CASE AUTH/2201/1/09

ASTRAZENECA v NOVARTIS

Femara press release

AstraZeneca alleged that the title of a Novartis UK press release, 'Femara (letrozole) FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen when taken for five years after breast cancer surgery' was misleading as it exaggerated study results (Breast International Group (BIG) 1-98 study) which had failed to show statistical significance (p=0.08).

AstraZeneca noted that consumer journalists were able to access the press release online and the outputs were most likely to be read by the public. The press release raised unfounded hopes of increased survival that could not be substantiated by the current evidence. Patients reading this information would be encouraged to demand letrozole over other aromatase inhibitors. There was no evidence of survival benefit for any aromatase inhibitor used in this setting.

AstraZeneca alleged that the intention of the headline to mislead readers into believing letrozole had achieved a survival benefit over tamoxifen was further evidenced by the quotation in the press release by a senior company spokesman that 'The survival data shown may offer new promise for breast cancer patients'. All aromatase inhibitors had shown benefits in disease-free survival in the adjuvant setting. However there was no 'new promise' for these patients. Based on these data it would still be inappropriate for health professionals to counsel their patients on the 'promise' of a survival benefit from any aromatase inhibitor, letrozole included.

AstraZeneca was further concerned by the statement 'Long-term follow-up from major, independent BIG 1-98 trial adds further evidence that starting with Femara may be the optimal treatment strategy versus *tamoxifen*' (emphasis added). There was no new evidence from this analysis that suggested this was the case. Novartis had tried to use a non-significant survival benefit to suggest that letrozole was superior to anastrozole (AstraZeneca's product Arimidex), the only other licensed aromatase inhibitor in this setting. This was incorrect as neither had shown a statistically significant overall survival benefit in the adjuvant setting. Patients reading this information would be encouraged to demand letrozole over other aromatase inhibitors.

AstraZeneca stated that the press release referred to a separate censored analysis, which was 'in favour' of letrozole, but did not clearly state that the analysis was not protocol defined and performed *post hoc* in a population that had been un-blinded, which severely limited the ability to assess the significance of the result. This was further evident in the slides from the presentation of the data which did not refer to event numbers, nor to a p value. The press release did not make clear any of the caveats of this analysis, further misleading readers as to the robustness of the data.

During inter-company dialogue Novartis suggested it qualified the statement by adding a non-significant p value. However the consumer media could not be expected to understand the subtleties of complex data and it could potentially mislead readers eg a Daily Mail article clearly stated that letrozole reduced the risk of death by 20% but did not state that the results were non-significant. The article would encourage patients to demand a specific aromatase inhibitor. A non-significant survival result did not justify providing information to the public in this manner. AstraZeneca alleged that Novartis had failed to maintain high standards, and press releases of this nature brought discredit to, and reduced confidence in, the pharmaceutical industry.

The detailed response from Novartis is given below.

The Panel noted the results from the new data. The reduced risk of death for Femara vs tamoxifen was not statistically significant (p= 0.08) in the intention to treat analysis. The Panel considered that the heading to the press release that Femara was the '… FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen… ' was not a fair reflection of the study results; it gave the clear impression that a clinically significant difference had been established between the products which was not so. The Panel did not consider that the use of the word 'indicate' negated the otherwise misleading impression as submitted by Novartis. The Panel considered that the heading was misleading as alleged and a breach of the Code was ruled.

The Panel considered that the press release raised unfounded hopes of successful treatment and would in effect encourage patients to ask for a specific prescription only medicine, Femara, as alleged. A breach of the Code was ruled.

With regard to the claim 'Long-term follow-up from major independent BIG 1-98 trial adds further evidence that starting with Femara may be the optimal treatment strategy versus tamoxifen' the Panel noted that there were no clinical studies comparing Femara and anastrozole. There were treatment strategies other than Femara. The Panel

considered that the press release did not make this sufficiently clear. In the Panel's view the use of the phrase 'may be' did not negate the impression that Femara was the optimal treatment strategy vs tamoxifen. The Panel considered that patients would be inclined to ask for Femara in preference to other aromatase inhibitors. The Panel considered that the claim in question was misleading in this regard and a breach of the Code was ruled.

