire'.

Janssen noted that Astellas failed to provide any reference to substantiate its 'understanding' which was in any case incorrect. The European Medicines Agency had provided guidance on the measurement of Patient Reported outcomes and HRQOL in Appendix 2 to the guideline on

the evaluation of anticancer medicinal products in man. The use of patient-reported outcome (PRO) measures in oncology. At no point was FACT-P mentioned as being the only validated assessment for HRQoL. Indeed, if it were, then it would be the only assessment used in clinical trials for men with prostate cancer, which was clearly not the case.

b) FACT-P values not shown

Astellas stated that 'The Khalaf paper reported significant FACT-P differences between the treatments were only noted in the >75 years of age population'.

Janssen agreed that this was correct, for half the patient population (75 years was the median age), the FACT-P score for abiraterone showed a significant benefit over enzalutamide (p=0.003). For the other half of the population, this benefit was not seen. Even though Janssen could have included a promotional claim relating to the 50% of patients who were aged 75 and over, as the authors stated

> 'We showed that abiraterone was associated with superior HRQoL over time compared with enzalutamide. The difference between arms was seen across many HRQoL domains and was of clinically significant magnitude for patients aged >75 years'.

The company decided not to include it and simply added the statement, which was shown directly above the bar chart 'For all other measures, no statistically significant difference was seen'. Furthermore, and as already mentioned by Astellas the authors stated that 'our study included the relatively small number of patients, which resulted in large confidence intervals at individual time points for FACT-P assessments'.

c) Functional Well Being and Physical Well Being

Astellas stated that Janssen materials only highlighted functional wellbeing (FWB) and physical well being (PWB) sub-scales of the FACT-P analysis, whereas there were four subscales (plus additional concerns) in this instrument. This selective use of data clearly did not warrant an all-encompassing HRQoL superiority claim.

Janssen noted that Astellas' opinion contrasted with the authors who described the FACT-P questionnaire as 'consisting of four quality of life domains Physical (PWB) functional (FWB) emotional (EWB) and social (SWB)'.

The inclusion of the PWB and EWB in the promotional item simply reflected the main results given in the abstract of the publication which stated

> 'A higher proportion of patients experienced clinically meaningful worsening with enzalutamide for the physical and functional well-being domains (37% vs 21%, p=0.013: 39% v 23%, p =0.015).

It was clearly stated 'for all other measures, no statistically significant difference was seen'.

Janssen therefore denied that the above claim was inaccurate, unbalanced, unfair, not objective, ambiguous, or misleading, or that the artwork did not conform to the letter and spirit of the Code and denied any breach of Clauses 7.2, 7.3, and 7.8. The alleged breach of Clause 7.8 was the sixth new alleged breach of the Code that was never discussed at ICD.

Patients reported less clinically significant worsening with Zytiga plus low doses prednisolone vs enzalutamide (all patients) for PWB and FWB (Figure 4 Khalaf).

Astellas alleged that this claim related to an adapted graph that had been cut and presented to show positive data for abiraterone plus prednisolone only, and that the adapted figure only presented 2 of the original 9 outcome measures across a variety of HRQoL measures.

Janssen stated that this was correct, the adapted bar chart only showed the results for PWB (Physical Well Being) and FWB (Functional Well Being) with the clear accompanying statement that 'For all measures, no statistical significant difference was seen'. Therefore, the reader was provided with relevant and accurate information about the results to allow them to interpret the data, which Janssen believed was adequate to support the claim. The bar chart simply displayed the results relating to the above claim.

Astellas then alleged that 'this is cherry picking the data, and that the figure obscures the full data that would have provided the reader a more comprehensive view of the overarching webpage claim for HRQoL'. Janssen submitted that Astellas did not acknowledge the conclusion from the study that:

> 'Our study demonstrated improved PROs in patients with mCRPC treated with first line abiraterone compared with enzalutamide, based on FACT-P, HRQoL scores and PHQ-9 depression scores'.

Astellas made a new accusation about patient numbers for FACT-P and the open label design of the study which Janssen stated were not discussed at ICD, so this was the seventh instance of a new complaint being raised.

Janssen denied any alleged breach of Clauses 7.3 and 7.8.

Post hoc analysis change in PHQ-9 scores from baseline significantly favoured Zytiga over Enzalutamide at Weeks 4, 8 and 12 (Figure 5 Khalaf)

a) <u>PHQ-9</u>

Astellas alleged that 'promotion of a graph that shows PHQ-9 outcomes is a clear sign-post to the insinuation that enzalutamide causes depressive symptoms and/or depression despite the absence of any evidence of this from a number of randomised placebo-controlled Phase II clinical trials'. Astellas alleged that by showing this graph that Janssen was in breach of Clauses 7.3, 7.9, and 8.1.

