CASE AUTH/2726/8/14

ANONYMOUS, NON CONTACTABLE HEALTH PROFESSIONAL v GLAXOSMITHKLINE

Promotion of Seretide

An anonymous, non contactable health professional complained about the use of the TORCH (TOwards a Revolution in COPD (chronic obstructive pulmonary disease) Health) study (Calverley *et al* 2007) in the promotion of Seretide (salmeterol/fluticasone) by GlaxoSmithKline UK.

The complainant noted that an editorial (Gøtzsche 2014) published in the Journal of the Royal Society of Medicine, 'Questionable research and marketing of a combination drug for smoker's lung', challenged both the design and analysis of the TORCH study and questioned the quality of the data.

The complainant noted that data from the TORCH study had been used to promote Seretide over at least the last six years. TORCH was perceived as a 'landmark' trial involving over 6,000 patients that confirmed the efficacy of Seretide in COPD. It was probable that over a number of years this promotion also shaped, rightly or wrongly, the perception of health professionals and influenced key prescribing decisions.

The complainant stated that the central issue was that the TORCH study did not meet its primary endpoint. Despite this, both historical and current promotional claims for Seretide referred to favourable secondary endpoints. The complainant alleged it was misleading to make promotional claims based on secondary endpoints (and/or post-hoc analyses) from a study that did not meet its pre-defined primary endpoint. It might be that the primary and secondary endpoints were clearly and prominently stated in Seretide promotion. However, it was unrealistic to expect time-pressured health professionals to be able to correctly apportion appropriate weighting and context to this evidence when making key prescribing decisions. The complainant stated that the criticism by Gøtzsche further supported the view that the TORCH study results should never have been used in the promotion of Seretide.

The complainant noted that Seretide promotion was accessible to the public. A search using 'healthcare professional + Seretide + TORCH study' revealed the following link as the first hit which directly led to an unsecured area of the GlaxoSmithKline website in the UK where prior registration as a health professional was not necessary in order to gain access.

The detailed response from GlaxoSmithKline is given below.

The Panel noted that at its inception the TORCH study (Calverley *et al* 2007) was the largest ever multicentre, long-term chronic obstructive pulmonary disease study and the first to investigate the effect of the salmeterol/fluticasone propionate combination and its components on chronic obstructive pulmonary disease mortality. It was a prospective randomized double-blind trial comparing a combination regimen of salmeterol and fluticasone in a single inhaler with placebo, salmeterol alone or fluticasone propionate alone for three years. The primary endpoint was the time to death from any cause for the comparison between the combination regimen and placebo. Key secondary endpoints included the reduction in COPD morbidity and the difference in quality of life (QoL), each between the combination regimen and placebo. Other endpoints included difference in composite endpoint made up of overall mortality and COPD admissions, COPD-related mortality, clinic post-bronchodilator FEV1, other COPD exacerbation endpoints, health status and health utilisation. The reduction in death from all causes amongst COPD patients in the combination therapy group as compared to placebo did not reach the predetermined level of statistical significance. Treatment with the combination regimen resulted in significantly fewer exacerbations compared with placebo including those exacerbations requiring hospitalization. The combination regimen was also significantly better than each of its components alone in preventing exacerbations and these benefits were accompanied by sustained improvements in health status and FEV1. It was noted that the greater number of patients withdrawing from the placebo group was likely to have resulted in an underestimation of the effect of the combination regimen on all the secondary outcomes. The study authors also noted that the size of the TORCH study was modest compared with studies of mortality associated with other major chronic illnesses such as cardiovascular disease and thus the results of the mortality analysis should be viewed in this context.

The Panel noted that there was a post-hoc analysis of the TORCH study secondary endpoint data which was referred to in some of the materials provided by GlaxoSmithKline.

The Panel considered that, in principle, when a primary endpoint failed to achieve statistical significance it was not necessarily unreasonable to refer to secondary endpoint data so long as this was placed within the context of the overall study findings. The nature of the material might also be relevant.

The Panel examined the materials provided and only considered those items which referred to the secondary endpoint data from the TORCH study

including the post-hoc analysis as these were the only items covered by the complaint.

The Panel examined the material published at Seretide.co.uk. The Panel noted that the 'Efficacy and Clinical Evidence' page summarized clinical data from five studies including the TORCH study. Each reference to the TORCH secondary endpoint data was preceded by the statement 'The primary endpoint of the effect of Seretide 500 Accuhaler on all-adverse mortality did not meet statistical significance p=0.052'. The Panel considered that the secondary endpoint data was placed within the context of the study. No breach was ruled.