The statement 'To explore the impact of the selective crossover, an additional analysis was conducted censoring follow-up times at the date of crossover to letrozole for 25% of the patients in the tamoxifen arm. In this analysis a 19% reduction in risk of death (HR 0.81, 95% CI: 0.69-0.94) was observed in favour of Femara' did not in the Panel's view reflect the nature of the data. This analysis was not protocol defined and was performed *post-hoc* with the tamoxifen arm un-blinded. The Panel considered the statement was misleading as insufficient detail was provided about the nature of the data. A breach of the Code was ruled. In the Panel's view the Daily Mail article provided by AstraZeneca to support its complaint demonstrated that the press release was misleading.

The Panel did not consider that it was a breach of the Code *per se* to issue a press release about non-significant survival results and on this narrow point no breach of the Code was ruled.

The Panel was concerned that a misleading press release had been issued about data that would be of great interest to the public and health professionals. High standards had not been maintained and a breach of the Code was ruled.

With regard to the alleged breach of Clause 2 the Panel considered it was very important that press releases, particularly those that were made available to consumer journalists about sensitive issues such as survival in cancer patients, were fair, factual and not misleading. Clause 2 was used as a sign of particular censure and reserved for such use. The Panel considered that the circumstances warranted such a ruling and a breach of Clause 2 was ruled.

AstraZeneca UK Limited complained about a UK press release (ref FEM08000117) issued by Novartis Pharmaceuticals UK Ltd. The press release dated 11 December, was headed 'Femara (letrozole) FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen when taken for five years after breast cancer surgery'.

The press release referred to results released that day from a protocol defined intent-to-treat (ITT) analysis of the Femara and tamoxifen monotherapy arms in the Breast International Group (BIG) 1-98 study. Also included were results from an additional post-hoc censored analysis. The results were presented at the San Antonio Breast Cancer Symposium, an international symposium for scientists and clinicians in breast cancer.

Femara was indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer and treatment of early invasive breast cancer in postmenopausal women who had received prior standard adjuvant tamoxifen therapy. It could be used as first line treatment in postmenopausal women with advanced breast cancer. It was indicated for treatment of advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy had failed and could be used as pre-operative therapy in some defined postmenopausal women to allow subsequent breast conserving surgery.

COMPLAINT

AstraZeneca noted that the press release, specifically tailored for the UK media, related to the latest results of a large international study comparing letrozole with tamoxifen in the treatment of early breast cancer which were released at a prestigious conference.

The title of the press release 'Femara (letrozole) FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen when taken for five years after breast cancer surgery' implied a significant survival benefit for letrozole over tamoxifen, which would be considered a major breakthrough in this field, worthy of significant press coverage. However, only upon further reading did it become evident that the title was in fact an exaggeration of a study result that failed to reach statistical significance (p=0.08). AstraZeneca alleged that the press release was therefore misleading in breach of Clause 22.2.

Novartis Oncology issued this press release via a web information distribution service. AstraZeneca noted that consumer journalists accessed this web information distribution service and the outputs were most likely to be read by the public. The press release raised unfounded hopes of successful treatment (an increase in survival), a claim that could not be substantiated by the current evidence in breach of Clause 22.2. Patients reading this information would be encouraged to demand letrozole over other aromatase inhibitors breaching Clause 22.2. There was no evidence of survival benefit for any of the aromatase inhibitors used in this setting.

The intention of the headline was to mislead readers into believing letrozole had achieved a survival benefit over tamoxifen. This was further evident by the quotation in the press release by a senior company spokesman, that 'The survival data shown may offer new promise for breast cancer patients'. All aromatase inhibitors had shown benefits in disease-free survival in the adjuvant setting. However there was no 'new promise' for these patients. Based on these data it would still be inappropriate for health professionals to counsel their patients on the 'promise' of a survival benefit from any aromatase inhibitor, letrozole included.

AstraZeneca was further concerned by the statement 'Long-term follow-up from major, independent BIG 1-98 trial adds further evidence that starting with Femara may be the optimal treatment strategy **versus tamoxifen**' (emphasis added). There was no new evidence from this analysis that suggested this was the case. Novartis had tried to use a non-significant survival benefit to suggest that letrozole was superior to anastrozole (AstraZeneca's product Arimidex), the only other licensed aromatase inhibitor in this setting. This was incorrect as neither had shown a statistically significant overall survival benefit in the adjuvant setting, and in any case this claim would only be appropriate in the context of a clinical trial directly comparing letrozole with other aromatase inhibitors. Patients reading this kind of information would be encouraged to demand letrozole over other aromatase inhibitors in breach of Clause 22.2.