Janssen submitted that the table was adapted from Figure 3 of Khalaf *et al* and had all the statistical considerations included on it that were cited in the paper for weeks, 4, 8 and 12. Similarly all the caveats as per the publication were given ie, this was a post hoc analysis, the results were not prespecified and that they should be considered to be hypothesis generating.

Janssen submitted that Astellas' claim that the NICE Clinical Guideline 123 recommended PHQ-9 as a specific assessment tool for depression was incorrect. The PHQ-9 Questionnaire was only mentioned once in the NICE Guideline, page 17, Section 1.3.2.3 which stated:

> 'When assessing a person with a suspected common mental health disorder consider using a validated measure relevant to the disorder or problem being assessed, for example the 9-item Patient Health Questionnaire'.

There was no mention of PHQ-9 being a specific assessment tool for depression.

Janssen submitted that the NICE Guideline also made no mention of a psychiatric assessment being required for the PHQ-9 to validate it, so this assertion by Astellas was also incorrect with such an approach not being part of routine clinical practice in the UK.

Janssen had simply reproduced the table in the Khalaf publication and made no mention of the word depression in the promotional item.

Astellas made the new assertion that depression was not mentioned as being a feature in clinical trials. Janssen submitted that this was incorrect. In the head-to-head comparative study of abiraterone acetate vs enzalutamide (Parimi *et al*) it was seen that significantly more patients in the enzalutamide arm had a worsening of depression severity score 19% v 4% (P=0.03).

Depression was also listed as a recognised Adverse Event for enzalutamide (7 cases) on the MHRA Website for Drug Analysis Profiles and on the Cancer McMillan Webpage depression was listed as an acknowledged side effect for enzalutamide, stating that patients might feel low or depressed whilst on this treatment.

Janssen failed to see how it could be held accountable for the study findings of an investigator who also received funding from Astellas, and that by showing this box plot, which had been adapted from this publication, Janssen was misleading, providing information about an adverse reaction which was not capable of substantiation by clinical experience and was disparaging to enzalutamide. Janssen therefore denied any breach of Clauses 7.3, 7.9, 8.1.

PANEL RULING

> ***'PATIENTS REPORTED IMPROVED HRQoL‡ WITH ZYTIGA® PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE[2].'***
>
> ***'Patients reported less clinically significant worsening with ZYTIGA® plus low- dose prednisolone vs. enzalutamide (all patients) for PWB and FWB[2].'***
>
> **'Post-hoc analysis: Change in PHQ-9 scores from baseline significantly favoured ZYTIGA® over enzalutamide at Weeks 4, 8 and 12.'**

The Panel noted that despite Janssen's amendment following inter-company dialogue, Astellas alleged that the Khalaf *et al* study, the cited reference to the above claims, was not robust enough to support a promotional superiority claim for abiraterone over enzalutamide and that to go as far to claim clinical significance based on these data was misleading in breach of Clause 7.3.

The Panel noted that according to Khalaf *et al*, FACT-P was a validated patient self-administered questionnaire comprising 39 questions, and consisted of four quality-of-life domains (physical [PWB], functional [FWB], emotional [EWB], and social [SWB] well-being.

Khalaf *et al* stated that evaluation of HRQoL, depression, and cognitive function was a secondary objective.

The Panel noted Janssen's submission that PHQ-9 and Montreal Cognitive Assessment (MoCA) were post hoc analyses and had always been clearly labelled as such on the website. The Panel further noted that reference to Khalaf *et al*, beneath a chart that supported the claim, was accompanied by the statement 'this analysis was not prespecified, and results should [not] be considered to be hypothesis generating'. The Panel noted that the statement appeared to form part of a footnote in smaller font size than the rest of the page. Whilst it had been corrected as part of the inter-company dialogue, the Panel considered that the corrected statement below the bar chart was not sufficiently clear for readers to be able to make an informed comparison between the products. Therefore, a breach of Clause 7.3 was ruled.

The Panel noted that Janssen had transcribed an error from Sternberg *et al* with regard to the dosing of prednisolone into the material at issue (the Sternberg publication erroneously stated 5mg prednisolone once daily when the study actually used 5mg prednisolone twice daily). This was highlighted by Astellas during inter-company dialogue and Janssen had amended the website accordingly to read prednisolone 5mg bd or 10mgs OD. The Panel considered that this matter had thus been settled during inter-company dialogue as previously decided by the case preparation manager and the Panel therefore made no ruling in relation to Clause 3.2.

