CASE AUTH/3528/6/21

ANONYMOUS v ADVANCED ACCELERATOR APPLICATIONS

Promotional presentation on a third party website and email invitations

An anonymous contactable complainant, who described himself/herself as a doctor, complained about email invitations from a third party about prostate-specific membrane antigen (PSMA) targeted therapy for the treatment of prostate cancer patients.

The complainant received three emails in April 2021 about a continuing professional development (CPD) activity called 'understanding novel therapeutic options for metastatic castration resistant prostate cancer' and stated that it was a tad excessive to get invited to the same module three times in 12 days.

The complainant stated that this activity was supported by Advanced Accelerator Applications (AAA), a Novartis company and was intended for an international, non-US audience. The company pushed the invitation to a UK health professional distribution list and even had CPD accreditation from a UK College to make it more attractive. The activity made a few claims about the therapy, including how it compared to chemotherapy.

The complainant referred to one slide stating that it was a new agent which benefited patients with advanced prostate cancer and could be given safely before cabazitaxel. However, what was omitted was that this treatment could not be prescribed in the UK yet. Efficacy and safety claims were made about a treatment that was claimed to be new but in fact was unlicensed in the UK or anywhere in the world.

The complainant stated that it was brave to say some novel (read unlicensed and unproven) treatment was safe, instead of a licensed treatment that had been around for years. The presenters boldly endorsed this unlicensed treatment for clinical practice suggested combining it with other treatments. The complainant could find no study which had ever investigated such a combination.

Another slide discussed a patient who had 10 cycles of treatment, deteriorated, and subsequently died but allegedly had an improved quality of life while his bone marrow failed. The complainant stated that claiming anecdotally that the patient said he felt better while his bone marrow failed and he died, was a suspect medical statement to make. He also appeared to have been overtreated. All protocols suggested six cycles of treatment and this patient received 10 cycles.

The complainant stated that it was statements like these, under the sponsorship of a pharmaceutical company, which made him/her and other clinicians suspicious about the promotional practices of pharmaceutical companies.

The complainant shared another CPD activity on the same treatment: exploring systemic therapies in mCRPC: targeting PSMA to improve patient outcomes..

The complainant concluded that firstly, a pharmaceutical company was paying to generate a series of CPD activities on a 'novel treatment' for prostate cancer. The company declared sponsorship as an unrestricted educational grant. The company must have reviewed the slides and seen the wild claims and allowed them to be made.

Secondly, the complainant stated that he/she was registered with the third party as a doctor based in the UK and the programme was clearly planned to target UK doctors.

The complainant alleged that neither of the two speakers declared any financial involvement with Advanced Accelerator Applications or Novartis. One of the speakers was an investigator in a named study where he/she disclosed working as a speaker and advisory board member for Novartis. The complainant stated that surely this was important information to know when listening to his/her opinion on this compound and queried why was this not disclosed.

The complainant stated that Novartis planned to licence the treatment discussed in this CPD activity and that it was 'a bit naughty' to keep the disclosure so vague that it was not immediately apparent that the company that intended to profit from selling this treatment was the one that sponsored this activity. That disclosure was subtly yet grossly misleading by omission.

In addition, it was nearly impossible to believe that neither of these two experts had received any further payment from the Novartis family of companies.

The detailed response from Novartis was given below.

The Panel noted AAA's submission that a Master Funding Agreement was signed in November 2020 between its global medical affairs department, based in Switzerland, and the third party.

The Panel noted that it was a well-established principle under the Code that UK companies were responsible for the acts or omissions of overseas parents or affiliates that came within the scope of the Code. The videos in question were available for UK health professionals as well as others in Europe and the rest of the world (not the US). 'Understanding novel therapeutic options for metastatic castration-resistant Prostate Cancer' material had UK accreditation for CPD by the Faculty of Pharmaceutical Medicine (FPM). The Panel considered that the arrangements came within the scope of the UK Code.

The Panel noted AAA's submission that the agreement provided that the third party would develop independent medical educational activities following a request for funding from AAA for a specific educational activity and AAA's explanation of the process for submission and review of a funding request.

The Panel noted that it was possible for a company to sponsor material produced by an independent organisation which mentioned its own products and not be liable under the Code for its contents, but only if, *inter alia*, there has been a strictly arm's length

arrangement between the parties. In practical terms the arrangements must be such that there can be no possibility that the pharmaceutical company had been able to exert any influence or control over the final content of the material.

The Panel noted that the first activity 'Understanding novel therapeutic options for metastatic castration-resistant Prostate Cancer' consisted of two health professionals discussing case studies and deciding on the best treatment options to suggest for each patient.

In the first case study, the first speaker stated that he/she would certainly consider the patient for lutetium PSMA-617 and that he would have been eligible to participate in the TheraP and VISION trials, provided he met other eligibility for these trials. However, following further discussions of the trials, it was determined that the patient was not suitable for lutetium PSMA-617.

In the second case study, the patient was referred for the TheraP trial (a randomised phase 2 study comparing lutetium PSMA-617 to cabazitaxel). Whilst the second speaker stated that if the patient was not able to join a clinical trial, he/she would probably advise cabazitaxel treatment. The first speaker stated that the man had a very good response to docetaxel which might be another reason to try cabazitaxel but considered lutetium PSMA as another option. He/she further stated that

> **'when we embarked on the TheraP trial, we had uncertainty on how lutetium would compare to cabazitaxel. Now we have the results of that trial published in The Lancet. I think it's certainly a good treatment option if it's available. However, it's not yet available in most parts of the world, so cabazitaxel is certainly a good option'.**

The second speaker further stated

> **'I look at the course of treatment in this man, both cabazitaxel and lutetium PSMA have been effective. The durability, perhaps of both, a little disappointing, but when we combine them, he's done well. I think this is a message with lutetium PSMA-617 that it's not an alternative to cabazitaxel, but a new treatment option and we can sequence it either before or after. Here we can see that cabazitaxel can be delivered safely after lutetium PSMA-617, that's certainly my clinical experience. This is a good treatment option and you can use it the other way as well, lutetium is quite easy to deliver after cabazitaxel'.**

In the third case study, the first speaker suggested the patient would have been a suitable candidate for the VISION trial; he had already had cabazitaxel so he would not have been a candidate for the TheraP trial. It was explained that the patient's PSA became undetectable after the third dose of lutetium PSMA-617 which was described as being remarkable particularly after not being able to achieve undetectable PSA after prior lines of therapy including 4 lines of systemic therapy, docetaxel, abiraterone, enzalutamide, and cabazitaxel. The speaker pointed out that this was not typical and was not seen very often with lutetium PSMA-617, perhaps only in 5% of cases but it was rather spectacular when it was. The patient was described as having had a total of 10 cycles of lutetium PSMA-617 but after the last treatment, his PSA rose sharply again and he eventually developed a pancytopenia and PSMA-PET scan showed diffuse marrow

infiltration and he died at around 55 months; it was noted that his quality of life was exceptionally good; his pain improved after the very first dose of lutetium. It was described as a very impressive case, where the patient received great benefit for a long time.