AstraZeneca stated that the press release referred to a separate censored analysis, which was 'in favour' of letrozole, but did not clearly state that the analysis was not protocol defined and performed *post hoc* in a population that had been un-blinded, which severely limited the ability to assess the significance of the result. This was further evident in the slides from the presentation of the data which did not refer to event numbers, nor to a p value. The press release did not make clear any of the caveats of this analysis, further misleading readers as to the robustness of the data.

During inter-company dialogue Novartis suggested it qualified the statement by adding a non-significant p value to the press release. However companies could not expect consumer media to understand the subtleties of complex data and it could potentially mislead readers by misunderstanding press releases. There was further evidence that this press release had been taken out of context; a Daily Mail article clearly stated that letrozole reduced the risk of death by 20%, with no reference to the fact that the results were non-significant. The article would encourage patients to demand a specific aromatase inhibitor. A non-significant survival result did not justify providing information to the public in this manner and was in breach of Clause 22.2. Novartis had failed to maintain high standards, and press releases of this nature brought discredit to, and reduced confidence in, the pharmaceutical industry.

In summary AstraZeneca believed that this press release grossly misled health professionals and the public into believing that Femara had achieved a significant survival benefit over tamoxifen breaching Clauses 22.2, 9.1 and 2.

RESPONSE

Novartis stated that BIG 1-98 was an international, double-blind, controlled trial of postmenopausal women with hormone receptor positive early breast cancer (n=8,010). Patients were randomised to adjuvant treatment with either Femara for 5 years, tamoxifen for 5 years or a sequence of the two in either order. In summary -

- The study was independently led by the International Breast Cancer Study Group (IBCSG) with financial and monitoring support provided by Novartis.

- Two previous analyses of several endpoints, undertaken with median follow up of 26 and 51 months respectively, demonstrated that 5 years of Femara was superior to tamoxifen through assessment of several endpoints, most notably the primary endpoint of disease-free survival and time to distant recurrence (metastases). The first of these reports, in 2005, resulted in the approval of the indication, 'Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer'.

- The results also led IBCSG to take the ethical decision to un-blind the tamoxifen 5 year arm and offer those patients a choice of switching to Femara.

- ITT analysis presented at the conference included the 4,922 patients that were randomised to Femara or tamoxifen for 5 years. This was pre-specified in the protocol to occur when 10 years had elapsed since the start of randomisation in 1998. The median follow up for this analysis was 76 months.

- Following un-blinding in 2005, approximately a quarter (25.2%) of the patients originally randomised to tamoxifen selected to cross over to Femara. The median duration of treatment with Femara in these patients was 18 months. These patients remained in the tamoxifen arm for the ITT analysis and therefore, the ITT analysis included significant bias towards tamoxifen. Despite this bias, statistically significant differences favouring Femara were observed in the primary endpoint of disease-free survival and time to distant recurrence and a p value of 0.08 was observed for the secondary endpoint of overall survival.

- To estimate the impact of the selective crossover, IBCSG did a censored analysis of the ITT population. Data was censored from patients at the time of crossover. In this second analysis, a hazard ratio (HR) of 0.81 was observed for overall survival, representing a relative risk reduction of 19% for Femara versus tamoxifen. This was statistically significant, with the 95% confidence interval not crossing 1.00 (95% CI: 0.69 – 0.94).

Novartis submitted that pharmaceutical companies normally announced results from major clinical trials and the communication of these newsworthy results was in order to inform people in the UK who were interested in the treatment of breast cancer, including health professionals, the media and the public.

Clause 22.2 allowed such information to be made available via a press release to members of the public as long as this was factual and presented in a balanced way. Novartis believed that the press release presented the data from the reported analyses in a factual and balanced manner and objectively represented the IBCSG findings. Furthermore it did not believe that the results as presented raised unfounded hopes of successful treatment as alleged or would encourage members of the public to ask their health professionals to prescribe Femara.

Novartis noted that the full press release heading was:

Femara (letrozole) FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen when taken for five years after breast cancer surgery

- *Femara showed reduced risk of death by 13% (P=0.08) versus tamoxifen, despite inclusion of patients who had switched over from tamoxifen to Femara during the study period, following the study's unblinding*

- *In a separate censored analysis excluding patients after they crossed over to Femara, reduction in risk of death was 19% (HR= 0.81, 95% CI: 0.69-0.94)*

- *Long-term follow-up from major independent BIG 1-98 trial adds further evidence that starting with Femara may be the optimal treatment strategy versus tamoxifen.*

As described above, it was important to consider both analyses from the BIG 1-98 study presented at the December meeting. Both analyses were presented in the press release header and the explanatory text below and therefore faithfully represented the IBCSG presentation of the BIG 1-98 study update in a balanced way.