In relation to the Seretide campaign materials the Panel noted that the Seretide TR Campaign pilot appeared to be a 24-page slide deck. Slide 12 onwards referred to Seretide in COPD. Slides 14 and 15 each headed '… And benefit over the long term' discussed the clinical benefits of Seretide 500 Accuhaler over three years with reference to the secondary endpoints of the TORCH study. Slide 16 introduced the TORCH study and made it clear that the primary endpoint did not achieve statistical significance. More detailed information about the TORCH study appeared at Slide 17. The Panel was concerned that the information about the primary endpoint of the TORCH study appeared after the slides discussing the secondary endpoint data. The Panel considered that the secondary endpoint data on Slides 14 and 15 could not take the benefit of the subsequent qualification about the non-statistically significant primary endpoint on Slides 16 and 17 and thus had not been placed within the context of the TORCH study. The slide deck was misleading and the misleading impression was incapable of substantiation. Breaches were ruled.

The Panel noted that 'Seretide COPD slides for RVT' referred to Seretide in COPD in relation to NICE guidelines, clinical benefits and appropriate prescribing. The Panel noted that with the exception of Slide 4, none of the other slides which discussed clinical secondary endpoint data from the TORCH study had placed such data within the context of the non-statistically significant primary endpoint. The slide deck was misleading in this regard and the misleading impression was incapable of substantiation. Breaches were ruled.

The Panel noted that the COPD Cost-Effectiveness slides discussed a multinational economic analysis of the TORCH study, (Briggs *et al* 2010) based on health outcome data including cost and EQ-5D utility data. The presentation did not appear to have any mention of clinical data from TORCH. The TORCH study was referred to on Slide 13. The Panel considered that whilst it would have been helpful to provide additional relevant information about the TORCH study on Slide 13, the failure to do so did not render that slide misleading or incapable of substantiation. No breach was ruled.

The Secondary Care Campaign Detail Aid included the statement 'TORCH was a three-year study. The primary endpoint of the effect of Seretide on mortality did not meet statistical significance p=0.052' at the beginning of every page which discussed the secondary endpoint data. The data had been placed in the context of the non-statistically significant primary endpoint. No breach was ruled.

The Panel noted that two items were each designed to be made into cubes the sides of which discussed the TORCH study. It was made clear that the primary endpoint did not achieve statistical significance. No breach was ruled in relation to each item. This ruling also applied to another item described as 'Seretide COPD DXS click – through content'.

The Panel had no information about how the Primary Care Campaign iPad 2012 was used. It considered that overall the secondary endpoint data was not sufficiently qualified. There was no reference to the primary endpoint data. The material was misleading. The misleading impression was incapable of substantiation. Breaches were ruled.

The Panel noted the large number of pages of the Secondary Care Campaign iPad 2012 but had no information about how representatives were directed to use the material. The Panel noted that sometimes the material referred to the non-statistically significant primary endpoint when discussing secondary endpoint data and sometimes it did not. The material was inconsistent in this regard. The Panel considered that the failure to refer to the non statistically significant primary end point was such that certain pages were misleading and the misleading impression was incapable of substantiation in relation to secondary endpoint data. Breaches were ruled.

The Panel noted that site architecture was more difficult to decipher in the balance of the secondary care campaign ipad material which comprised the specialist modules. Most pages discussing TORCH secondary endpoint data featured the primary endpoint as a prominent and integral part of the page. In the absence of any detailed allegation from the complainant in relation to the secondary care campaign ipad 2012 detail and its layout and noting the complainant bore the burden of proof, the Panel considered the specialist modules provided were not misleading or incapable of substantiation in relation to secondary endpoint data and ruled no breach. With regard to the allegation that GlaxoSmithKline promotional material based on secondary endpoints from the TORCH study were accessible to the public as a search including the terms 'health professional, Seretide and TORCH study' identified a promotional site for Seretide did not, in the Panel's view, mean that the site was therefore promoting Seretide to the public. Access to such sites did not have to be restricted to health professionals so long as the requirements in the relevant supplementary information were met. No breach was ruled.

The Panel noted its rulings of breaches of the Code above. There did not appear to have been a consistent approach in relation to the certification of material which discussed secondary endpoint data from TORCH. Some material was qualified in relation to the non-statistically significant primary

endpoint and some was not. The Panel considered that high standards had not been maintained and a breach was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 and no breach was ruled accordingly.