The second speaker stated

> **'Now we have PSMA-targeting agents with PSMA lutetium being the most developed agent in parallel to bites and actinium-based drugs. We're waiting for the readouts of the VISION trial, which is the very 1st phase 3 trial for PSMA lutetium, but we are quite confident that the randomized phase 2 trial conducted in Australia, will continue to show efficacy with cabazitaxel as a comparator.'**

The first speaker's summary was that lutetium PSMA-617 was a new class of therapy. The phase 2 data were fairly convincing, and they had quite a lot of clinical experience with it as well, but it was an additional option. It did not replace existing options or current options which were still on the table. He further stated

> **'Hopefully the results of the VISION trial will make this therapy widely available and FDA-approved with all the global consequences of that. When that happens, I think the situation will move to one of deciding when to best sequence lutetium therapy amongst all these other treatment options, and that will need multidisciplinary discussion'.**

The Panel noted AAA's submission that prostate-specific membrane antigen (PSMA) was the protein linked to prostate cancer and targeting these proteins with a standardised therapy was a new approach; there were currently 36 PSMA targeting compounds in development other than PSMA-617, 7 of which were owned by AAA (including PSMA-617). The Panel noted, however, that the activity appeared to focus on PSMA-617 and included what in the Panel's view were promotional claims for the unlicensed medicine.

The Panel noted that the email sent by the third party to AAA with the funding request attached stated:

> **'I am pleased to attach an Independent Medical Education Grant proposal in the PDF doc. for your consideration together with a line item budget spreadsheet in excel doc. The proposal contains some cost efficiencies we applied in order to keep within the budget stated. We did need to also remove the Podcasts to come in line with budget, however, if you did want them added we could always discuss pricing options.**
>
> **I hope you like the proposal and it is in line with your expectations and as always please reach out to discuss any aspect as you feel appropriate…'**

The Panel noted AAA's submission that the first activity, titled 'Understanding Novel Therapeutic Options For Metastatic Castration-Resistant Prostate Cancer', was aimed at oncologists, urologists, radiologists, pathologists, and other clinicians involved in managing patients with metastatic castration-resistant prostate cancer (mCRPC). The Panel noted that the funding request proposal listed the learning objectives for the activity as being increased knowledge regarding the latest clinical data for emerging

treatment modalities for mCRPC and greater competence related to treat patients with mCRPC based on disease-specific characteristics. The funding request proposal included that the content would include focus on, *inter alia*, current approaches with Checkpoint-blockade immunotherapy, PARP inhibitors and PSMA targeted therapies including PSMA-Radioligands; PSMA-targeted CAR-T therapy, and PSMA-targeted Bi-specific T-cell engagers (BiTEs). The Panel noted that according to the second speaker, it appeared that PSMA lutetium was the most developed PSMA-targeting agent in parallel to bites and actinium-based medicines.

The Panel noted that it appeared from the email from the third party and the funding request that AAA would have had a clear idea of what would be covered before deciding whether or not to fund the request; the Panel considered that AAA could exercise its discretion to elect an activity and queried whether the arrangements with the third party were truly arm's length. It appeared from the proposal that the project would only go ahead with AAA's support and that it had some influence over the project, for example, whether to include podcasts or not, or if the proposal was 'in line with expectations'. The Panel thus considered that there was no strictly arm's length arrangement and in that regard the company was responsible under the Code for the content. The Proposal at a Glance referred to minimum audience guarantees and that copies of the slides and transcripts would be made available. The payment was referred to as a grant to develop the initiative.

The Panel noted that the activity by the third party was advertised and made available to UK health professionals as well as others in Europe and the rest of the world. In the Panel's view, it was clear from the funding proposal that the activity would, on the balance of probabilities, include discussions about AAA's pipeline products, 68Ga-PSMA-11 and 177Lu-PSMA-617, which were not yet licensed. The Panel queried whether it would ever be acceptable for a pharmaceutical company to sponsor an activity which it could not do itself.

The Panel further noted that Endocyte, Inc., a US subsidiary of Novartis, had sponsored the clinical studies on 177Lu-PSMA-617 and it was the results of these studies that were discussed in the third party activities. Based on these clinical studies, AAA intended to apply for marketing authorisation for the two compounds. One of the speakers was an experienced clinician in the treatment of prostate cancer with PSMA targeted therapies and had been one of the investigators and the second speaker was also an investigator where the published study disclosed the he/she worked as a speaker and advisory board member for Novartis.

Noting its comments and the content of the first activity above, in the Panel's view, it promoted AAA's unlicensed medicine which AAA would be aware of from the proposal and therefore, in funding the project, AAA was responsible for the promotion of an unlicensed medicine and a breach of the Code was ruled.

The Panel noted that AAA reiterated that it had no involvement in the development of the contents of the material and thus did not believe that it could be held responsible for any alleged breach of Clause 7.2. The Panel noted its comments above, that in its view, the activity was not truly an arm's length arrangement and thus considered that AAA was responsible for the content of the material in relation to its provision to UK health professionals.

The Panel noted the complainant's allegation that the patient in the third case study had been overtreated with ten cycles of treatment when protocols suggested six cycles and his/her further concern that the presenter claimed an improvement in quality of life (QoL) when the patient's bone marrow failed and died. The Panel noted AAA's submission that metastatic prostate cancer was a terminal disease and one of the objectives of treating a patient with this condition was to improve their quality of life and not just survival and whilst most clinical trials treated patients with Lu-PSMA-617 for six cycles there were studies investigating the impact on additional treatment cycles in patients who responded to the treatment.

The Panel noted that according to the transcript provided by AAA, the patient described in the third case study was actually a patient who participated in 'our' 1st phase 2 trial, which was a 30-patient trial which was published in Lancet Oncology, a single-arm study back in 2018. The patient received a 68Ga-PSMA-PET scan which showed very intense uptake at all sites of disease and the speaker explained that when a very high uptake on the PSMA-PET scan was seen, as in this case, it was very likely that the patient would respond to lutetium PSMA treatment but the durability of the response was not known. The speaker noted that the patient was treated as part of 'our' phase two trial and received 3 doses of lutetium PSMA-617. The speaker explained that the patient who had already progressed after cabazitaxel and had few treatment options left participated in a clinical trial and received the experimental treatment [PSMA-617] and did well. The speaker stated that he/she now had almost 50 months follow-up in this man which was remarkable and he had had a total of 10 cycles of lutetium PSMA-617. After that last treatment, his PSA rose sharply again, the patient eventually developed a pancytopenia and the PSMA-PET scan showed diffuse marrow infiltration and he died at around 55 months. The speaker noted, however, that his quality of life was exceptionally good; his pain improved after that very first dose of lutetium. When the patient came back 24 hours after the treatment, he stated that his pain was already starting to feel better. The Panel noted that Lu-PSMA-617 did not yet have a marketing authorisation and therefore had no proven dosage regimen or proven efficacy. The statements made in this regard, in the Panel's view, meant that that the medicine had been promoted prior to the grant of its marketing authorisation and the Panel ruled a breach of the Code in relation to each of the complainant's allegations.

The Panel noted, however, that it was clear that the treatment was given in a clinical trial setting. The Panel did not consider that the complainant had established that referring to 10 cycles of treatment within the clinical trial setting or the effect the treatment appeared to have on the patient's quality of life within that trial was misleading as alleged and no breach of the Code was ruled in relation to each allegation.

