CASE AUTH/2203/1/09

JOHNSON & JOHNSON v PFIZER

Champix journal advertisement

Johnson & Johnson alleged that the claim 'CHAMPIX [varenicline] at 12 weeks provides significantly greater quit success vs. NRT [nicotine replacement therapy] (NiQuitin CQ clear)' in a journal advertisement issued by Pfizer was misleading and not supported by robust data. The study from which the claim was derived was an open-label comparison of Champix tablets and NRT patches and almost half of the subjects had previously, unsuccessfully, used NRT patches to quit smoking. The significant biases in the study could have easily been overcome by using a double-dummy design and excluding patients who had previously used NRT. The study was not a fair comparison and should not be used to substantiate a superiority claim for Champix vs NRT.

The detailed response from Pfizer is given below.

The Panel noted that the study from which the claim was derived was an open-label, randomised comparison of a 12 week standard regimen of Champix with a 10 week standard regimen of NRT for smoking cessation. All patients were motivated to quit and had not used any form of NRT in the previous 6 months. The Panel noted each party's submission about the study methodology and limitations. The study authors noted that a limitation was its open-label design and a detailed discussion of the study's limitations appeared in the published paper.

The Panel noted that whilst an open-label design would not necessarily preclude the use of study data in promotional material, readers had to be provided with sufficient information to enable them to assess the data. The Panel noted the study authors' conclusions that 'motivational influences are likely to exist in a real-world setting and the outcomes of this study show that varenicline is more effective than transdermal nicotine in enhancing quit rates in *an open-label setting*' (emphasis added). The Panel did not consider that the claim at issue was a fair reflection of the study findings in this regard. The main body of the advertisement gave no relevant details about the study design and so the reader would be unaware of the basis of the data. The Panel considered the claim 'Champix at 12 weeks provides significant greater quit success vs NRT (NiQuitin CQ Clear)' was misleading in this regard and a breach of the Code was ruled.

Johnson & Johnson Limited complained about a Champix (varenicline) advertisement (ref CHA432a) issued by Pfizer Limited and published in GP, 11 April 2008.

COMPLAINT

Johnson & Johnson alleged that the claim 'CHAMPIX at 12 weeks provides significantly greater quit success vs. NRT [nicotine replacement therapy] (NiQuitin CQ clear)' was misleading and not supported by robust data. This claim should not be referenced to Gonzales *et al* (2006) but to Aubin *et al* (2008). Pfizer had agreed that future advertising would reference this study correctly.

Aubin *et al* (2008) used an open-label design which immediately introduced a significant level of bias. The International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline on Statistical Principles for Clinical Trials clearly stated in section 2.3 Design Techniques to Avoid Bias: 'The most important design techniques for avoiding bias in clinical trials are blinding and randomisation…'.

The ICH guidelines referred to the following points:

- Along with randomisation, blinding was one of the two most important techniques to avoid bias in clinical trials, and therefore ensure a fair comparison between two treatments
- Blinding should be considered a normal feature in clinical trials
- 'Extensive efforts' should be made to overcome any difficulties in achieving blinding – if two treatments were clearly different a double-dummy technique should be used
- If a double-blind design was not possible, then single blinding should be considered.

Any non-blinded study had serious limitations, and interpretation of results from non-blinded studies should be made very carefully and with these limitations in mind. It was difficult to envisage a scenario in which a clear statement claiming superiority of one treatment over another could ever be justifiably supported solely from a non-blinded study. A non-blinded study inevitably introduced bias which applied to both subjects and investigators and this bias could extend to selection, motivation, measurement and analysis.

Expectations were likely to be much higher for any new product and the fact that patients in the Champix group knew they had been allocated a novel smoking cessation treatment significantly biased the study outcome in favour of Champix. In two of Pfizer's pivotal studies comparing Champix and bupropion (Jorenby *et al* 2006 and Gonzales *et al*), varenicline demonstrated abstinence rates of around 44% for the same time point used in Aubin *et al* (last four weeks of treatment). Despite similarities between the studies in terms of the level

of intervention and the demographics of the smokers, these abstinence rates were considerably lower than the 55% observed by Aubin *et al*. This suggested that knowledge of treatment in patients receiving Champix resulted in greater motivation to quit than those receiving NRT. As motivation to quit was a key factor in the likelihood of a successful quit attempt, this was likely to have biased the results in favour of Champix.

