EMPLOYEE v SERVIER

Arrangements for an advisory board

A contactable complainant who described him/herself as a Servier employee complained about an advisory board on the management of metastatic colorectal cancer (mCRC) held on 23 June 2017. Servier marketed Lonsurf (trifluridine/tipiracil) which was used in certain patients with mCRC.

The complainant noted that advisory boards were meant to seek answers to unknown questions. The complainant alleged that from the beginning, two senior managers decided that the representatives should influence which health professionals should be invited to the advisory board. According to the complainant, one of the senior managers nominated health professionals who contributed heavily to sales and representatives suggested and got their favourite health professional to attend. The other senior manager then added a few health professionals that he/she knew well and who had attended a previous advisory board in 2016 on very similar topics. The complainant provided a copy of an email, between senior managers, sent after the advisory board, which he/she stated clearly acknowledged that attendees were selected by representatives and medical science liaison (MSL) staff. The complainant further alleged that a colleague in medical was put under extreme pressure from a more senior commercial manager to accept recommendations for health professional attendees.

With regard to content, the complainant explained that in 2017, some representatives pushed the idea that neutropenia, a common and at times serious side effect of Lonsurf, was a predictor of efficacy ie neutropenia meant that the medicine was working. This was challenged within the company and although some representatives were reprimanded by their local MSL for compromising patient safety, Servier continued to pursue the line that 'neutropenia was an indicator of efficacy'. At the advisory board in question, a number of case studies were discussed on this topic and clinicians shared examples of neutropenia and other adverse events; however, no effort was made to document these via pharmacovigilance or adverse event reporting. The complainant alleged that this clearly compromised patient safety.

The complainant stated that Servier put a positive spin on neutropenia because it had recently been reported that the incidence of neutropenia and febrile neutropenia was higher in clinical practice than previously documented. Rather than protecting patient safety and ensuring that representatives were adequately briefed on this finding, Servier promoted the idea that neutropenia was good and equalled efficacy. The complainant stated that evidence of this could be seen in the advisory board agenda and also in an email between senior managers in which it was stated that 'Neutropenia being a predictor (or not) of response' would be discussed. This showed the carefree attitude towards patient safety.

In summary, the complainant alleged that the advisory board was organised as a meeting for loyal users of Lonsurf and patient safety was compromised by not reporting adverse events. Representatives influenced attendee selection. The complainant further alleged that given the involvement of the commercial colleagues, the advisory board was a disguised promotional meeting; if this was not so then why did one senior manager in medical acknowledge the commercial functions in an email immediately after the advisory board, and not include a relevant medical colleague and team of MSLs?

The detailed response from Servier is given below.

The Panel noted that while it was acceptable for companies to pay health professionals and others for relevant advice, the arrangements for advisory boards had to comply with the Code. To be considered a legitimate advisory board the choice and number of participants should stand up to independent scrutiny; each should be chosen according to their expertise such that they would be able to contribute meaningfully to the purpose and expected outcomes of the meeting.

The Panel noted the complainant's allegation that advisor selection was influenced by representatives and a senior manager who nominated health professionals who contributed heavily to sales. The Panel noted Servier's submission that one of the meeting objectives was to gain feedback on the practical use of Lonsurf and so advisors needed to have clinical experience with the medicine. In the Panel's view, it was not necessarily unacceptable for representatives to identify health professionals with relevant clinical experience to provide the clinical insights required. Regardless of the source of the recommendation, the criteria for selection must be directly related to the identified need and must not be, *inter alia,* an inducement to prescribe a medicine or a reward for previous prescriptions. The Panel noted Servier's submission that the final decision of who to invite lay with the medical department.

The Panel further noted the complainant's allegation that, to increase numbers, some health professionals were invited who had attended a very similar advisory board the previous year. The Panel noted Servier's submission that some of the attendees had indeed attended one or both of two previous Lonsurf advisory boards in January 2016 (before the product launch) and one of the two held in May 2016. The Panel noted the time-periods between the advisory boards, the different time-points in the product's lifecycle, and the largely different meeting objectives.

The Panel noted it comments above. A judgement had to be made on the available evidence. In the Panel's view, the complainant had not proved, on the balance of probabilities, that the selection of advisors was not directly related to the identified need or that the selection was an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. No breach of the Code was ruled.

The Panel was concerned about the complainant's serious allegation that one manager was put under extreme pressure to accept recommendations for attendees from a more senior manager but noted that he/she had provided no evidence in this regard. The Panel considered that the complainant had not discharged the burden of proof and no breach of the Code was ruled.

The Panel noted the allegation that promoting neutropenia with Lonsurf as a predictor/indicator of response at the meeting demonstrated the company's carefree attitude towards patient safety. The complainant provided a copy of a presentation used at the meeting entitled 'Neutropenia – is it a predictor of response to trifluridine/tipiracil?'. The Panel noted that the objectives of the advisory board did not include obtaining feedback on neutropenia being a predictor of response. This topic was allocated 45 minutes on the agenda, including a 10-minute presentation. The Panel noted Servier's submission that the conclusion in the executive summary of the meeting minutes stated: 'Neutropenia is a manageable toxicity, but certainly not a predictor of response, but (it) is more of a reflection that an adequate dose has been given. Observations of improved overall survival (OS) and progression free survival (PFS) with the neutropenia cohort is more likely a testimony to them being a biologically different group, and not strong enough evidence to change clinical practice i.e. to induce neutropenia in patients who don't experience it'.