The Panel noted the complainant's allegation that the activity further suggested combining Lu-PSMA-617 with other treatments but he/she could find no study which had ever investigated such a combination. The Panel, whilst noting its ruling above of a breach of Clause 3.1, in relation to promotion of a medicine prior to the grant of its marketing authorisation, did not consider that the complainant had established that referring to a combination of treatments within the clinical trial setting was in itself misleading as alleged and no breach of the Code was ruled.

With regard to the complainant's allegation that AAA's new agent could be given safely before cabazitaxel in patients with advanced prostate cancer, the Panel noted that the

transcript, stated 'Here we could see that cabazitaxel could be delivered safely after lutetium PSMA-617, that's certainly my clinical experience'. In the Panel's view, the statement related to cabazitaxel, which did not appear to be an AAA nor Novartis affiliated product. The Panel therefore ruled no breach of the Code.

The Panel noted the complainant's concerns that the two speakers involved in the activities were likely to have been consultants for Novartis, AAA or Endocyte, but that this had not been disclosed.

The Panel noted AAA's submission that the speakers had no direct involvement for any AAA UK based activities in the past but other AAA affiliates had engaged them as consultants. The Panel further noted that one of the speakers was referred to as an experienced clinician in the treatment of prostate cancer with PSMA targeted therapies and had been an investigator on multiple trials and the second speaker was an investigator in a study published in the NEJM and there he disclosed working as a speaker and advisory board member for Novartis. The Panel considered, therefore, that the disclosure of the speakers' involvement with AAA and its associated affiliates was particularly important given that the presentations mentioned AAA's pipeline products and failure to do so was concerning. However, the Panel noted that Clause 23.1 required that contracts included provisions regarding the obligation of the consultant to declare that he/she was a consultant to the company in certain circumstances. The Panel noted that this appeared to be a requirement of the contracts provided by AAA and the speakers were required to disclose all financial relationships with any pharmaceutical, medical device, biologics, or diagnostics company so that the third party might provide this disclosure prior to participation in any such activity. The Panel therefore ruled no breach of the Code.

The Panel noted its comments and rulings of breaches of the Code above and considered that AAA had failed to maintain high standards and a breach of the Code was ruled.

The Panel noted that the complainant provided a list of the three emails with the same heading, 'Selecting Appropriate mCRPC Patients for PSMA-Targeted Therapy'. Whilst the Panel considered that three emails in the space of twelve days in relation to an activity was likely to be seen as excessive, it noted, from screenshots provided by the complainant and from various documents provided by AAA, that there were two components to the activity. It was not clear from the emails provided by the complainant whether they were promoting the overall activity, the separate parts or a combination of the two. The Panel noted that the Code stated, *inter alia*, that restraint must be exercised on the volume and frequency of distribution of promotional material distributed. The Panel did not have before it the contents of the emails to determine whether they were promotional and to be sure what exact activity each related to. Based on the evidence before it, the Panel did not consider that the complainant had established that AAA had failed to maintain high standards in this regard and no breach of the Code was ruled.

Clause 2 was a sign of particular censure and reserved for such use. The Panel noted the examples in the supplementary information to this clause included promotion prior to the grant of a marketing authorisation. The Panel noted its rulings above and considered that AAA had brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

An anonymous contactable complainant, who described himself/herself as a doctor, complained about a series of email invitations he/she received from a named third party inviting him/her to learn more about PSMA targeted therapy for the treatment of prostate cancer patients.

COMPLAINT

The complainant stated he/she received three emails in April 2021 (15, 22 and 27) from the third party about a CPD activity called ‘understanding novel therapeutic options for metastatic castration resistant prostate cancer' and stated that it was a tad excessive to get invited to the same module three times in 12 days.

The complainant stated that this activity was supported by Advanced Accelerator Applications (AAA), a Novartis company. The activity was intended for an international, non-US audience and had CPD accreditation from the Royal Colleges of Physicians of the United Kingdom. The company sponsoring this activity must have known very well that this would land in front of several UK doctors. The company pushed the invitation to a UK health professional distribution list and even had CPD accreditation from a UK College to make it more attractive. The activity made a few claims about the therapy, including how it compared to chemotherapy.

The complainant referred to one slide stating that it’ was a new agent which benefited patients with advanced prostate cancer and could be given safely before cabazitaxel. However, what was omitted was that this treatment could not be prescribed in the UK yet. Efficacy and safety claims were made about a treatment that was claimed to be new but in fact was unlicensed in the UK or anywhere in the world.

The complainant stated that it was brave to say some novel (read unlicensed and unproven) treatment was safe, instead of a licensed treatment that had been around for years. The presenters boldly endorsed this unlicensed treatment for clinical practice. Then went further and suggested combining it with other treatments. The complainant could find no study which had ever investigated such a combination.

Another slide, case 3 discussed a patient who had 10 cycles of treatment, deteriorated, and subsequently died. But allegedly had an improved quality of life while his bone marrow failed. The complainant stated that claiming anecdotally that the patient said he felt better while his bone marrow failed and he died, was a suspect medical statement to make. He also appeared to have been overtreated. All protocols suggested six cycles of treatment and this patient received 10 cycles.

The complainant stated that it was statements like these, under the sponsorship of a pharmaceutical company, which made him/her and other clinicians suspicious about the promotional practices of pharmaceutical companies.

The complainant shared another CPD activity on the same treatment: exploring systemic therapies in mCRPC: targeting PSMA to improve patient outcomes.

The complainant stated that this activity came with the same disclaimer: this activity was supported by Advanced Accelerator Applications, a Novartis company. The activity also had CPD accreditation from the Royal Colleges of Physicians of the United Kingdom.

The complainant drew the following conclusions from these email invitations. Firstly, a pharmaceutical company was paying good money to generate a series of CPD activities on a 'novel treatment' for prostate cancer. The company declared sponsorship as an unrestricted educational grant. The complainant stated that unrestricted or not, this company was responsible for this activity and should be accountable for all activities it paid for. The company must have reviewed the slides and seen the wild claims and allowed them to be made.

Secondly, the complainant stated that he/she received these invitations because he/she was registered with the third party as a doctor based in the UK. This programme was clearly planned to target UK doctors.

The complainant stated that whilst he/she was doing these two CPD activities, a few facts became apparent. One, this 'novel new therapy' was not a licensed medicine yet. It was still in research/development. This company was promoting this yet unproven treatment to UK doctors before it was licensed.

The complainant questioned although it was supported by an unrestricted educational grant, surely the company had a responsibility to tell readers this treatment was not licensed yet? Words like new and novel without the word unlicensed was deceptive. Claims made in these activities seemed rather exaggerated. Boldly claiming a treatment was safe before it had even received a licence was reckless.

The complainant stated that he/she had read the financial disclaimers of two named speakersand nowhere did one of the speakers declare any financial involvement with Advanced Accelerator Applications or Novartis. Another speaker did not declare any financial relationship with Advance Accelerator Applications or Novartis either. Yet he/she was an investigator in a study published in the New England Journal of Medicine (NEJM) and there he/she disclosed working as a speaker and advisory board member for Novartis. The complainant stated that surely this was important information to know when listening to his/her opinion on this compound and queried why was this not disclosed.