Novartis believed that the title was factually correct. The word 'indicate' clearly conveyed that overall superiority had not been proven and did not exaggerate the study results. This was further supported by bullet points immediately below the title which stated, together with corresponding statistical data, the trial results from two separate analyses presented at the meeting. The second paragraph of the main body of the press release specifically stated that the difference in overall survival in the ITT analysis was not statistically significant.

No indication of an overall survival benefit versus tamoxifen had previously been demonstrated in an adjuvant aromatase inhibitor trial. The Arimidex, Tamoxifen, Alone or in Combination trial in the adjuvant setting failed to demonstrate a significant benefit for anastrozole versus tamoxifen in terms of overall survival, despite 100 months' median follow up (HR, 0.97; 95% CI, 0.86-1.11; p=0.7); the first report from the Tamoxifen Exemestane Adjuvant Multinational trial was presented at the San Antonio Breast Cancer Symposium in December 2008 and no significant overall survival benefit for exemestane (Pfizer's product Aromasin) was demonstrated over tamoxifen. The use of the term 'first' was therefore justified in this context.

Novartis believed that the two analyses of overall survival in the BIG 1-98 study, which included 4,922 patients and was independently led by IBCSG was newsworthy for health professionals and others interested in the treatment of breast cancer.

Novartis also believed that because the results from this independent presentation at the prestigious meeting had been presented in a factual and balanced way, the press release did not mislead readers to draw inaccurate conclusions.

The press release did not include statements that encouraged members of the public to demand Femara over other treatments currently offered for the adjuvant treatment of hormone receptor positive early breast cancer. Novartis did not believe that the title of the press release was in breach of Clause 22.2 as alleged.

Novartis believed the press release to be relevant and of interest to consumer journalists and their readers. The information included in the IBCSG presentation of the BIG 1-98 study update substantiated a favourable benefit of Femara over tamoxifen and the results were faithfully and accurately presented in a balanced manner by the press release. No 'unfounded' hopes of successful treatment were given by the press release, in fact, it informed journalists of results from a large, international, independent clinical study that were important and significant to anyone interested in the treatment of early breast cancer.

AstraZeneca had included an article from the Daily Mail Online, which was published the day after the results were presented. As far as Novartis was aware, this was the only resulting article published in the national consumer press. Novartis noted that the article in the newspaper edition of the Daily Mail was a relatively small, quarter page article, published on page 28. Novartis believed that AstraZeneca had based its assertion that patients would be led to 'demanding' Femara on this one short article. The article reported the results from the study in a balanced way and then referred to aromatase inhibitors in general and placed their use in context against the use of tamoxifen. Therefore Novartis did not accept that the press release was in breach of Clause 22.2 based on the allegation that unfounded hopes of successful treatment would be raised and patients could be encouraged to ask their health professional to prescribe Femara.

Novartis noted the conclusions in the BIG 1-98 slide set: 'Updated results of BIG 1-98 suggest superior overall survival with letrozole compared with tamoxifen'. The quotation in question accurately

represented the conclusions that this data 'suggests' superiority of Femara over tamoxifen and that it 'may' offer new promise for a significant number of patients with breast cancer. A large proportion of women with early breast cancer who were appropriate for adjuvant endocrine treatment (eg tamoxifen, aromatase inhibitors), received tamoxifen.

The new evidence presented at the meeting confirmed previous results from the BIG 1-98 study with a median follow up of 76 months, which demonstrated through the analysis of several endpoints that Femara was superior to tamoxifen. This statement clearly referred to a comparison of Femara and tamoxifen with the words 'versus tamoxifen'. The comparator medicine, tamoxifen, in the BIG 1-98 trial was mentioned throughout the press release heading and in four paragraphs of the body of the press release text. No statement in the press release suggested that Femara was superior to anastrozole. As AstraZeneca correctly pointed out, there were no direct clinical comparisons of these two aromatase inhibitors in the adjuvant treatment setting. The press release would not encourage patients to demand Femara over other aromatase inhibitors and therefore, Novartis believed there was no breach of Clause 22.2.