The Panel was concerned to note that the briefing documents to this session's speaker and to the meeting chair stated: 'To their knowledge does any company leverage this information in the promotion of their products?' and 'If a patient did not experience neutropenia what would this mean for the prescribing of trifluridine/tipiracil?'.

In the Panel's view, Servier intended to get feedback on neutropenia as a predictor of response with Lonsurf, including use of such a claim in the promotion of Lonsurf. Feedback from the advisors included 'A degree of caution should be exercised if using this argument commercially …' and 'These observations of improved [progression free survival] and [overall survival] do not suggest that clinicians should induce neutropenia in patients who don't present with it (i.e. by increasing the dose) for improved outcomes'.

Whilst the Panel had serious concerns about the acceptability of claiming that neutropenia was a predictor of response, it considered that it was not necessarily unacceptable to discuss the clinical data in an advisory board in order to gain advice. There was no evidence that the claim was used to promote Lonsurf. Noting its comments above, the Panel considered that the complainant had not discharged the burden of proof in this regard and ruled no breach of the Code.

The Panel then considered the allegation that Servier had not reported the adverse events from patient cases. The title page of the clinical case presentation slides used at the meeting included the statement 'Please note that all of the following case scenarios are hypothetical'. The speaker's briefing document stated that this section of the advisory board was not to prompt the discussion of adverse events ie events related to a specific patient. It also stated that if any events were discussed, Servier would have to follow them up. The chair's briefing had similar statements and that the speaker would make attendees aware of the pharmacovigilance statement. The Panel noted Servier's submission that, from the meeting minutes, there was no specific patient or group of patients discussed, and adverse events were discussed only in general terms prompted by the hypothetical cases presented.

The Panel noted the importance of reporting adverse events and that Servier had briefed the speaker and chairman. It appeared that if adverse events that required reporting had been raised, relevant personnel knew what to do. The Panel considered that the evidence supplied by the complainant did not show, on the balance of probabilities, that Servier had not met the requirements of the Code in relation to adverse event reporting and therefore ruled no breach of the Code.

The Panel noted the further allegation that some Servier representatives had promoted the concept of neutropenia with Lonsurf as an indicator of efficacy and that this compromised patient safety. The Panel noted that, *inter alia,* briefing material must not advocate, directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The Panel noted Servier's submission that its sales materials and briefing documents did not mention, claim or compare any evidence that neutropenia was an indicator of efficacy and that it had no record of representatives being reprimanded for such activity as alleged. The Panel considered that as the complainant had provided no evidence to support this allegation, he/she had not discharged the burden of proof. The Panel therefore ruled no breach of the Code.

The Panel noted the complainant's general allegation that the advisory board in question was a disguised promotional meeting for loyal Lonsurf customers. The Panel noted that although a disputed email was not copied to the MSLs or a relevant member of the medical team and the medical team member was not acknowledged in the email, this did not in itself indicate that the advisory board was a disguised promotional meeting as alleged. Nor did the role of commercial colleagues necessarily indicate that the advisory board was a disguised promotional meeting as alleged.

The Panel noted that ten health professionals and three Servier employees attended the meeting in

question. The Panel noted the meeting objectives, the expected outputs in the certified rationale document and Servier's submission regarding the expertise and experience of the advisors selected in relation to the advice sought. Servier had retrospectively analysed sales data and found no evidence that any of the advisors were 'loyal users of Lonsurf' as alleged.

The Panel noted from the agenda that just over 80% of the meeting which was held from 10am-4pm was allocated to discussion. There was 40 minutes of presentation time. Feedback and advice obtained from the advisory board was documented in the meeting executive summary along with actions for Servier.

The Panel noted its comments above. A judgement had to be made on the evidence provided by the parties. Whilst there were some concerns, in the Panel's view, the complainant had not proved, on the balance of probabilities, that the advisory board meeting was disguised promotion and no breach of the Code was ruled.

The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. The Panel noted its comments and rulings above and ruled no breach of Clause 2.

A contactable complainant who described him/herself as a Servier employee complained about an advisory board on the management of metastatic colorectal cancer (mCRC) held by Servier on 23 June 2017. Servier marketed Lonsurf (trifluridine/tipiracil) which was used in certain patients with mCRC.

COMPLAINT

A Selection of advisors

The complainant noted that advisory boards were meant to have a very specific purpose of seeking answers to unknown questions. The complainant alleged that from the beginning, two senior managers decided that the representatives should take an active role in determining which health professionals should be invited to this advisory board. According to the complainant, one of the senior managers (commercial) decided to nominate a range of health professionals who contributed heavily to sales and each representative suggested and got their favourite health professional to attend and then, to increase numbers, the other senior manager (medical) added a few health professionals that he/she knew well and who had attended a previous advisory board in 2016 on very similar topics. The complainant stated that an email between senior managers immediately after the advisory board, showed clear acknowledgement that the attendees were selected by the representatives and medical science liaison (MSL) staff. The complainant stated that no member of medical affairs other than the sender was included in the email as only the commercial senior manager and the representatives had been consulted on advisor selection and not the MSLs. At the time the manager of the oncology MSLs was not included in the email and was put under extreme pressure from a more senior commercial manager to accept recommendations for health professional attendees. The complainant noted that the senior manager who sent the email acknowledged the role of the representatives in selecting advisors and copied in the commercial senior manager who had attended the advisory board in full; his/her attendance was challenged given that part of his/her role was to serve as a sales manager in a named disease area. The complainant stated that although the email implied that the commercial senior manager was just copied in for information purposes, he/she had, in fact, heavily influenced the selection of attendees and the content of the advisory board.