An anonymous, non contactable health professional complained about the use of the TORCH (TOwards a Revolution in COPD (chronic obstructive pulmonary disease) Health) study (Calverley *et al* 2007) in the promotion of Seretide (salmeterol/fluticasone) by GlaxoSmithKline UK Limited. Seretide's indications included the symptomatic treatment of patients with COPD, with an FEV1 (forced expiratory volume in one second) <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who had significant symptoms despite regular bronchodilator therapy.

COMPLAINT

The complainant noted that an editorial (Gøtzsche 2014) published in the Journal of the Royal Society of Medicine, 'Questionable research and marketing of a combination drug for smoker's lung', challenged both the design and analysis of the TORCH study and questioned the quality of the data derived. The complainant stated that Gøtzsche prompted a personal, deeper consideration of the use of data from the TORCH study in the promotion of Seretide.

The complainant noted that data from the TORCH study had been used to promote Seretide over at least the last six years such as in historical journal advertisements and in Seretide promotional literature used at booths/symposia at past respiratory conferences in the UK and in Europe. TORCH was perceived as a 'landmark' trial involving over 6,000 patients that confirmed the efficacy of Seretide in COPD. It was probable that over a number of years this promotion also shaped, rightly or wrongly, the perception of many UK health professionals and influenced key prescribing decisions directly or indirectly.

Putting aside the perceived 'landmark' status of the TORCH study, the complainant stated that the central issue was that the TORCH study did not meet its primary endpoint. Despite this, both historical and current promotional claims for Seretide referred to favourable secondary endpoints. The use of the TORCH study in promotion seemed to have missed closer scrutiny by responsible authorities for a very long time, in part possibly because of its perceived 'landmark' status although Case AUTH/2006/5/07 did perhaps provide an early opportunity to assess the wider consideration, beyond the issue raised by the complainant, of whether the TORCH study was actually suitable to support secondary endpoint claims in the promotion of Seretide given that the primary endpoint of the study was not met.

Raising awareness and encouraging debate about the TORCH study in a scientific non-promotional setting was understandable. However, in a promotional setting, the complainant alleged it was misleading to make promotional claims based on secondary endpoints (and or *post-hoc* analyses) from a study that did not meet its pre-defined primary endpoint. This fell well below expectations in relation to the promotion of prescription medicines.

It might be the case that the primary and secondary endpoints were clearly and prominently stated in Seretide promotion. However, in the UK time-pressured healthcare environment where health professionals were subject to Seretide promotion, it was unrealistic to expect them all to be able to correctly apportion appropriate weighting and context to this evidence when making key prescribing decisions based on favourable secondary endpoints when the associated primary endpoint was not met.

The complainant stated that the criticism by Gøtzsche about the TORCH study and marketing of Seretide further supported the view that the TORCH study results should never have been approved for use in the promotion of Seretide. Also, the title of Gøtzsche impacted on the wider pharmaceutical industry reputation and came when intense media spotlight on allegations related to sales practices in China and Poland had only just abated.

The complainant noted that GlaxoSmithKline continued to make claims based on secondary endpoints from the TORCH study in the promotion of Seretide. This was Seretide promotion that was accessible to the public. A Google search using 'healthcare professional + Seretide + TORCH study' revealed the following link as the first hit which directly led to an unsecured area of the GlaxoSmithKline website in the UK where prior registration as a health professional was not necessary in order to gain access to the information below: http://hcp.gsk.co.uk/products/seretide/prescribing-seretide/efficacy.html.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 2, 7.2, 7.4, 7.10, 9.1 and 23.1.

RESPONSE

GlaxoSmithKline noted that the anonymous complainant stated that his/her complaint related to the use of data from the TORCH study in the promotion of Seretide and was prompted after reading an article entitled 'Questionable research and marketing of a combination drug for smoker's lung' (Gøtzsche 20140).

GlaxoSmithKline noted that the complainant did not complain about any specific promotional materials for Seretide in particular, but referred to the promotion of Seretide over the last six years at the very least such as in historical journal advertisements and in Seretide promotional literature used at booths/symposia at past respiratory conferences in the UK and Europe'. The case preparation manager confirmed that it was unclear as to exactly which pieces of promotional material the complainant was complaining about.