With regard to the heading *'PATIENTS REPORTED IMPROVED HRQoL‡ WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE',* the Panel noted Astellas' allegation that the material did not make clear that significant FACT-P differences were only noted in the >75 year age group. In addition, Astellas' alleged that Janssen's materials only highlighted functional wellbeing (FWB) and physical wellbeing (PWB) sub-scales of the FACT-P analysis, whereas there were four sub-scales (plus 'additional concerns') in this instrument. Astellas alleged that this selective use of data clearly did not warrant an all-encompassing HRQoL superiority claim.

The Panel noted Janssen's submisison that the conclusion from the study stated:

> 'Our study demonstrated improved PROs in patients with mCRPC treated with first line abiraterone compared with enzalutamide, based on FACT-P, HRQoL scores and PHQ-9 depression scores'.

The Panel noted Janssen's submission that even though it could have included a promotional claim relating to the 50% of patients aged 75 and over, for the many HRQoL domains across which significant differences were demonstrated, it decided not to include it and simply added, directly above the bar chart "For all other measures, no statistically significant difference was seen".

The Panel noted that Khalaf *et al* stated that it

> 'showed that abiraterone was associated with superior HRQoL over time compared with enzalutamide' and that 'the difference between arms was seen across many HRQoL domains and was of clinically significant magnitude for patients aged ≥ 75 yr'.

Whilst the Panel considered that it would have been useful to have highlighted that clinical significance was only seen for patients aged 75 or over, the Panel nonetheless noted that the

claim '*PATIENTS REPORTED IMPROVED HRQoL‡ WITH ZYTIGA PLUS LOW-DOSE PREDNISOLONE VS. ENZALUTAMIDE'* was supported by a graph that focussed on FWB and PWB for all patients the graph appeared to reflect the cited data. The Panel, noting its comments above, did not consider that the claims were such that they misled readers and thus ruled no breach of Clauses 7.2, 7.3 and 7.8.

'*Patients reported less clinically significant worsening with ZYTIGA plus low-dose prednisolone vs. enzalutamide (all patients) for PWB and FWB'*

The Panel noted Astellas' concern that the figure supporting the claim depicted an adapted graph that had clearly been cut and presented to show positive data for abiraterone plus prednisolone only. The original graph depicted a total of 9 outcome measures across a variety of QoL questionnaires (including total FACT- P which represented global QoL outcomes) but the adapted figure only presented the 2 significant results which although reflected the associated sub-heading, obscured the full data that would have provided the reader a more comprehensive view of the overarching webpage claim for HRQoL improvement and was misleading and not reflective of all available evidence.

The Panel noted Janssen's submission that Astellas was correct in that the adapted bar chart only showed the results for PWB (Physical Well Being) and FWB (Functional Well Being) with the clear accompanying statement that *"For all other measures, no statistically significant difference was seen".* Therefore, the reader was provided with relevant and accurate information about the results to allow them to interpret the data, which Janssen considered was adequate to support the claim. The bar chart simply displayed the results relating to the above claim.

The Panel noted that according to Khalaf *et al*, the proportion of patients with clinically significant worsening was higher in the enzalutamide arm for the PWB domain (37% vs 21%; p=0.013) and the FWB domain (39% vs 23% p=0.015). The Panel considered that the chart illustrating the PWB and FWB data and the claim 'Patients reported less clinically significant worsening with ZYTIGA plus low-dose prednisolone vs. enzalutamide (all patients) for PWB and FWB' appeared to be reflective of the cited data. The Panel considered that in the circumstances it was not misleading to not present other HRQoL measures on the chart or in the claim. It was stated that no statistically significant differences were seen, (although this was not actually so). Readers would not be misled about the data that was presented. No breaches of Clauses 7.3 and 7.8 were ruled.

'*Post-hoc analysis: Change in PHQ-9 scores from baseline significantly favoured ZYTIGA over enzalutamide at Weeks 4, 8 and 12*'

The Panel noted Astellas' allegation that this promotional claim implied that enzalutamide might cause depression/depressive episodes which was inconsistent with the product's SPC (which did not list depression or depressive episodes as an adverse reaction to enzalutamide). This information, in isolation, misrepresented the benefit-risk evaluation for enzalutamide in this setting and was thus, both inaccurate and misleading. Astellas further alleged that this section disparaged its product. Of note, Khalaf *et al* also stated that 'no pre-planned formal psychiatric assessments were mandated to validate PHQ-9 results' highlighting the authors identification of the significant limitation to the interpretation of these results, which was not reflected in the material.