B Discussion of neutropenia as an indicator of response

The complainant further stated that the commercial senior manager, endorsed by the medical senior manager, attended the advisory board and discussed neutropenia as an indicator of response.

The complainant explained that in early 2017, some representatives promoted the idea that neutropenia, a common and at times serious side effect of Lonsurf, was a predictor of efficacy ie neutropenia meant that the medicine was working. This was challenged by the MSLs, and several representatives were reprimanded by their local MSL for compromising patient safety. The relevant manager within the company was informed about this reckless behaviour by some representatives, but Servier continued to pursue the line that 'neutropenia was an indicator of efficacy'.

At this advisory board, a number of case studies were discussed on this topic and clinicians openly shared their real-life patient examples of neutropenia and other adverse events; however, no effort was made to document or report these via pharmacovigilance or adverse event reporting. The complainant alleged that this clearly compromised patient safety.

The complainant stated that Servier put a positive spin on neutropenia because a recent clinical audit conducted by some UK sites on the Early Access Programme had found that the incidence of neutropenia and febrile neutropenia was higher in clinical practice than previously reported in the RECOURSE study. The complainant alleged that rather than protecting patient safety and ensuring that the representatives were given adequate briefing on this finding, Servier thought it would be a good idea to promote the idea that neutropenia was good and equalled efficacy.

The complainant stated that clear evidence of this could be seen in the advisory board agenda and in the email between senior managers referred to above which stated that one of three discussion topics would be the idea of 'Neutropenia being a predictor (or not) of response'. This again showed the carefree attitude towards patient safety ie trying to portray drug toxicity as an indicator of response and making no effort to report adverse events from health professional

cases. References and data promoting this idea were presented at the advisory board.

C General allegations

In summary, the complainant alleged that the advisory board was organised under the disguise of a meeting meant for loyal users of Lonsurf and patient safety was compromised by not reporting adverse events in the neutropenia session and discussion. Representatives influenced attendee selection and were thanked by the senior manager (medical) which clearly showed that this was a disguised promotional meeting heavily influenced and organised by the commercial senior manager and the representatives. The complainant queried that if this was not the case then why did the senior manager (medical) acknowledge the commercial senior manager and representatives in the email immediately after the advisory board, and not include a relevant medical colleague and team of MSLs.

When writing to Servier, the Authority asked it to consider the requirements of Clauses 2, 7.2, 7.4, 7.9, 9.1, 12.1, 15.9, 23.1 and 25.1 of the 2016 Code.

RESPONSE

Servier submitted that the advisory board in question was held to answer specific questions about the treatment of metastatic colorectal cancer (mCRC) and use of Lonsurf which received its marketing authorization from the European Medicines Agency (EMA) in April 2016 for heavily pre-treated patients with mCRC.

Servier recognised the importance of maintaining high standards and upholding regulatory values when conducting an advisory board, particularly given the compliance difficulties that companies could experience with these meetings and the high profile given to them in the UK recently. As such, Servier stated that it had taken the complaint very seriously and had thoroughly investigated it despite the difficulties of doing so given that the company was not told about any concerns regarding the advisory board until more than 18 months after it had taken place. Two key people had since left the company and so it was not feasible to interview them. Having conducted its investigation, however, Servier stated it was satisfied that the advisory board in question was a legitimate and compliant meeting.

Legitimate business need for advisory board

Servier refuted the complainant's allegation that the selection of participants was heavily influenced by commercial (sales) considerations and submitted that the advisors were chosen on the basis of their ability to help the company meet the objectives of the meeting by answering specific questions which related to the following four topics:

1 Develop a better understanding of re-challenge.

Servier explained that the European Society of Medical Oncology (ESMO) guidelines recommended a continuum of care approach. Patients would be given a successive sequence of active agents (eg chemotherapy alone or in combination with biological agents) until they progressed or could not continue due to toxicity. Therefore, as treatment improved there was an increasing proportion of heavily pre-treated patients with advanced disease who became eligible to receive third- and fourth-line care. Re-challenge was the strategy of re-introducing, after an intervening treatment, a previous therapy to which the tumour had been resistant. Despite recommendations for agents such as Lonsurf or regorafenib to be introduced as a third-line option prior to re-challenge, re-challenge remained a prevalent treatment choice in the UK; market research from 2017 reported that clinicians treated 28% of patients with re-challenge. It was therefore imperative that Servier understood why clinicians chose treatment options other than those recommended in the guidelines.