The complainant stated if one did a search about Endocyte it would become clear that Endocyte was acquired by Novartis in 2018 and that Novartis planned to licence the treatment discussed in this CPD activity. Advanced Accelerated Applications was also owned by Novartis. The complainant stated that it was 'a bit naughty' to keep the disclosure so vague that it was not immediately apparent that the company that intended to profit from selling this treatment was the one that sponsored this activity. That disclosure was subtly yet grossly misleading by omission.

In addition, it was nearly impossible to believe that neither of these two experts had received any further payment from the Novartis family of companies. It was common practice for investigators of a study to do the speaker circuit, paid for by the pharmaceutical company. It was hard to believe there were no other consulting, no other paid speaker events or any other research paid for by Novartis or Advanced Accelerator Applications or Endocyte. This just did not look like full disclosure.

When writing to Novartis, the Authority asked it to consider the requirements of Clauses 2, 3.1, 7.2, 7.9, 9.1 and 23.1 of the Code.

RESPONSE

Introduction

AAA (UK & Ireland) Ltd was the legal entity registered in the UK and the UK based affiliate of the AAA group of companies, having its registered offices in France (for facilitation purposes, for the purpose of this letter, a reference to AAA might also be a reference to any of the AAA affiliates outside of the UK as the case might be). AAA (UK & Ireland) Ltd was a subsidiary of AAA International which was in turn part of Novartis International AG (registered offices in Switzerland). Novartis acquired AAA in 2018 and AAA complied with all Novartis policies and standards. AAA was currently run as an independent organisation from Novartis with some indirect links between certain functions to allow sharing of knowledge, resources and expertise.

AAA currently marketed one targeted radioligand therapy in oncology and several precision imaging products mainly used in clinical oncology, cardiology, neurology and infectious/inflammatory diseases. AAA had a pipeline of products in development, two of which were mentioned in the educational activities relating to this complaint – ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617:

- ^{68}Ga-PSMA-11 was in development as a tracer for PET scans to better localise metastatic prostate cancer. Other variations of this ligant targeting the Prostate Specific Membrane Antigen existed and were being used as an unlicensed preparation, manufactured on site by hospitals;

and

- ^{177}Lu-PSMA-617 was in clinical development for the treatment of metastatic castration resistant prostate cancer. Other variations of ligants targeting the Prostate Specific Membrane Antigen existed and were being used as an unlicensed preparations manufactured on site by hospitals for their patients.

Endocyte, Inc., was also a subsidiary of Novartis, acquired in December, 2018, with registered offices in the United States of America and had sponsored the clinical studies on ^{177}Lu-PSMA-617. It was, amongst others, the results of these studies that were discussed in the third party activities which were the subject of this complaint. Based on these clinical studies AAA intended to apply for marketing authorization for the two compounds.

AAA was committed to ensuring patient safety and improving patient care across the entire organisation.

Funding arrangement for educational activities

AAA noted that the complainant referred to a health professional facing website, owned by a third party organisation which described itself as the leading online global destination for physicians and health professionals worldwide, offering the latest medical news and expert perspectives; essential point-of-care medicine and disease information; and relevant professional education and CME. The third party was highly regarded within the industry and by health professionals as a provider of independent medical education. The allegations were aimed towards two modules that were created by the third party and were funded through a hands-off educational grant targeting ex US countries provided by AAA.

<u>Master funding agreement</u>

A Master Funding Agreement was signed on 5 November 2020 between the AAA Global Medical Affairs department at AAA International, the AAA affiliate for global operations, based in Switzerland and the third party based in the United States of America.

The agreement provided that the third party would develop independent medical educational activities ('Educational Activity') following a request for funding from AAA for a specific educational activity.

The process for submission and review of a funding request by AAA was set out as follows, and was described in the funding agreement:

1. Each time the third party desired funding from AAA for an Educational Activity, it would submit a Funding Request. It would contain a description of the Educational Activity and the funding required for such Educational Activity. It would include a complete budget for the Educational Activity, and such other information as might be requested by AAA.
2. AAA would evaluate each Funding Request individually and notify the third party if it elected to fund the applicable independent Educational Activity.
3. If AAA elected to fund the Educational Activity, the parties would sign a Funding Commitment. This Funding Commitment would comply with the terms and conditions contained in the Master Funding Agreement.

AAA referred to the following relevant clauses of the Master Funding Agreement:

- Each Educational Activity was for scientific and/or educational purposes only and would not promote AAA products, directly or indirectly.

- Educational Activities would be independent, non-promotional and free from commercial influence or bias. The third party would submit the activity to a professional body for certification.

- AAA's sole responsibility was to provide the funding. AAA would be responsible for its compliance with all applicable laws and regulations in connection with the funding and agreed not to influence the contents of the activity.

- AAA agreed not to direct or influence the content of Educational Activities or to engage in scripting, targeting points of emphasis or other activities designed to influence Educational Activities' content. The third party would comply with (and shall be solely responsible for its failure to comply with) all applicable Laws and regulations and each educational activity would be compliant with all such requirements.

- If an Educational Activity involved the discussion of AAA products, or the comparison of AAA products with other products, that discussion and/or comparison must be objective, balanced, accurate, not misleading or deceptive and in compliance with all applicable laws, rules and regulations). Where appropriate, an Educational Activity would include a discussion of multiple treatment options and unmet medical needs, and would not focus on a single product.

- The third party was responsible for selection of presenters, moderators and collaborators for each Educational Activity.

- The third party was also required to disclose to audiences that AAA had provided the funding to support the Educational Activity and disclose any other relationships AAA had with any individual speakers, moderators or collaborators.

- AAA would not control the planning, contents, speaker selection or execution of any Educational Activity.

As could be seen from the above the Master Funding Agreement reflected the requirements under the 2019 Code.

A funding commitment was signed, dated 5 November 2020 and listed two activities:

Activity 1 was titled *'Understanding Novel Therapeutic Options For Metastatic Castration-Resistant Prostate Cancer'.*

AAA stated that this was aimed at oncologists, urologists, radiologists, pathologists, and other clinicians involved in managing patients with metastatic castration-resistant prostate cancer (mCRPC). Members of the public would not have been able to access this activity.

AAA was provided with the following information on the learning objectives for the activity:

- Increased knowledge regarding the latest clinical data for emerging treatment modalities for mCRPC
- Greater competence related to treat patients with mCRPC based on disease-specific characteristics

Activity 2 was titled '*Exploring Systemic Therapies in mCRPC: Targeting PSMA to improve patient outcomes'*.

AAA was provided with the following information on the learning objectives for this activity:

- Increased knowledge regarding the making of treatment recommendations for patients with PSMA upregulation
- Greater competence related to selection of appropriate patients with mCRPC for PSMA targeted therapy.

The target audience for this activity were oncologists and urologists.

AAA stated that it was therefore clear that no information was or could have been provided to AAA on the content of what would be discussed in the Educational Activity or the specific treatment options which would be discussed as it was an independent Educational Activity.

Position

AAA stated that it was not involved in the content's development. This was expressly provided for in the Master Funding Agreement discussed above and had been in place in relation to any funding provided by AAA to the third party for Educational Activities.

AAA merely provided funding for this Educational Activity.

At no point in the development of the Educational Activities which were the subject of this complaint did AAA have sight of or approval of the materials which formed part of these Educational Activities. AAA were not involved in the selection of the speakers.