Astellas did not consider that by avoiding the use of the word 'depression' or any other similar term in the material, a clinician would not link depression to enzalutamide when presented with data from the PHQ-9 questionnaire. The promotion of a graph that showed PHQ-9 outcomes was a clear sign-post to the insinuation that enzalutamide caused depressive symptoms and/or depression despite the absence of any evidence of this from a number of randomised placebo controlled Phase III clinical trials, that presented a much more robust evidence base than a single post-hoc exploratory analysis from a small open-label Phase II clinical trial.

The Panel noted Janssen's submission that the figure shown on the Janssen website was adapted from Figure 3 of the Khalaf publication and had all the statistical considerations included on it that were cited on the paper for weeks, 4, 8 and 12. Similarly all the caveats as per the publication were given ie, this was a post hoc analysis, the results were not prespecified and that they should be considered to be hypothesis generating.

With regard to Janssen's submission that it had simply reproduced the table in the Khalaf publication and made no mention of the word depression in the promotional item, the Panel noted that this was not so. A footnote on the item in question described PHQ-9 as consisting of nine diagnostic criteria for depressive episode from the Diagnostic and Statistical Manual of Mental Disorders.

The Panel noted Janssen's submission that the head-to-head comparative study of abiraterone acetate vs enzalutamide (Parimi *et al* 2016, Ref 7) showed that significantly more patients in the enzalutamide arm had a worsening of depression severity score 19% v 4% (P=0.03). The Panel further noted Janssen's submission that Parimi *et al* 2016 conclusions included**:** *'*In this preliminary analysis, there were more pts with a worsening severity of reported depression symptoms and a trend towards an increase in cognitive impairment with ENZA as compared to ABI. These data help to characterize and define the incidence of these symptoms'. The Panel noted that the reference provided for Parimi *et al* 2016 was that of a poster when the study, NCT02125357, was ongoing; it appeared to the Panel that the poster illustrated a preliminary analysis of the data which was later presented in Khalaf *et al* 2019.

The Panel noted Janssen's submission that depression was listed as a recognised Adverse Event for Enzalutamide (7 cases) on the MHRA Website for Drug Analysis Profiles and on the Cancer McMillan Webpage depression was listed as an acknowledged side effect for enzalutamide, stating that patients may feel low or depressed whilst on this treatment. The Panel noted that the Cancer McMillan Webpage stated below the heading 'Mood changes' that 'You may have some mood changes during this treatment. You may feel low or depressed. Let your doctor or nurse know if you notice any changes'. In relation to enzalutamide common side effects, the Panel, however, noted that it could not find a reference to 7 cases of depression within the MHRA Website for Drug Analysis Profile for enzalutamide as provided by Janssen.

The Panel noted that PHQ-9 was a self-administered questionnaire consisting of the nine diagnostic criteria for depressive episode and had been validated and shown to perform well in patients with a diagnosis of cancer. The Panel noted that below the claim 'Post-hoc analysis: Change in PHQ-9 scores from baseline significantly favoured ZYTIGA over enzalutamide at Weeks 4, 8 and 12' which was referenced to Khalaf *et al* 2019 was a graphical illustration, accompanied by the statement 'this analysis was not prespecified, and results should [not] be considered to be hypothesis generating'. In the Panel's view, PHQ-9 was a depressive scale and one of many HRQoL measures that would help inform health professionals' understanding. The Panel considered that the claim and illustration implied that there was some unfavourable

data in relation to depression for patients taking enzalutamide, when compared to abiraterone. The Panel noted its comments above regarding the nature of the data submitted by Janssen to support the differences between the medicines in relation to depression severity. It considered however that the material in question was a misleading comparison which disparaged Astellas' product, particularly as there was no mention of the absence of a reference to depression in the enzalutamide SPC. The Panel thus ruled breaches of Clauses 7.3 and 8.1.

The Panel noted Clause 7.9, *inter alia*, stated that information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product has no adverse reactions, toxic hazards or risks of addiction or dependency. The Panel noted its comments above and considered that the misleading representation of differences between the medicines in relation to depression severity did not reflect available evidence and a breach of Clause 7.9 was ruled.

Complaint received **7 July 2021**

Case completed **1 December 2022**