2 Practical issues with Lonsurf in clinical practice; dose delays and reductions, and adverse event management

Servier explained that Lonsurf was dosed according to body surface area and, based on the toxicity experienced by the patient, might be delayed, reduced or stopped. Its dosing schedule was different from other oral chemotherapies (eg capecitabine) which caused some initial confusion about administration. Ensuring that administration was consistent with the recommendations in the summary of product characteristics (SPC) was key to ensure patients received appropriate care. Many of the Lonsurf sales materials (copies provided) related to appropriate dosing eg when to stop, delay or reduce dose. Therefore, at just one year after launch of the product, another key objective of this advisory board was to ensure there was no unmet need for further guidance from the company to clinicians on this topic.

3 Should Servier conduct a Phase IV observational study?

Servier submitted that it had asked this question because the global team had proposed a Phase IV observational study in patients with mCRC to include collecting quality of life data. To help ensure that the study would generate information that would be useful to UK clinicians when managing their patients, Servier UK wanted to gain feedback regarding this proposed study and whether there were any potential amendments that should be made or gain insight on whether Servier should support alternative studies.

4 Was neutropenia an indicator of efficacy?

This question was asked because the patient population who required treatment with Lonsurf had a very poor prognosis and although a significant proportion of them would receive clinical benefit from Lonsurf, some would not. Thus, clinicians were often keen for any data on prognostic factors that would help them to pre-select those more likely to benefit from Lonsurf treatment. There had been several publications (Kasi *et al* 2016 and Ohtsu *et al* 2016) which had associated a survival benefit for

patients who experienced neutropenia while treated with Lonsurf. This was an exploratory question on whether neutropenia was a predictor of efficacy. Servier submitted that these questions were a legitimate reason to hold an advisory board meeting and that an advisory board would be the most appropriate method to help answer them as they required a range of extensive qualitative opinions from experts within the field. The meeting was structured in order to ensure that the advisors had ample time to discuss the questions and provide meaningful advice to the company, as demonstrated by the meeting materials and outputs (copies provided). A meeting report was generated which included various outputs. This report which included feedback on a Global Phase IV study and other study suggestions, was circulated within the UK team and to Servier's global colleagues.

A Selection of advisors

Servier refuted the allegation that health professionals were selected based on any promotional intent. The nature of the questions that the advisory board sought to answer required the advisors to have specific knowledge and experience and selection was made on this basis.

The invited clinicians were all experienced with a wide range of clinical and trial experience that allowed them to contribute meaningfully to the advisory board discussions. The advisory board rationale document noted that advisors selected would be: oncologists experienced in re-challenge as a treatment strategy; those who had used Lonsurf clinically and in the third-line mCRC setting; experienced researchers or investigators in mCRC or, as a minimum, considered suitable to be investigators and researchers.

There were 10 attendees who were paid in line with Servier's standard operating procedures (SOPs) (copies provided). Servier considered that the payments represented fair market value for the advisors' level of experience and time given to the advisory board (honoraria and travel expenses for each advisor was provided).

The selection of the attendees was based on the above criteria and was the responsibility of medical and not the responsibility of a commercial manager. Servier stated that it had no evidence to support the allegation that a medical colleague was put under extreme pressure from the more senior commercial manager to accept recommendations for attendees; nothing was reported to its HR department that would corroborate it.

Servier submitted that none of the representatives interviewed could recall recommending any advisors for the advisory board although the company acknowledged that they might have either forgotten (given the timeframe) or felt uncomfortable divulging this information (despite reassurance). It would not necessarily be unreasonable for field staff to give recommendations to ensure that advisors with the relevant experience (including prescribing experience) were identified. However, the final decision on who to invite was medical's responsibility. Servier's standard for selection would be based solely on the attendees' scientific and medical expertise and the anticipated value of their contributions to the advisory board, in line with the rationale document. The invitation was prepared and sent out by medical (copy provided).

Servier stated that it could not confirm the authenticity of the email referred to by the complainant and allegedly sent by medical 18 months ago as it was not recoverable from the accounts of any of the three staff who were included in the message; two of the staff had subsequently left the company. The email stated that both the representatives and the MSLs 'suggested [the attendees] would give us useful insights'. Servier submitted that contrary to the complainant's allegation that the advisory board was a disguised promotional meeting, the wording supported its contention that advisory board members were chosen for their medical and scientific insights, irrespective of the alleged source of the recommendations.

Servier submitted that it had retrospectively analysed which sales territories the attendees came from (copy of analysis provided) and had not been able to discern any evidence that advisors were selected due to any commercial reason or that they were 'loyal users of Lonsurf' as alleged. One advisor had extensive clinical trial experience but his/her hospital had bought no Lonsurf in the 6 months before the advisory board.

With regard to attendees' attendance at previous Lonsurf advisory boards, Servier noted that it had held four such meetings (copies of agendas and details of the meeting objectives were provided) two in January 2016 (before the product was licensed) and two in May 2016 (after the product was licensed), ie more than a year before the meeting in question. Servier submitted that each of the previous advisory boards explored different business needs from the one in question, at a different stage of the company's knowledge and understanding of the environment. Servier noted that some of the attendees of the meeting in question had already provided advice at Servier advisory boards in 2016, most notably an advisory board held in January 2016, 18 months before the one in question, and prior to launch of the product; six clinicians had attended that meeting and the one now in question (two of the clinicians had also attended the other meeting in January 2016). At that time Servier would have had limited relationships with any clinicians. Those who attended were prominent and highly specialised in the field and thus able to effectively contribute to the discussion at an advisory board. Given their expertise and their proven ability to contribute meaningfully to an advisory board, Servier stated that it was not surprising to see that they were invited to attend a different advisory board asking different questions 18 months later. Servier submitted that one attendee at one of the May 2016 advisory boards had attended the meeting now at issue. None of the attendees at the second meeting in May 2016 attended the meeting now at issue.