AAA was not able to (nor would it) exert any control or influence over the contents of the material which was presented on, or the speakers for these events. Also, AAA had no control or influence over who the educational activity was to be made available to.

The third party submitted a funding request for the Education Activities which were the subject of this complaint, and these were not initiated by AAA. The third party was the entity which had full control over the contents, materials, speakers, and the way and manner in which the training was delivered and AAA had not and could not have reviewed, endorsed or approved the content.

AAA stated that the activities funded would lead to fair and balanced education for health professionals and would not lead to promotion of a AAA product.

AAA (UK & Ireland) Ltd was not informed of this activity.

Addressing the highlighted clauses of the Code

Alleged breach of Clause 3.1.

A medicine must not be promoted prior to the grant of the marketing authorization which permits its sale or supply.

AAA stated that first of all, it should be borne in mind that PSMA itself was the protein, prostate-specific membrane antigen (PSMA), which was linked to prostate cancer. Given that targeting these proteins with a standardized therapy was a new approach and that there were currently 36 other PSMA targeting compounds than PSMA-617 in development, 7 of which were owned by AAA (including PSMA-617), it was clear AAA did not fund an activity where the field would only allow clinicians to discuss AAA products. Secondly, an independent review carried out by the third party confirmed that the content was fair, accurate and balanced, and not biased towards AAA products. Nor was it known by AAA which products would be discussed.

Furthermore, the title of this module did not promote PSMA-617 but rather explained that a new approach was to target PSMA. As mentioned above, PSMA-617 was not the only PSMA targeting compound and other independent research and/or medical activities were being funded and supported by other companies than AAA. It could not be inferred that an Educational Activity that referred to PSMA was necessarily referring to PSMA- 617 as there were 36 other PSMA compounds than PSMA-617 currently under development and only 7 of them were owned by AAA.

AAA stated that a clear declaration of the unapproved nature within its medical information response letters showed its awareness and intent to provide full transparency to health professionals:

> '[177Lu]Lu-PSMA-617 (177Lu-PSMA-617) is an investigational compound that has *undergone clinical testing in the Phase 3 VISION trial (NCT03511664)1 for the treatment of progressive PSMA-positive mCRPC. 177Lu-PSMA-617 has not been approved or*

cleared as safe and effective for use by the European Medicines Agency (EMA) and/or is not commercially available. This letter is provided to address your unsolicited medical inquiry to Advanced Accelerator Applications, a Novartis Company."

AAA stated that it was not involved in the contents developed in these activities. After reviewing the activity title and objectives, AAA agreed to fund an independent medical education related activity and had no further involvement in the development. The agreement with the third party stated explicitly that the contents of these activities must be educational in content and not promote any AAA product.

Due to the hands-off approach under the Master Funding Agreement and in order to ensure independence of the Educational Activities, AAA was not aware of any alleged claims or and potential product specific discussions before the activity went live on the third party website. AAA was not permitted to review the final version of the activity before it was published.

As emphasized, the Master Funding Agreement expressly stated that Educational Activities were for scientific and/or educational purposes only and would not promote AAA's products, directly or indirectly.

Once again, however, AAA reiterated that it had always maintained an arms' length approach to funding independent educational activities, and in order to ensure independence and avoid any bias, did not consider that it would be appropriate for it to review or approve the materials. The third party developing the educational material was responsible for ensuring the third party did not promote unlicensed medicines.

AAA stated that as it did not produce, review or approve the training materials, it believed it was more appropriate for the third party to comment on the extent to which the materials were promotional in nature and include their response hereto. It was however AAA's view that educational materials which provided an update on the development of new medicines not yet licensed would not be prohibited under the Code.

Alleged breach of Clause 7.2.

Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis. Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine.

AAA reiterated that it had no involvement in the development of the contents of the training. On that basis, the company did not believe that it could be held responsible for any alleged breach of Clause 7.2. Responsibility for compliance sat with the third party, as the entity responsible for producing the training materials.

Having now reviewed the training materials, AAH made the following observations, in the event that they assisted the assessment of this matter.

AAA stated that one of the speakers was an experienced clinician in the treatment of prostate cancer with PSMA targeted therapies. He/she had been an investigator. As part of the discussion of the case studies, he/she offered an opinion on the place of this therapy, supported

by results from published clinical trials and responses seen in patients under his/her treatment in clinical trial. He/she suggested the patient's profiles discussed, would be candidates for enrolment in clinical studies and openly discussed treatment options (only as an example), mentioning that

> 'To be honest, at this time point, particularly when we embarked on the TheraP trial, we had uncertainty on how lutetium would compare to cabazitaxel. Now we have the results of that trial published in The Lancet. I think it's certainly a good treatment option if it's available. **However, it's not yet available in most parts of the world, so cabazitaxel is certainly a good option.'.**

AAA submitted that this educational activity also made very clear that the treatment was not yet licensed.

AAA stated that the complainant mentioned the discussion of a patient case study where the patient received 10 courses of treatment instead of the 6 in pivotal studies and questioned how the presenter could claim an improvement of quality of life when the patient died. Unfortunately, metastatic prostate cancer was a terminal disease and one of the objectives of treating a patient with this condition was to improve their quality of life for as long as one could. Most clinical trials treated patients with Lu-PSMA-617 for six cycles but there were studies investigating the impact on additional treatment cycles in patients who responded to the treatment. The speaker would have seen patients undergo these treatments and gave his/her opinion on that for the case study in question. In the slides, the presenter showed the patient's PSA response with the treatment and explained the rationale for why this patient received more cycles as part of clinical research.

AAA stated that it was acknowledged that the speaker was a key expert in this novel (Def: new active compound which had not been previously approved by the FDA/EMA/MHRA) therapy and it appeared to AAA that the statements about the efficacy and safety of the product in the speaker's research was balanced, accurate, fair and objective. In each case study where the speaker suggested this patient was suitable for this treatment, the speaker justified that statement by mentioning the clinical trial he/she would have entered the patient in, based on his/her own clinical experience. According to the response from the third party (copy provided), the company audited its development process, consulted with their medical education director and both activities were reviewed by an independent peer reviewer who concluded that the content of the Educational Activities were both accurate and fair balanced and complied with all international standards (as the Educational Activities were not intended specifically for UK based health professionals) including the Accreditation Council for Continuing Medical Education's Standards for Integrity and Independence in Accredited Continuing Education (SIIACE) and Academy of Medical Royal Colleges' Standards and Criteria for CPD Activities A Framework for Accreditation.

<u>Alleged breach of Clause 7.9</u>

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 had no adverse reactions, toxic hazards or risks of addiction or dependency. The word 'safe' must not be used without qualification.

AAA submitted that Clause 7.9 was not relevant as AAA was not responsible for the contents of the modules, given the hands-off educational grant, as documented within the Master Funding Agreement. AAA understood that the third party had carried out its own investigation into the claims, and had concluded that no safety claims were made in the education training.

In parallel, and following the receipt of the complaint, AAA conducted its own investigation. The complainant alleged that the term 'safe' was used to describe Lu-PSMA-617 in the following sentence taken from the complaint; 'In this slide they stated it is a new agent which benefits patients with advanced prostate cancer and can be given safely before cabazitaxel'. AAA stated that it was its understanding that the speaker (which could be shown in the slide and transcript) actually suggested 'Here we could see that cabazitaxel could be delivered safely after lutetium PSMA-617, that's certainly my clinical experience'. This did not suggest that a AAA product was safe. The word 'safe' was not used in either of the transcripts.