The fact that three patients randomised to NRT refused such treatment clearly suggested there would be a motivational bias in favour of Champix. Moreover, it appeared likely that some patients might have only participated in this study to receive varenicline. The authors stated that 'a refusal to participate further was less likely with varenicline than with NRT. A double blind design may have avoided such biases'. The authors further acknowledged that 'the differential dropout rate after medication assignment and before the first dose of treatment suggests that some motivational bias may have influenced the results'.

Johnson & Johnson disagreed with Pfizer's claim that it was acceptable to use this open-label study as the basis for strong comparative claims against NRT products. This study was open to a number of critically important biases and the Code required that all claims were supported by the appropriate evidence. In the case of comparative claims, it was particularly important that appropriately robust studies demonstrated that one treatment was more effective than another.

Aubin *et al* accepted the limitations of an open-label design, noting that a double-dummy design would have enabled the study to be appropriately blinded. They stated that a double-dummy design was not possible as 'technical problems made it difficult to create NRT and placebo patches that were indistinguishable from one another in appearance and odour'. This was very difficult to understand as nicotine was colourless and odourless and when the study was performed Pfizer manufactured and marketed a range of NRT products, including NRT patches, and had sponsored a number of placebo-controlled studies which included a placebo NRT patch. The obvious conclusion was that 'extensive efforts' were not made to overcome difficulties in achieving blinding.

In addition to the contention that a properly blinded study was not possible, Pfizer also argued that an open-label design was appropriate because it reflected the 'real world' situation. Johnson & Johnson did not accept this as a valid argument; it was clearly at odds with the guidance given in the ICH Harmonised Tripartite Guideline on Statistical Principles for Clinical Trials. A clinical trial should be a controlled experiment and variables other than those being investigated (in this case medical treatment) should be eliminated where possible. The purpose of a controlled clinical trial was not to represent the real world situation but rather to detect genuine differences between two treatments in a controlled setting. Unless a clinical trial had been designed to eliminate the biases which existed in the real world, fair conclusions about the comparative efficacy of two treatments could not be made. If the intention of the study had been to examine the real world scenario, then randomisation was not appropriate, and patients should have been able to select treatment. In this scenario, an audit rather than clinical trial would have been more appropriate.

As regards the applicability of the trial to the real world, the authors suggested that motivational influences were likely to exist in the real world. This might be the case. However, this did not negate the fact that the study was not designed to examine the real world. In addition, motivation within the real world would change over time as some smokers would inevitably fail to quit with varenicline. Hence, in the real world, the expected improved motivation with varenicline was likely to be the highest when the product was first introduced and would reduce over time. The authors cited the open-label design of the study as a key limitation.

Pfizer submitted that Aubin *et al* was included in the Cochrane Systematic review on varenicline, and noted that the reviewers stated: 'One open-label trial of varenicline versus nicotine replacement therapy demonstrated a modest benefit of varenicline over NRT with a RR at week 52 of 1.31 (95% CI 1.01 to 1.71)'. However, Pfizer failed to mention that the reviewers also stated 'Aubin 2008 was an unblinded open-label trial, which may have led to the differential drop-out rates after randomization, with nine participants assigned to nicotine patch declining to take part compared with two in the varenicline group'. Hence the Cochrane review acknowledged potential bias within the trial.

A further limitation of the study which introduced significant bias was the fact that almost half the subjects (46.2% in the NRT group) had previously used NRT patches in a quit attempt. The fact that when enrolled into the study, all subjects smoked at least 15 cigarettes per day meant that any of them who had previously used NRT patches in a quit attempt had been unsuccessful, as they had relapsed. Johnson & Johnson believed this represented a significant source of bias for a number of reasons and was compounded by the use of an open-label design.