Servier submitted that along with the ten invited clinicians, three Servier staff attended the advisory board in question – two from medical and one commercial employee - all of whom had since left Servier (copies of job descriptions provided).

Servier stated that the complainant had questioned the legitimacy of the commercial senior manager's attendance at the advisory board as he/she had a role in management of the sales team. No-one had questioned his/her presence or conduct at the meeting at the time. The manager's role included oversight of the sales team but also, more notably, marketing strategy. As the questions the advisory board sought to answer directly impacted on marketing strategy, the senior manager was present to help ensure that the company obtained a clear understanding of the environment and challenges and that any advice that would help inform strategy was appropriately implemented. Thus, his/her attendance at the advisory board was to facilitate Servier's understanding of the answers to the questions.

Servier stated that in summary in relation to the selection of advisors:

- A clear agreement and rationale for the services rendered were put in place in advance of the commencement of the clinicians' services at the advisory board. Servier denied breaches of Clause 23.1.
- Servier had demonstrated a clear rationale for the selection of advisors to the advisory board meeting, who were then selected based on this criteria by medical. Servier denied breaches of Clause 23.1.
- This advisory board was not a 'token consultancy arrangement' but a legitimate and compliant meeting, for which the advisors were paid commensurate with their experience and time given. Servier denied breaches of Clause 23.1.
- Servier had maintained high standards throughout this process; it had adhered to Code requirements and company SOPs. Servier denied breaching Clause 9.1.

B Discussion of neutropenia as an indicator of response

Servier explained that the Early Access Program the complainant referred to was actually the named patient programme (NPP), where under guidance from the Medicines and Healthcare products Regulatory Agency (MHRA) for supply of unlicensed medicines, Lonsurf was available to UK patients for 8 months from November 2015. A retrospective audit of 78 patients from the NPP from 3 UK sites showed a similar overall survival benefit to that seen in the RECOURSE study (6.6 months vs 7.1 months in the RECOURSE study) but 40% of patients experienced neutropenia and 13% experienced febrile neutropenia vs 38% and 4% respectively in the RECOURSE study.

Servier submitted that it would not make any unsubstantiated claims and patient safety was a key priority at all times. Neutropenia was discussed at the advisory board because various published studies associated neutropenia as an indicator of efficacy for Lonsurf treatment. Servier submitted that this was a legitimate exploratory question to ask at an advisory board and so there was a 10-minute presentation asking 'Neutropenia: Is it a predictor of response with trifluridine/tipiracil?' using 8 slides, including the title slide, disclosures and summary slides. A further three slides discussed evidence of chemotherapy-induced neutropenia in general, not specifically related to Lonsurf, and two slides examined 2 different data sources that associated neutropenia with a survival benefit in patients treated with Lonsurf. There was 35 minutes allowed for discussion.

From the meeting minutes the conclusion in the executive summary was that:

> 'Neutropenia is a manageable toxicity, but certainly not a predictor of response, but (it) is more of a reflection that an adequate dose has been given. Observations of improved overall survival (OS) and progression free survival (PFS) with the neutropenia cohort is more likely a testimony to them being a biologically different group, and not strong enough evidence to change clinical practice i.e. to induce neutropenia in patients who don't experience it.'

Servier stated that in summary in relation to the content of the advisory board:

- The content of this presentation (and following discussion) was given in a clear objective and balanced manner and was not misleading. Servier denied a breach of Clause 7.2.
- All the information given to advisors could be substantiated. Servier denied a breach of Clause 7.4.
- The data presented reflected available evidence, and Servier did not try to mislead the advisors as to the toxicity profile of Lonsurf. Servier denied a breach of Clause 7.9.
- Servier had maintained high standards throughout this process by adhering to the Code and company processes. Servier denied a breach of Clause 9.1.

Servier stated that there was no evidence to support the allegation that representatives promoted neutropenia as an indicator of efficacy or that sales or briefing materials (copies provided) referred to neutropenia as such. There was no record of any representative being reprimanded by an MSL and none of the MSLs (including the MSL that had since left Servier) or the representatives consulted, nor a relevant manager, had any memory of this occurring.

Servier stated that in summary:

- Sales materials and briefing documents did not mention, claim or compare any evidence of neutropenia being an indicator of efficacy. Servier denied any breach of Clauses 7.2 and 7.4.
- Servier had maintained high standards throughout this process. Servier denied any breaches of Clause 9.1.

- No formal report of any kind of reprimand for any of the representatives compromising patient safety appeared to have been made, and none of the staff consulted were able to verify the veracity of this claim. Servier denied breaches of Clause 15.1.