AAA denied that there had been a breach of Clause 7.9.

Alleged breach of Clause 23.1

In their written contracts or agreements with consultants, companies must include provisions regarding the obligation of the consultant to declare that he/she was a consultant to the company whenever he/she wrote or spoke in public about a matter that was the subject of the agreement or any other issue relating to that company. Similarly, companies that employed, on a part-time basis, health professionals that were still practising their profession, must ensure that such persons were obliged to declare their employment arrangement with the company whenever they wrote or spoke in public about a matter that was the subject of the employment or any other issue relating to that company.

AAA pointed out that both speakers were not UK based, details were provided. The contract for this activity was between the speakers and the third party directly and not AAA and therefore AAA was not responsible for their disclosures. Full disclosure of conflicts for these activities were the responsibility of the third party and the speakers as required within AAA's contract with the third party, highlighted above. As AAA was not involved in and had no control over the training or the materials (and provided the funding only), the company was not able to verify that the disclosures were made.

AAA (UK & Ireland) Ltd did not have any direct involvement with these speakers for any UK based activities in the past. Other AAA affiliates had engaged the speakers for events and advisory boards.

Alleged breach of Clause 9.1 and Clause 2

High standards must be maintained at all times.

Activities or materials associated with promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry.

AAA provided funding to the third party with the overarching objective to educate health professionals and improve patient care. The Master Funding Agreement included appropriate clauses to ensure that the third party complied with its legal obligations and was required to

ensure for example that educational activities were well balanced, independent, non-promotional and free from commercial bias or influence.

Whilst AAA agreed with the fundamental importance of the above clauses, given AAA was not involved in the planning, development, delivery and evaluation of the materials, and had no control over the contents, AAA did not believe that it was in breach of Clause 9.1. and Clause 2.

Conclusion
AAA stated that it was committed to the highest ethical standards when supporting independent medical education as a critical element to advance medicine and ensure that the right therapy was available to the right patient at the right time in compliance with all applicable laws, regulations and industry codes.

AAA hoped the above assisted in setting out the particular role it played in relation to the funding of the hands off educational activity which was the subject of the complaint.

AAA valued and respected the ABPI's commitment to operating in a professional, ethical and transparent manner to ensure the appropriate and rational use of medicines and to support the provision of high quality healthcare.

In response to a request for further information, AAA provided copies of the funding request from the third party to AAA in respect of what was referred to as an educational initiative entitled 'the "Understanding Novel Therapeutic Options For Metastatic Castration-Resistant Prostate Cancer" activities which included two components. Firstly 'an extended curbside consult' entitled 'Understanding Novel Therapeutic Options For mCRPC' and activity two "Exploring Systemic Therapies in mCRPC: Targeting PSMA to improve patient outcomes". AAA also provided the Master Funding Agreement between AAA International SA and WebMD Global LLC dated 5 November 2020; and the Funding Commitment between AAA International SA and WebMD Global LLC dated on or around 5 November 2020.

AAA submitted that it did not invite or advertise the webinars to anyone external or internal. However, for the avoidance of any doubt, the information about the webinars was, according to AAA, internally shared with its medical affairs teams once the modules were live.

PANEL RULING

The Panel noted that the complainant stated that he/she had received three emails from the third party about an online activity titled 'Understanding novel therapeutic options for metastatic castration-resistant Prostate Cancer'.

The complainant also included a link to the third party and referred to a similar CPD activity titled 'Exploring Systemic Therapies in mCRPC: Targeting PSMA to improve patient outcomes' and noted that both activities included the declaration 'supported by an independent educational grant from Advanced Accelerator Applications, a Novartis company'.

The Panel noted AAA's submission that a Master Funding Agreement was signed in November 2020 between its global medical affairs department, based in Switzerland, and the third party, based in the United States of America covering both activities.

The Panel noted that it was a well-established principle under the Code that UK companies were responsible for the acts or omissions of overseas parents or affiliates that came within the scope of the Code. The videos in question were available for UK health professionals as well as others in Europe and the rest of the world (not the US). 'Understanding novel therapeutic options for metastatic castration-resistant Prostate Cancer' material had UK accreditation for CPD by the Faculty of Pharmaceutical Medicine (FPM). The Panel considered that the arrangements therefore came within the scope of the UK Code.

The Panel noted AAA's submission that the agreement provided that the third party would develop independent medical educational activities ('Educational Activity') following a request for funding from AAA for a specific educational activity and AAA's explanation of the process for submission and review of a funding request.

The Panel noted AAA's reference to clauses within the Master Funding Agreement including, *inter alia*, that:

- Each Educational Activity was for scientific and/or educational purposes only and would not promote AAA products, directly or indirectly.

- Educational Activities would be independent, non-promotional and free from commercial influence or bias. The third party would submit the activity to a professional body for certification.

- AAA agreed not to direct or influence the content of Educational Activities or to engage in scripting, targeting points of emphasis or other activities designed to influence Educational Activities' content. The third party would comply with (and shall be solely responsible for its failure to comply with) all applicable Laws and regulations and each educational activity would be compliant with all such requirements.

- If an Educational Activity involved the discussion of AAA products, or the comparison of AAA products with other products, that discussion and/or comparison must be objective, balanced, accurate, not misleading or deceptive and in compliance with all applicable laws, rules and regulations). Where appropriate, an Educational Activity would include a discussion of multiple treatment options and unmet medical needs, and would not focus on a single product.

- The third party was responsible for selection of presenters, moderators and collaborators for each Educational Activity.

- The third party was also required to disclose to audiences that AAA had provided the funding to support the Educational Activity and disclose any other relationships AAA had with any individual speakers, moderators or collaborators.

- AAA would not control the planning, contents, speaker selection or execution of any Educational Activity.

The Panel noted that it was possible for a company to sponsor material produced by an independent organisation which mentioned its own products and not be liable under the Code for its contents, but only if, *inter alia*, there has been a strictly arm's length arrangement between the parties.

In practical terms the arrangements must be such that there can be no possibility that the pharmaceutical company has been able to exert any influence or control over the final content of the material.

Factors which might mean there had not been a strictly arm's length arrangement would include, but not be restricted to:

- Initiation of the material, or the concept for it, by the pharmaceutical company
- Influence from the pharmaceutical company on the content/balance/scope of the material
- Choice/or direct payment of the authors by the pharmaceutical company
- Influence from the pharmaceutical company on the list of persons to whom the material was sent.

It had previously been decided, in relation to material/activities aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests.

Companies should remember that use of material for a promotional purpose would mean that material was subject to the Code.

The Panel noted that the first activity 'Understanding novel therapeutic options for metastatic castration-resistant Prostate Cancer' consisted of two health professionals discussing case studies and deciding on the best treatment options to suggest for each patient.

In the first case study, the first speaker stated that he/she would certainly consider the patient for lutetium PSMA-617 and that he would have been eligible to participate in the TheraP trial and would also have been a suitable candidate for the VISION trial, provided he met other eligibility for these trials. However, following further discussions of the trials, it was determined that the patient would have been deemed not suitable for lutetium PSMA-617.