GlaxoSmithKline submitted that the TORCH study was a three-year, randomised, double-blind, controlled study of 6,112 patients with moderate-to-severe COPD. The study commenced in

September 2000 and took place in 42 countries and 444 centres. Patients were randomised to three years of twice-daily treatment with either Seretide 50/500 Accuhaler, fluticasone propionate 500µg, salmeterol xinafoate 50µg, or placebo. The primary endpoint was all-cause mortality for the comparison of the Seretide 50/500 Accuhaler vs placebo. The key secondary endpoints were reduction in COPD morbidity between Seretide 50/500 Accuhaler and placebo (measured by rate of moderate and severe exacerbations) and difference in quality of life (QoL) between Seretide and placebo (measured by the St George's Respiratory Questionnaire (SGRQ)). Lung function and safety endpoints including adverse events and bone fracture information were also evaluated.

The results showed that for the primary endpoint, Seretide 50/500 Accuhaler did not meet statistical significance on all-cause mortality (p=0.052) and that for the two key secondary endpoints Seretide 50/500 Accuhaler reduced the rate of moderate/severe COPD exacerbations by 25% vs placebo (p<0.001) and produced a statistically significant (p<0.001) improvement in quality of life score as measured by the SGRQ vs placebo (-3.1 units).

The authors concluded that 'The reduction in death from all causes among patients with COPD in the combination therapy group did not reach the predetermined level of statistical significance. There were significant benefits in all other outcomes among these patients'.

GlaxoSmithKline submitted that the complainant inferred several criticisms and concerns. These were:

a) The perception that TORCH was a 'landmark' study.

b) The use of positive secondary endpoints in promotional materials when the primary endpoint for the study was not met.

c) That Seretide promotion was accessible to the public.

and in addition that

d) The responsible authorities seemed to have 'missed closer scrutiny' of the use of the TORCH study in promotion.

a) The perception that TORCH was a 'landmark' study

GlaxoSmithKline noted the complainant's submission that 'The TORCH study was perceived as a "landmark" trial .... that confirmed the efficacy of Seretide in COPD'. The complainant inferred that 'landmark' was an inappropriate descriptor for the study by placing it in inverted commas throughout his/her letter, but did not expressly state this was the case as such. Indeed the complainant hinted at slight ambivalence in this regard by stating that 'The TORCH study was perceived as a "landmark" trial ..... It is probable that this promotion [by GlaxoSmithKline] also shaped (**rightly** or wrongly) the perception of many UK health professionals' (emphasis added). GlaxoSmithKline noted that, nonetheless, it had been asked to consider whether 'landmark' might exaggerate the importance (of TORCH) and thus might not encourage the rationale use of Seretide.

GlaxoSmithKline noted that the Oxford Dictionary defined 'landmark' as 'An event or discovery marking an important stage or turning point in something'.

GlaxoSmithKline submitted that at the time of its inception and initiation the TORCH investigators stated that:

> 'The "TOwards a Revolution in COPD Health" survival study will be the largest ever, multicentre, long-term chronic obstructive pulmonary disease study, and the first to investigate the effect of salmeterol/fluticasone propionate combination and its components on chronic obstructive pulmonary disease mortality. A significant effect of salmeterol/ fluticasone propionate combination on chronic obstructive pulmonary disease morbidity and mortality would represent a real step forward in the pharmacological management of chronic obstructive pulmonary disease. Even if this does not prove to be the case, the data gathered will shed new light on the natural history of this disorder.'

GlaxoSmithKline submitted that two years later, when the TORCH results were first made available in November 2006, an article in the CHEST Physician (The Official News Publication of the American College of Chest Physicians) described TORCH as a 'landmark' study.

GlaxoSmithKline submitted that in February 2007 the TORCH study results were published in the New England Journal of Medicine (NEJM). The fact that they were published in such a prestigious international journal with an Impact Factor of 54.42, indicated that the results were considered to be of major importance to the scientific and medical community. The NEJM stated on its website that 'Of the thousands of research reports submitted each year, about five per cent are eventually published in NEJM .... And that they employ a highly rigorous peer-review and editing process to evaluate manuscripts for scientific accuracy, **novelty, and importance**' (emphasis added).

Furthermore, a Google search on 20 August 2014 showed that that there had been 1,460 citations of the TORCH study, further emphasising the impact that it had had on the medical and scientific community worldwide since its publication in 2007.

TORCH had been the subject of four complaints to the PMCPA - two, 'no breaches', one breach of Clause 4.1 and the one breach of Clauses 7.2 and 7.4. In two of the cases, the case report showed that TORCH was referred to as a 'landmark' study at the time of the evaluation of the case; a descriptor which was never questioned by the complainant nor the PMCPA at the time.

GlaxoSmithKline submitted that the original

promotional material for TORCH referred to it as a 'landmark' study, which again was never questioned by the Medicines and Healthcare Products Regulatory Agency (MHRA) when it pre-vetted material between May and September 2007 and again between July and November 2012.