Firstly, it was well accepted that some patients, for instance those who were more highly dependent, or those who had failed to quit with single NRT therapy, might benefit from higher doses of nicotine. This was why the National Institute for Health and Clinical Excellence (NICE) and Action on Smoking and Health (ASH) recommended use of combination NRT therapy (a patch plus an acute format) in some smokers. Hence, by including smokers who had failed to quit previously using NRT, this study might have included a large number of recalcitrant smokers who required higher dose NRT treatment.

Secondly, as described previously, it was widely accepted that motivation to quit was important in treatment success. Therefore, with full knowledge of their treatment allocation and an awareness that they had previously used NRT patches unsuccessfully, almost half the subjects in the NRT group were likely to have had much lower expectations of treatment success and lower motivation to quit. Taking these factors into consideration, it was very likely that the inclusion of a significant number of patients in the NRT group who had previously failed on their allocated treatment resulted in a lower overall quit rate in that group. Again, this would significantly and unfairly bias the study outcome in favour of Champix.

This difference in motivation was likely to be responsible for the differential drop out rates following randomisation of patients to the two treatment arms. Aubin *et al* and the Cochrane Collaborative acknowledged the difference in drop out rates between the groups. Furthermore, the authors clearly stated 'The differential drop out rate after medication assignment and before the first dose of treatment suggests that some motivational bias may have influenced the results'. Therefore, it seems likely that differences in motivation would have biased the results in favour of varenicline.

In Jorenby *et al* and Gonzales *et al*, patients who had previously been exposed to bupropion were excluded in order to minimalise potential negative bias towards bupropion. Pfizer argued that subjects who had previously been treated with bupropion were excluded in these studies because of evidence suggesting that re-treatment with bupropion reduced efficacy. In support of this, Pfizer also quoted Gonzales *et al* (2001).

Gonzales *et al* (2001) did not assess the effect of previous treatment with bupropion on the efficacy of varenicline and in any case the authors concluded that bupropion was effective for re-treatment of smokers, regardless of previous smoking medication used. The authors however stressed that 'An understanding of the impact of these previous attempts to quit is vital for selecting medications that may be more successful in a future attempt to quit'. In this context, and given that prior use of bupropion was an exclusion criteria in Pfizer's pivotal studies of Champix, it was clearly inappropriate to include subjects who had previously relapsed following NRT therapy in a study comparing the efficacy of Champix with NRT. Interestingly, Gonzales *et al* (2001) stated that re-treatment with NRT of smokers who had previously used NRT had been only somewhat successful. In the absence of data, it was not safe to assume that previous treatment had no effect on subsequent treatment, and it was difficult to understand why patients who had relapsed following NRT were included in the study.

Johnson & Johnson noted that Jorenby *et al* and Gonzales *et al*, comparing varenicline and bupropion, were both double-blind.

Finally, Aubin *et al* conceded that the difference between the groups in treatment duration introduced yet another source of bias. It was likely that subjects in the varenicline group receiving a 12-week course of treatment would have better expectations and motivation than subjects in the NRT group who received a 10-week course of treatment.

In conclusion, Aubin *et al* was of very poor methodological quality and introduced a number of significant biases which could easily have been overcome by implementing a double-dummy design and excluding patients who had previously used NRT. This trial could not possibly be held up as a fair comparison of Champix and NRT and should not be used to substantiate a superiority claim for the efficacy of Champix over NRT.

The use of this claim was in breach of Clause 7.2 of the Code as it provided an unfair comparison without adequate supporting data.

RESPONSE

Pfizer stated that although the advertisement was no longer in use it was important to respond to the general critique of Aubin *et al*. Aubin *et al* was used in the Champix sales aid where Pfizer described the study design. Pfizer's presentation of Aubin *et al* in the sales aid was reviewed in a previous case, Case AUTH/2142/7/08, and was found not to be in breach of Clause 7.2.

Pfizer believed the design of Aubin *et al* was robust, and therefore it was appropriate to use the results in promotional materials. Pfizer did not agree that the claim 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' was in breach of Clause 7.2.