In the second case study, the patient was referred for the TheraP trial, which was a randomised phase 2 study comparing lutetium PSMA-617 to cabazitaxel. Whilst the second speaker stated that if the patient would not be a candidate for clinical trial or if there would be no available clinical trial at his place, he/she would probably advise cabazitaxel treatment. The first speaker stated that the man had a very good response to docetaxel which might be another reason to try cabazitaxel but considered lutetium PSMA as another option. He/she further stated that

> 'when we embarked on the TheraP trial, we had uncertainty on how lutetium would compare to cabazitaxel. Now we have the results of that trial published in *The Lancet*. I think it's certainly a good treatment option if it's available. However, it's not yet available in most parts of the world, so cabazitaxel is certainly a good option'.

The second speaker further stated

> 'I look at the course of treatment in this man, both cabazitaxel and lutetium PSMA have been effective. The durability, perhaps of both, a little disappointing, but when we combine them, he's done well. I think this is a message with lutetium PSMA-617 that it's not an

> alternative to cabazitaxel, but a new treatment option and we can sequence it either before or after. Here we can see that cabazitaxel can be delivered safely after lutetium PSMA-617, that's certainly my clinical experience. This is a good treatment option and you can use it the other way as well, lutetium is quite easy to deliver after cabazitaxel'.

In the third case study, the first speaker suggested the patient would have been a suitable candidate for the VISION trial; he had already had cabazitaxel so he would not have been a candidate for the TheraP trial. It was explained that the patient's PSA became undetectable after the third dose of lutetium PSMA-617 which was described as being remarkable particularly after not being able to achieve undetectable PSA after prior lines of therapy including 4 lines of systemic therapy, docetaxel, abiraterone, enzalutamide, and cabazitaxel. The speaker pointed out that this was not typical and was not seen very often with lutetium PSMA-617, perhaps only in 5% of cases but it was rather spectacular when it was. The patient was described as having had a total of 10 cycles of lutetium PSMA-617 but after the last treatment, his PSA rose sharply again and he eventually developed a pancytopenia and PSMA-PET scan showed diffuse marrow infiltration and he died at around 55 months; it was noted that his quality of life was exceptionally good; his pain improved after the very first dose of lutetium. It was described as a very impressive case, where the patient received great benefit for a long time.

The second speaker stated

> 'Now we have PSMA-targeting agents with PSMA lutetium being the most developed agent in parallel to bites and actinium-based drugs. We're waiting for the readouts of the VISION trial, which is the very 1st phase 3 trial for PSMA lutetium, but we are quite confident that the randomized phase 2 trial conducted in Australia, will continue to show efficacy with cabazitaxel as a comparator.'

The first speaker's summary was that lutetium PSMA-617 was a new class of therapy. The phase 2 data were fairly convincing, and they had quite a lot of clinical experience with it as well, but it was an additional option. It did not replace existing options or current options which were still on the table. He/she further stated

> 'Hopefully the results of the VISION trial will make this therapy widely available and FDA-approved with all the global consequences of that. When that happens, I think the situation will move to one of deciding when to best sequence lutetium therapy amongst all these other treatment options, and that will need multidisciplinary discussion'.

The Panel noted AAA's submission that prostate-specific membrane antigen (PSMA) was the protein linked to prostate cancer and targeting these proteins with a standardised therapy was a new approach; there were currently 36 PSMA targeting compounds in development other than PSMA-617, 7 of which were owned by AAA (including PSMA-617). The Panel noted, however, that the activity appeared to focus on PSMA-617 and included what in the Panel's view were promotional claims for the unlicensed medicine.

The Panel noted that the email sent by the third party to AAA with the funding request attached stated:

> 'I am pleased to attach an Independent Medical Education Grant proposal in the PDF doc. for your consideration together with a line item budget spreadsheet in excel doc. The proposal contains some cost efficiencies we applied in order to keep within the budget

> stated. We did need to also remove the Podcasts to come in line with budget, however, if you did want them added we could always discuss pricing options.
>
> I hope you like the proposal and it is in line with your expectations and as always please reach out to discuss any aspect as you feel appropriate…'

The Panel noted AAA's submission that the first activity, titled 'Understanding Novel Therapeutic Options For Metastatic Castration-Resistant Prostate Cancer', was aimed at oncologists, urologists, radiologists, pathologists, and other clinicians involved in managing patients with metastatic castration-resistant prostate cancer (mCRPC). The Panel noted that the funding request proposal listed the learning objectives for the activity as being increased knowledge regarding the latest clinical data for emerging treatment modalities for mCRPC and greater competence related to treat patients with mCRPC based on disease-specific characteristics. The funding request proposal included that the content would include focus on, *inter alia*, current approaches with Checkpoint-blockade immunotherapy, PARP inhibitors and PSMA targeted therapies including PSMA-Radioligands; PSMA-targeted CAR-T therapy, and PSMA-targeted Bi-specific T-cell engagers (BiTEs). The Panel noted that according to the second, speaker it appeared that PSMA lutetium was the most developed PSMA-targeting agent in parallel to bites and actinium-based medicines.

The request for the second activity titled 'Exploring Systemic Therapies in mCRPC: Targeting PSMA to improve patient outcomes' stated that the learning objectives were increased knowledge regarding the making of treatment recommendations for patients with PSMA upregulation and greater competence related to selection of appropriate patients with mCRPC for PSMA targeted therapy. The Panel noted the proposal stated that the activity would include case-based discussion of 3 patients presenting with different disease and treatment needs in the context of mCRPC. The Panel noted that there were general comments about the alleged promotion of an unlicensed medicine and alleged failure to provide information about possible conflicts of interest. There were no specific allegations about the content of this activity and therefore the Panel made no rulings in relation to this second activity.

The Panel noted that it appeared from the email from the third party and the funding request that AAA would have had a clear idea of what would be covered before deciding whether or not to fund the request; the Panel considered that AAA could exercise its discretion to elect an activity and queried whether the arrangements with the third party were truly arm's length. It appeared from the proposal that the project would only go ahead with AAA's support and that it had some influence over the project, for example, whether to include podcasts or not, or if the proposal was 'in line with expectations'. The Panel thus considered that there was no strictly arm's length arrangement and in that regard the company was responsible under the Code for the content. The Proposal at a Glance referred to minimum audience guarantees and that copies of the slides and transcripts would be made available. The payment was referred to as a grant to develop the initiative.

The Panel noted that the activity by the third party was advertised and made available to UK health professionals as well as others in Europe and the rest of the world. In the Panel's view, it was clear from the funding proposal that the activity would, on the balance of probabilities, include discussions about AAA's pipeline products, ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617, which were not yet licensed. The Panel queried whether it would ever be acceptable for a pharmaceutical company to sponsor an activity which it could not do itself.

The Panel further noted that Endocyte, Inc., a US subsidiary of Novartis, had sponsored the clinical studies on ^{177}Lu-PSMA-617 and it was the results of these studies that were discussed in the third party activities. Based on these clinical studies, AAA intended to apply for marketing authorisation for the two compounds. One of the speakers was an experienced clinician in the treatment of prostate cancer with PSMA targeted therapies and had been an investigator and the second speaker was also an investigator and in a study publication disclosed working as a speaker and advisory board member for Novartis.