C General allegations

Servier denied that the advisory board in question was held for any promotional intent, disguised or otherwise. Servier stated that it could be clearly demonstrated that:

- The meeting was organised and led by the medical affairs team, not the commercial;
- The advisory board was held to answer legitimate business questions as set out in the meeting rationale document and agenda;
- Attendees were selected based on their scientific and medical experience to be able to discuss and advise Servier on its business questions;
- The overall balance of the agenda between presentation and discussion time (excluding break and opening and closing times) was over 80% discussion time;
- Three presentations (copies provided) were given over the course of the day:

  Presentation 1: Rechallenge vs re-introduction – what does this mean in the third line mCRC setting? The 33-slide presentation was prepared by the presenting clinician (as part of the requirement for attendees to advise the company at this advisory board) and given over 20 minutes. It ran through guidelines and data on re-challenge. Within this, Lonsurf along with other therapeutic options was first mentioned on slide 13. Lonsurf was mentioned on 4 slides, and only factual information was presented; no claims were made.

  Presentation 2: Neutropenia: Is it a predictor of response with Lonsurf? This 8-slide presentation, also prepared by the presenting clinician was given over 10 minutes. It outlined evidence for neutropenia as a marker of efficacy in general chemotherapy and in 2 slides objectively outlined data which associated neutropenia with improved survival in patients treated with Lonsurf.

  Presentation 3: Potential future R&D options for Servier products. This 25-slide presentation was given over 10 minutes. It gave a run through of Lonsurf's current development program, without making any claims and solicited feedback on an observational study.

- The meeting minutes clearly recorded that Servier asked for advice and feedback and did not promote Lonsurf.

In relation to the allegations about patient safety, Servier categorically denied any wrong doing and had a firm commitment to patient safety. This included both adverse event reporting and ensuring that clinicians fully understood the toxicity profiles of Servier products and how to manage them appropriately.

Servier submitted that its pharmacovigilance department had robust systems in place to ensure all adverse events were reported and processed appropriately. This included annual training for all staff, including those who had attended the advisory board meeting in question (copy of training records provided). The company was confident that the highly experienced and trained staff who organized and attended the meeting would have reported any adverse event mentioned, in line with its pharmacovigilance SOP.

Servier submitted that as the advisory board included discussion on adverse event management and dosing guidelines, it was to be expected that this might elicit adverse event reports and the matter was discussed with Servier's pharmacovigilance department beforehand to ensure all appropriate action was taken. Following an email discussion with the pharmacovigilance department a briefing document was prepared for the relevant discussion that stated:

> 'Please make all attendees aware of the following important pharmacovigilance information:
>
> This section of the advisory board is not to prompt the discussion of adverse events, i.e. events related to a specific patient. If any events are discussed (or situations of special interest) that may be considered to fall into this category, Servier will have a requirement to follow these events up according to usual procedures (even if they have been reported by the Yellow Card Scheme).'

Servier stated that this showed that it was fully aware of the potential that adverse events might be discussed and was prepared to handle this appropriately. However, no adverse events were reported based on the discussions from this advisory board. There was no transcript of the meeting, but from the meeting minutes, although adverse events were discussed in general terms (prompted from the hypothetical case studies presented), no specific patient or group of patients were discussed. Servier noted that prior to the advisory board there were 17 reported adverse events from 7 of the attendees, including 13 neutropenia cases.

Servier stated that in summary it had:

- Demonstrated that the advisory board was clearly not held with any promotional intent, disguised or otherwise. Servier denied any breach of Clause 12.1.
- Shown that it had robust systems and training in place to capture all adverse events reported; that it made clear preparation prior to the advisory board to account for any adverse events reported; and that the advisory board was a legitimate and compliant non-promotional meeting. Servier denied breaching Clause 2.
- Maintained high standards throughout this process. Servier denied breaching Clause 9.1.
- Shown that it had robust systems and training in place to capture all adverse events reported; and that it made clear preparation prior to the advisory board to account for any adverse

events reported. Servier denied breaching Clause 25.1.

Servier submitted that the complainant had not given any evidence that would support his/her allegations that the advisory board was held with promotional intent or that patient safety was not prioritised. Servier submitted that it had provided detailed and robust evidence that demonstrated that the advisory board was an appropriate means of gaining information from advisors, and that patient safety was maintained throughout. Servier categorically denied all allegations in this complaint including a Clause 2.

In conclusion, Servier submitted that it had presented comprehensive arguments supported by evidence which demonstrated that it had complied with the Code in relation to the advisory board. Servier noted that the complainant's language was highly inflammatory and personal.

Following the Authority's receipt of Servier's response, the complainant provided annotated copies of the advisory board agenda, meeting rational document and slides from two sessions titled, 'Neutropenia - Is it a predictor of response to trifluridine/tipiracil?' and 'Lonsurf - clinical cases: What is your current approach to these scenarios?'. The case preparation manager provided this additional information to Servier for comment.

Servier stated that the complainant had provided an old and incomplete version of the advisory board rationale document. It had an old job reference number (used in a previous advisory board rationale document) and was clearly used as a template for the final approved version. The final approved version had been supplied by Servier in its initial response. Servier stated that the agenda and the PowerPoint presentation 'Is neutropenia an indicator of efficacy?' provided by the complainant were the final approved versions which were also supplied by Servier in its initial response.