Aubin *et al* was published online in Thorax, an international peer-reviewed journal. As detailed in the advertisement, the results showed that varenicline at 12 weeks provided significantly greater quit success compared with NiQuitin CQ Clear patch. This claim was supported by data from the study, which showed that the primary endpoint, continuous abstinence rate at end of treatment, was significantly greater for varenicline (55.9%) than NiQuitin CQ Clear (43.2%) ($p<0.001$, odds ratio 1.70, 95% confidence interval 1.26 to 2.28 as also included in the advertisement).

The authors concluded that 'The outcomes of this trial established that abstinence from smoking was greater and craving, withdrawal symptoms and smoking satisfaction were less, at the end of treatment with varenicline than with transdermal NRT'.

Aubin *et al* was a randomized, open-label clinical trial. Smokers had often made multiple failed quit attempts, including using various forms of NRT. As discussed by the authors, this population might

demonstrate a motivation towards trying an alternate therapy. Given the immense difficulty faced by this population in giving up smoking, it was an important question to ask whether varenicline, even with this motivation, could offer significantly greater quit rates compared with NRT at the end of treatment.

Pfizer submitted that blinding would have been technically difficult in this population. The authors stated that 'technical problems made it difficult to create NRT and placebo patches that were indistinguishable from one another in appearance and odour'. Before entering this trial, almost half of the patients had already tried to quit smoking with a nicotine patch. This fact presented technical difficulties to the study designers, who assumed that any difference between the therapeutic nicotine patch and the placebo patch would be detected. Skin irritation caused by nicotine in the therapeutic patch could not be duplicated in a placebo patch, for example – nor could the distinctive smell of the therapeutic patch.

Almost half the subjects (46.2% in the NRT group) had previously tried to quit and failed using a transdermal nicotine patch and in Johnson & Johnson's view this might have favoured varenicline. However, patients were excluded if they had used NRT within the previous 6 months. In addition, treatment by baseline covariate analysis demonstrated that there was no interaction ($p > 0.10$) with prior quit attempt using NRT or transdermal patch, suggesting that this did not influence the efficacy.

Johnson & Johnson raised the issue of the use of combination NRT therapy. Aubin *et al* was designed to address the efficacy of varenicline in comparison with a single form of NRT, it would require a separate study to assess efficacy of varenicline in comparison with combination therapy. The claim used in the advertisement clearly indicated that the results were comparing varenicline with a single form of NRT 'vs NRT (NiQuitin CQ Clear)'.

The study was included in the recently updated Cochrane review published online in 'Nicotine receptor partial agonists for smoking cessation' on 16 July 2008. The authors included the Aubin *et al* data in their review and in their results they stated that 'One open-label trial of varenicline versus nicotine replacement therapy demonstrated a modest benefit of varenicline over NRT with a RR at week 52 of 1.31 (95%CI 1.01 to 1.71)'. The Cochrane reviewers also stated that 'Aubin 2008 was an unblinded open-label trial, which may have led to the differential drop-out rates after randomisation, with nine participants assigned to nicotine patch declining to take part compared with two in the varenicline group'. It should be noted that the primary analysis population for the study was all randomized and treated, so the data set used to calculate the primary endpoint in Aubin *et al* used the population following the drop out of nine in the nicotine patch group and two in the varenicline group.

Within Aubin *et al* the analysis of the all randomized population was also included. The continuous abstinence rate at the end of treatment was significantly greater for varenicline (55.6%) than NiQuitin CQ Clear (42.2%), odds ratio 1.76 $p<0.001$. When comparing these results to those of the primary analysis population (all randomized and treated) the odds ratio for the all randomized and treated population (1.70) was numerically less favourable for varenicline than if the odds ratio all randomized population had been used (1.76). In order to address the possible bias from differential drop outs following randomization the authors prespecified in the study design that they would use the all randomized and treated population as the primary analysis population.

The NRT course of treatment finished 1 week earlier than the varenicline course of treatment and this in Johnson & Johnson's view might have favoured varenicline. The duration of therapy was as defined in the respective summaries of product characteristics (SPCs) for the products. To explore this further a prespecified sensitivity analysis compared, like for like, 4 week continuous rates for weeks 9–12 in both treatment groups and weeks 8–11 in both treatment groups and found that the overall conclusions remained unchanged.