The information relating to the censored analysis read:

> 'To explore the impact of the selective crossover, an additional analysis was conducted censoring follow-up times at the date of crossover to letrozole for 25% of the patients in the tamoxifen arm. In this analysis, a 19% reduction in risk of death (HR=0.81, 95% CI: 0.69-0.94) was observed in favour of Femara.'

This was an accurate and balanced representation of the facts released by the IBCSG at the meeting. The language expressly indicated that this was an extra analysis to explore the impact of selective crossover in the ITT analysis results. It was clearly stated that the censored analysis was performed as 'an additional analysis' to the protocol-defined ITT analysis described in the preceding paragraph. Due to the un-blinding and subsequent unplanned, selective crossover to Femara in the ITT analysis, it was important to consider both analyses in context to better estimate the effect of Femara versus tamoxifen if the trial had remained fully blinded. The press release had presented these data in a factual and balanced manner, and there was no attempt to mislead readers as alleged.

In summary, Novartis believed that the press release presented the data in a factual and balanced way. The title was not an unqualified claim for superiority but highlighted that the data indicated that an improvement was seen versus tamoxifen over 5 years. The press release was clear throughout that the data reported was versus tamoxifen. It did not raise unfounded hopes of successful treatment or contain statements which would encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. Therefore Novartis did not believe that the press release warranted breaches of Clause 22.2 nor that it had failed to maintain high standards or brought discredit to, or reduced confidence in, the pharmaceutical industry warranting breaches of Clauses 9.1 or 2.

PANEL RULING

The Panel noted the results from the new data. The reduced risk of death for Femara versus tamoxifen was not statistically significant (p= 0.08) in the ITT analysis. The Panel considered that the heading to the press release that Femara was the '… FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen… ' was not a fair reflection of the study results. The Panel considered that the heading gave the clear impression that a clinically significant difference had been established between the products which was not so. The difference was not statistically significant. The Panel did not consider that the use of the word 'indicate' negated the otherwise misleading impression as submitted by Novartis. The Panel considered that the heading was misleading as alleged and a breach of Clause 22.2 was ruled.

The Panel considered that the press release raised unfounded hopes of successful treatment and would in effect encourage patients to ask for a specific prescription only medicine, Femara, as alleged. A breach of Clause 22.2 was ruled.

With regard to the claim 'Long-term follow-up from major independent BIG 1-98 trial adds further evidence that starting with Femara may be the optimal treatment strategy versus tamoxifen' the Panel noted that there were no clinical studies comparing Femara and anastrozole. There were treatment strategies other than Femara. The Panel considered that the press release did not make this sufficiently clear. In the Panel's view the use of the phrase 'may be' did not negate the impression that Femara was the optimal treatment strategy versus tamoxifen. The Panel considered that patients would be inclined to ask for Femara in preference to other aromatase inhibitors. The Panel considered that the claim in question was misleading in this regard and a breach of Clause 22.2 was ruled.

The statement 'To explore the impact of the selective crossover, an additional analysis was conducted censoring follow-up times at the date of crossover to letrozole for 25% of the patients in the tamoxifen arm. In this analysis a 19% reduction in risk of death (HR 0.81, 95% CI: 0.69-0.94) was observed in favour of Femara' did not in the Panel's view reflect the nature of the data. This analysis was not protocol defined and was performed *post-hoc* with the tamoxifen arm un-blinded. The Panel did not accept Novartis' submission that it was clear that the analysis was additional to the ITT analysis. The Panel

considered the statement was misleading as insufficient detail was provided about the nature of the data. A breach of Clause 22.2 was ruled.

In the Panel's view the Daily Mail article provided by AstraZeneca to support its complaint demonstrated that the press release was misleading.

The Panel did not consider that it was a breach of the Code *per se* to issue a press release about non-significant survival results and on this narrow point no breach of Clause 22.2 was ruled.

The Panel was concerned that a misleading press release had been issued about data that would be of great interest to the public and health professionals. High standards had not been maintained and a breach of Clause 9.1 was ruled.

With regard to the alleged breach of Clause 2 the Panel considered it was very important that press releases, particularly those that were made available to consumer journalists about sensitive issues such as survival in cancer patients, were fair, factual and not misleading. Clause 2 was used as a sign of particular censure and reserved for such use. The Panel considered that the circumstances warranted such a ruling and a breach of Clause 2 was ruled.

Complaint received **20 January 2009**

Case completed **24 February 2009**