Regarding the PowerPoint presentation 'Clinical cases: What is your current approach to these scenarios?', Servier submitted that due to an oversight this was mistakenly not previously supplied by Servier. This presentation was intended as a prompt to facilitate the discussion. It included three hypothetical case scenarios and posed questions such as: 'In your practice, what is your approach to the management of Grade 3-4 non-haematological toxicities e.g. fatigue?'. The presentation provided by the complainant was the final approved version but not in the correct order. Servier provided a copy of the final approved version of this presentation and stated that it had re-reviewed the materials previously sent and this was now the complete material list.

PANEL RULING

A Selection of advisors

The Panel noted that it was acceptable for companies to pay health professionals and others for relevant advice. Nonetheless, the arrangements for advisory board meetings had to comply with the Code, particularly Clause 23. To be considered a legitimate advisory board the choice and number of participants should stand up to independent scrutiny; each should be chosen according to their expertise such that they would be able to contribute meaningfully to the purpose and expected outcomes of the meeting.

The Panel noted the complainant's allegation that advisor selection was influenced by representatives and a senior commercial manager who nominated health professionals who contributed heavily to sales. The Panel noted Servier's submission that one of the meeting objectives was to gain feedback on the practical issues with the use of Lonsurf, including dosing, stop and delay criterion, and therefore advisors needed to have clinical experience with Lonsurf in the third-line mCRC setting. The Panel noted that this was stated in the advisory board rationale document which was certified on 26 April 2017. The Panel further noted the email provided by the complainant which was allegedly sent by the medical senior manager after the meeting and stated that the advisors were '…a testament to the [representative] and MSLs who suggested they would give…[Servier] useful insights'.

In the Panel's view, it was not necessarily unacceptable for a company to ask its representatives for names of health professionals with relevant clinical experience, including with its medicine, who could therefore provide the clinical insights that the company needed. Regardless of the source of the recommendation, the criteria for selection must be directly related to the identified need and must not be, *inter alia*, an inducement to prescribe a medicine or a reward for previous prescriptions. The Panel noted Servier's submission that the final decision of who to invite was the responsibility of medical.

The Panel further noted the complainant's allegation that, to increase numbers, the senior medical manager invited health professionals who had attended a very similar advisory board the previous year. The Panel noted Servier's submission that it had held an advisory board in January 2016, prior to the launch of Lonsurf, which was attended by six of the ten clinicians who attended the advisory board in question. Servier had also held another advisory board in January 2016, which was attended by two of the clinicians who attended the advisory board in question, and had held a further two advisory boards in May 2016: one was attended by one clinician who attended the advisory board in question and the other was not attended by any clinicians from the advisory board in question. The Panel noted the time-periods between the advisory boards, the different time-points in the product's lifecycle, and the largely different meeting objectives.

The Panel noted it comments above. A judgement had to be made on the available evidence. In the Panel's view, the complainant had not proved, on the balance of probabilities, that the selection of advisors was not directly related to the identified need or that the selection was an inducement to

prescribe, supply, administer, recommend, buy or sell any medicine. The Panel therefore ruled no breach of Clause 23.1.

The Panel was concerned about the complainant's serious allegation that a medical colleague was put under extreme pressure to accept recommendations for attendees from the senior commercial manager but it noted that he/she had provided no evidence in this regard. The Panel considered that the complainant had not discharged the burden of proof and no breach of Clause 9.1 was ruled in this regard.

B Discussion of neutropenia as an indicator of response

The Panel noted the allegation that neutropenia with Lonsurf as a predictor/indicator of response was promoted at the advisory board and this demonstrated the company's carefree attitude towards patient safety. The complainant provided a copy of a PowerPoint presentation, which Servier acknowledged was the final approved version presented at the meeting and titled 'Neutropenia – is it a predictor of response to trifluridine/tipiracil?'. The Panel noted that the complainant had referred to a slide which stated that neutropenia after starting Lonsurf was associated with better prognosis in patients with refractory mCRC and alleged that this was a clear attempt to link an adverse event of Lonsurf to overall survival and progression free survival. The Panel noted the questions on the following slide: 'Are these findings clinically relevant?' and 'Is there a potential for utility of [chemotherapy induced neutropenia at 1 month] as a prognostic and/or predictive biomarker of Lonsurf for patients with refractory metastatic CRC?'.

The Panel noted that the objectives of the advisory board in the rationale document did not include obtaining feedback on the topic of neutropenia being a predictor of response. This topic was allocated 45 minutes on the agenda, including a 10-minute presentation. The Panel noted Servier's submission that the conclusion in the executive summary of the meeting minutes stated:

> 'Neutropenia is a manageable toxicity, but certainly not a predictor of response, but (it) is more of a reflection that an adequate dose has been given. Observations of improved overall survival (OS) and progression free survival (PFS) with the neutropenia cohort is more likely a testimony to them being a biologically different group, and not strong enough evidence to change clinical practice i.e. to induce neutropenia in patients who don't experience it.'

The Panel was concerned to note that the briefing documents to this session's speaker and to the meeting chair stated: 'To their knowledge does any company leverage this information in the promotion of their products?' and 'If a patient did not experience neutropenia what would this mean for the prescribing of trifluridine/tipiracil?'.