Johnson & Johnson stated this study might have selected a population resistant to NRT, thereby favouring varenicline. Pfizer was not aware of any literature regarding the development of NRT resistance in people previously exposed to NRT. Two studies that compared varenicline with buproprion were also discussed which excluded patients who had previously been exposed to buproprion. The reason for this exclusion was because there was evidence that efficacy was reduced in individuals with prior exposure to bupropion compared with those who were bupropion naïve. The purpose of including Gonzales *et al* (2001) was to demonstrate the rationale for excluding patients who had previously been exposed to buproprion in the design of Jorenby *et al* and Gonzales (2006) *et al*; not to make any assessment about the effect of previous treatment with bupropion on the efficacy of varenicline as stated by Johnson & Johnson.

With the above in mind, Pfizer did not agree that this study should not be used to support comparisons between Champix and NRT.

PANEL RULING

The Panel noted that the title of the advertisement was 'The power to help them quit' which appeared above a visual of a cigarette splitting in half. The statement 'Now with direct NRT comparison' introduced three bullet points starting with the claim at issue 'Champix at 12 weeks provides significantly greater quit success vs. NRT (NiQuitin CQ Clear)'. The second bullet point read '1.7x greater odds of quitting smoking after Champix at 12 weeks vs. NRT

patch (odds ratio = 1.70; p<0.001)'. The first two bullet points were referenced in error to Gonzales *et al* (2006) instead of Aubin *et al*. The third bullet point read 'Champix also enables significantly more smokers to quit at 12 weeks than those who used bupropion or placebo' and was referenced to Gonzales *et al* 2006 and Jorenby *et al*. A footnote, asterisked to the second bullet point, explained that the recommended treatment course for Champix was 12 weeks and for NRT patch (NiQuitin CQ Clear) was 10 weeks. Continuous abstinence rate was [carbon monoxide] – confirmed at weeks 9-12 for Champix and at weeks 8-11 for NRT. No further details about Aubin *et al* were given.

The Panel noted that Pfizer referred to a previous case, Case AUTH/2142/7/08, wherein a comparison of the difference in quit success between Champix and NiQuitin at 12 weeks and 52 weeks, referenced to Aubin *et al*, was ruled not in breach of Clause 7.2. The Panel noted that the allegation currently before the Panel was not considered in Case AUTH/2142/7/08. The material at issue was also different.

The Panel noted that Aubin *et al* was an open-label, randomised trial to compare a 12 week standard regimen of Champix with a 10 week standard regimen of NRT for smoking cessation. All patients were motivated to quit and had not used any form of NRT in the previous 6 months. The study authors referred to the intent to treat analysis as a gold standard and explained that they reported the primary analysis population (those who were randomised and took at least one dose of medicine) in the efficacy results as this was the study's prespecified primary analysis population. The authors noted that this might underestimate the efficacy of Champix relative to NRT because of differential drop out after medication assignment.

The Panel noted each party's submission about the study methodology and limitations. The study authors noted that a limitation of the study was its open-label design and a detailed discussion of the study's limitations appeared in the published paper. The Panel noted the study authors' comment that technical problems made it difficult to create NRT and placebo patches that were indistinguishable in appearance and odour.

The Panel noted that whilst an open-label design would not necessarily preclude the use of data derived from Aubin *et al* in promotional material, readers had to be provided with sufficient information about the study to enable them to assess the data. The Panel noted the study authors' conclusions that 'motivational influences are likely to exist in a real-world setting and the outcomes of this study show that varenicline is more effective than transdermal nicotine in enhancing quit rates in **an open-label setting**' (emphasis added). The Panel did not consider that the claim at issue was a fair reflection of the study findings in this regard. The main body of the advertisement gave no relevant details about the study design and so the reader would be unaware of the basis of the data. The Panel considered the claim 'Champix at 12 weeks provides significant greater quit success vs NRT (NiQuitin CQ Clear)' was misleading in this regard and a breach of Clause 7.2 was ruled.

Complaint received **27 January 2009**

Case completed **5 March 2009**