Noting its comments and the content of the first activity above, in the Panel's view, it promoted AAA's unlicensed medicine which AAA would be aware of from the proposal and therefore, in funding the project, AAA was responsible for the promotion of an unlicensed medicine and a breach of Clause 3.1 was ruled.

The Panel noted that AAA reiterated that it had no involvement in the development of the contents of the material and thus did not believe that it could be held responsible for any alleged breach of Clause 7.2. The Panel noted its comments above, that in its view, the activity was not truly an arm's length arrangement and thus considered that AAA was responsible for the content of the material in relation to its provision to UK health professionals.

The Panel noted the complainant's allegation that the patient in the third case study had been overtreated with ten cycles of treatment when protocols suggested six cycles and his/her further concern that the speaker claimed an improvement in quality of life (QoL) when the patient's bone marrow failed and died. The Panel noted AAA's submission that metastatic prostate cancer was a terminal disease and one of the objectives of treating a patient with this condition was to improve their quality of life and not just survival and whilst most clinical trials treated patients with Lu-PSMA-617 for six cycles there were studies investigating the impact on additional treatment cycles in patients who responded to the treatment.

The Panel noted that according to the transcript provided by AAA, the patient described in the third case study was actually a patient who participated in 'our' 1st phase 2 trial, which was a 30-patient trial which was published in *Lancet Oncology*, a single-arm study back in 2018. The patient received a ^{68}Ga-PSMA-PET scan which showed very intense uptake at all sites of disease and the speaker explained that when a very high uptake on the PSMA-PET scan was seen, as in this case, it was very likely that the patient would respond to lutetium PSMA treatment but the durability of the response was not known. The speaker noted that the patient was treated as part of 'our' phase two trial and received 3 doses of lutetium PSMA-617. The speaker explained that the patient who had already progressed after cabazitaxel and had few treatment options left participated in a clinical trial and received the experimental treatment [PSMA-617] and did well. The speaker stated that he/she now had almost 50 months follow-up in this man which was remarkable and he had had a total of 10 cycles of lutetium PSMA-617. After that last treatment, his PSA rose sharply again, the patient eventually developed a pancytopenia and the PSMA-PET scan showed diffuse marrow infiltration and he died at around 55 months. The speaker noted, however, that his quality of life was exceptionally good; his pain improved after that very first dose of lutetium. When the patient came back 24 hours after the treatment, he stated that his pain was already starting to feel better. The Panel noted that Lu-PSMA-617 did not yet have a marketing authorisation and therefore had no proven dosage regimen or proven efficacy. The statements made in this regard, in the Panel's view, meant that that the medicine had been promoted prior to the grant of its marketing authorisation and the Panel ruled a breach of Clause 3.1 in relation to each of the complainant's allegations.

The Panel noted, however, that it was clear that the treatment was given in a clinical trial setting. The Panel did not consider that the complainant had established that referring to 10 cycles of treatment within the clinical trial setting or the effect the treatment appeared to have on the patient's quality of life within that trial was misleading as alleged and no breach of Clause 7.2 was ruled in relation to each allegation.

The Panel noted the complainant's allegation that the activity further suggested combining Lu-PSMA-617 with other treatments but he/she could find no study which had ever investigated such a combination. The Panel, whilst noting its ruling above of a breach of Clause 3.1, in relation to promotion of a medicine prior to the grant of its marketing authorisation, did not consider that the complainant had established that referring to a combination of treatments within the clinical trial setting was in itself misleading as alleged and no breach of Clause 7.2 was ruled.

With regard to the complainant's allegation that AAA's new agent could be given safely before cabazitaxel in patients with advanced prostate cancer, the Panel noted that the complainant appeared to be referring to the first activity in which the speaker, from the video and transcript, stated 'Here we could see that cabazitaxel could be delivered safely after lutetium PSMA-617, that's certainly my clinical experience'. In the Panel's view, the statement related to cabazitaxel, which did not appear to be an AAA nor Novartis affiliated product. The Panel therefore ruled no breach of Clause 7.9.

The Panel noted the complainant's concerns that the two speakers involved in the activities were likely to have been consultants for Novartis, AAA or Endocyte, but that this had not been disclosed by the speakers. The Panel noted AAA's submission that both speakers were not UK based and the contract for this activity was between the speakers and the third party directly and therefore AAA was not responsible for their disclosures. The Panel noted that companies were responsible under the Code for the acts and omissions of their third parties which came within the scope of the Code.

The Panel noted AAA's submission that the speakers had no direct involvement for any AAA UK based activities in the past but other AAA affiliates had engaged them as consultants. The Panel further noted that one of the speakers was referred to as an experienced clinician in the treatment of prostate cancer with PSMA targeted therapies and had been an investigator and the second speaker was also an investigator and in a published study had disclosed working as a speaker and advisory board member for Novartis. The Panel considered, therefore, that the disclosure of the speaker's involvement with AAA and its associated affiliates was particularly important given that the presentations mentioned AAA's pipeline products and failure to do so was concerning. However, the Panel noted that Clause 23.1 required that contracts included provisions regarding the obligation of the consultant to declare that he/she was a consultant to the company in certain circumstances. The Panel noted that this appeared to be a requirement of the contracts provided by AAA and the speakers were required to disclose all financial relationships with any pharmaceutical, medical device, biologics, or diagnostics company so that the third party might provide this disclosure to learners prior to their participation in any such activity. The Panel therefore ruled no breach of Clause 23.1.

The Panel noted its comments and rulings of breaches of the Code above and considered that AAA had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted that the complainant stated that he/she received three emails inviting him/her to the same module in twelve days (15/04/21, 22/04/21, 27/04/21) and questioned where this was a tad excessive. The Panel noted that AAA made no comments in this regard. The Panel noted that the complainant provided a list of the three emails which each had the same heading, 'Selecting Appropriate mCRPC Patients for PSMA-Targeted Therapy' followed by the start of the emails 'Educate yourself on best treatme…'. Whilst the Panel considered that three emails in the space of twelve days in relation to an activity was likely to be seen as excessive, it noted, from screenshots provided by the complainant and from various documents provided by AAA, that there were two components to the activity. It appeared from the material provided by the complainant that the subject heading to the emails 'Selecting Appropriate mCRPC Patients for PSMA-Targeted Therapy' appeared to be different to the title of the first activity 'Understanding novel therapeutic options for metastatic castration resistant prostate cancer' and that there were also references to 'Castration-Resistant Prostate Cancer' and that a reference to 'Alternative treatment recommendations for patients with prostate-specific membrane antigen (PSMA) was 'based on your interest'. It was not clear from the emails provided by the complainant whether they were promoting the overall activity, the separate parts or a combination of the two. The Panel noted that the Code stated, *inter alia*, that restraint must be exercised on the volume and frequency of distribution of promotional material distributed. The Panel did not have before it the contents of the emails to determine whether they were promotional and to be sure what exact activity each related to. Based on the evidence before it, the Panel did not consider that the complainant had established that AAA had failed to maintain high standards in this regard and no breach of Clause 9.1 was ruled.

Clause 2 was a sign of particular censure and reserved for such use. The Panel noted the examples in the supplementary information to this Clause included promotion prior to the grant of a marketing authorisation. The Panel noted its rulings above and considered that AAA had brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

Complaint received **28 June 2021**

Case completed **11 April 2022**