In the Panel's view, Servier intended to get feedback on neutropenia as a predictor of response with Lonsurf, including use of such a claim in the promotion of Lonsurf. The Panel noted the documented feedback from the advisors which stated: 'A degree of caution should be exercised if using this argument commercially…' and 'These observations of improved PFS [progression free survival] and OS [overall survival] do not suggest that clinicians should induce neutropenia in patients who don't present with it (i.e. by increasing the dose) for improved outcomes'.

Whilst the Panel had serious concerns about the acceptability of using a claim about neutropenia being a predictor of response, it considered that it was not necessarily unacceptable for a company to discuss the clinical data in an advisory board in order to gain advice from attendees. There was no evidence that the claim was used to promote Lonsurf. Noting its comments above, the Panel considered that the complainant had not discharged the burden of proof in this regard and ruled no breach of Clauses 7.2, 7.4, 7.9 and 9.1.

The Panel then considered the allegation that Servier made no attempt to report the adverse events from patient cases in the advisory board. The Panel noted with concern that the clinical case presentation slides were only provided by the complainant and had not been provided by Servier in its initial response. The slides included the following statement on the title page: 'Please note that all of the following case scenarios are hypothetical'. The complainant had annotated the document to state that during the presentation the health professionals were asked to share examples of cases with neutropenia and no attempt was made to report adverse events. The Panel noted Servier's submission that prior to the advisory board there were 17 reported adverse events from 7 of the attendees, including 13 neutropenia cases, and the fact that the advisory board might elicit adverse event reports was discussed with the company's pharmacovigilance department prior to the meeting and a statement was added to the briefing documents. The speaker's briefing document stated that this section of the advisory board was not to prompt the discussion of adverse events ie events related to a specific patient. It also stated that if any events were discussed, Servier would have to follow these up. The chair's briefing had similar statements and that the speaker would make attendees aware of the pharmacovigilance statement. The Panel noted Servier's submission that, from the meeting minutes, there was no specific patient or group of patients discussed, and adverse events were discussed only in general terms prompted by the hypothetical cases presented.

The Panel noted the importance of reporting adverse events and that Servier had briefed the speaker and chairman. It appeared that if adverse events that required reporting had been raised at the advisory board, Servier and the meeting chair and speaker knew what action to take. The Panel considered that the evidence supplied by the complainant did not show, on the balance of probabilities, that Servier had not met the requirements of the Code in relation to adverse event reporting and therefore ruled no breach of Clauses 9.1 and 25.1.

The Panel noted the further allegation that some Servier representatives had promoted the concept of neutropenia with Lonsurf as an indicator of efficacy and that this compromised patient safety. The Panel noted that briefing material must comply with the relevant requirements of the Code and must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The Panel noted Servier's submission that its sales materials and briefing documents did not mention, claim or compare any evidence that neutropenia was an indicator of efficacy. Further Servier stated it had no record of representatives being reprimanded for such activity as alleged by the complainant. The Panel considered that as the complainant had provided no evidence to support this allegation, he/she had not discharged the burden of proof. The Panel therefore ruled no breach of Clauses 7.2, 7.4, 7.9, 9.1 and 15.9 in this regard.

C General allegations

The Panel noted the complainant's general allegation that the advisory board in question was a disguised promotional meeting for loyal Lonsurf customers. The complainant queried that if the advisory board was not a disguised promotional meeting then why did the senior medical manager acknowledge the senior commercial manager and representatives in an email immediately after the advisory board, and not include a medical colleague and the team of MSLs.

The Panel noted that the disputed email was not copied to the MSLs or the medical colleague, however, the MSLs were mentioned in this email. The Panel considered that although the medical colleague was not acknowledged by the senior medical manager in the disputed email, this did not in itself indicate that the advisory board was a disguised promotional meeting as alleged. Nor did the role of the senior commercial manager and the representatives necessarily indicate that the advisory board was a disguised promotional meeting as alleged.

The Panel noted that there were ten health professionals and three Servier employees at the meeting in question. The Panel noted the meeting objectives and expected outputs in the certified rationale document. The Panel further noted Servier's submission regarding the expertise and experience of the advisors selected in relation to the advice sought. Servier had retrospectively analysed relevant sales data and submitted that it found no evidence that the advisors were 'loyal users of Lonsurf'; one advisor had extensive clinical trial experience but his/her hospital had not bought Lonsurf in the 6 months before the advisory board.

The Panel noted from the agenda that the advisory board started at 10am and finished at 4pm. Excluding introductions, lunch and meeting close, just over 80% of the time on the agenda was allocated to discussion. It appeared to the Panel that there were four presentations consisting of a total of 87 slides. The Panel queried whether so many slides were needed given that only 40 minutes of presentation time was on the agenda. The Panel noted Servier's submission that many of these slides built on each other, were one sentence asking a question or were title slides.

Feedback and advice obtained from the advisory board was documented in the meeting executive summary along with actions for Servier.

The Panel noted its comments above. A judgement had to be made on the evidence provided by the parties. Whilst the Panel had some concerns, in its view the complainant had not proved, on the balance of probabilities, that the advisory board meeting was disguised promotion and no breach of Clause 12.1 was ruled.

The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. The Panel noted its comments and rulings above and ruled no breach of Clause 2.

Complaint received **5 February 2019**

Case completed **30 May 2019**