In summary, TORCH was perceived as a 'landmark' study by health professionals within the UK and elsewhere and had held this status without question for the last ten years. GlaxoSmithKline therefore refuted that by describing TORCH as a 'landmark' study it might have exaggerated its importance and thus might not have encouraged the rational use of Seretide. Breaches of Clauses 7.2, 7.4 and 7.10 were denied.

b) The use of positive secondary endpoints in promotional materials when the primary endpoint for the study was not met

GlaxoSmithKline submitted that TORCH was a highly ambitious study not least as its primary endpoint was all-cause mortality at the end of a three-year treatment period. Prior to TORCH, no trials had assessed the effect of inhaled corticosteroids and long-acting bronchodilators, alone or in combination, on mortality in COPD patients, despite their known benefit in reducing symptoms and exacerbations. Since TORCH, the Cochrane review showed that there had been four trials where all-cause mortality had been the primary outcome for combination therapies in COPD. However, the overall conclusion of the Cochrane review was that for 'ICS/LABA [inhaled corticosteroid/long acting beta agonist] combination therapies compared to placebo, an overall reduction in mortality was seen, but this outcome was dominated by the results of one study (TORCH) of fluticasone/salmeterol ... and that generally, deaths in the smaller, shorter studies were too few to contribute to the overall estimate'.

Thus, even though a statistical difference was not seen between the Seretide and the placebo treatment arms in TORCH, the level of statistical significance was close to being significant, with a P value of 0.052, which was acknowledged as such in the Cochrane review as well as in the Seretide summary of product characteristics (SPC). Section 5.1 of the SPC stated that 'There was a trend towards improved survival in subjects treated with Seretide compared with placebo over 3 years however this did not achieve the statistical significance level $p \leq 0.05$'.

GlaxoSmithKline submitted two documents from the Medicines Healthcare Regulatory Agency (MHRA) which gave guidance on the use of secondary endpoints from clinical trials in promotional materials. The first related to the pre-vetting of promotional materials and stated that for 'Clinical Studies – Findings from secondary endpoints of clinical studies should be set within the context of the primary endpoint and companies should not 'cherry-pick' favourable findings'. The second in a general communication in MAIL related to advertising and the presentation of clinical data and stated that 'If the main study endpoint showed no differences in efficacy between two products, it would usually be misleading to highlight data from one of the other efficacy parameters measured which showed a difference unless this information is placed in context of the overall study findings'.

GlaxoSmithKline maintained that Seretide had been promoted in accordance with the above guidances, a practice which had been confirmed by the MHRA which reviewed all promotional material related to Seretide in the immediate pre-vetting period (May-September 2007) and then again in an audit (July-November 2012). At no point did the MHRA raise any concerns in the way in which the secondary endpoints had been portrayed nor that TORCH was described as a 'landmark' study.

GlaxoSmithKline submitted that as stated above, TORCH had been the subject of four complaints with the PMCPA and none of these related to the inappropriate use of secondary endpoints in promotional material.

GlaxoSmithKline noted in particular that in Case AUTH/2006/5/07 breaches of Clauses 7.2 and 7.4 were ruled as 'The Panel considered that overall the exhibition panel detailing the mortality data did not make it sufficiently clear that the data was not statistically significant particularly given the description of TORCH as a landmark study'. What was important to mention in this case was that at no time was the use of secondary outcome questioned by either the complainant or the PMCPA and even in this case the non-significance of the primary endpoint was mentioned albeit not sufficiently clear enough.

Secondary endpoints were routinely included in promotional material in the UK as they provided information which might be of particular interest to the health professional, allowing them to make informed decisions as to which treatment might be appropriate for individual patients. Information about the secondary endpoints in the TORCH study was of particular interest to health professionals in the therapeutic area of COPD as no currently available combination products had had a statistically significant impact on all-cause mortality and the secondary endpoints used in the TORCH study were frequently used as primary endpoints in other studies.

c) That Seretide promotion was accessible to the public

GlaxoSmithKline noted that the complainant had deliberately used the term healthcare professional in his/her search to access the site, as well as the acronym for the study TORCH, which had never been used in any non-promotional materials/websites for patients and which it would be reasonable to assume, that the general public did not know about.

The PMCPA guidance on Digital Communications stated that 'Generally speaking it would not be unreasonable for a company to try to ensure that its sites are ranked high on lists when the search is for that company or one of its medicines (brand or generic)'. The guidance also allowed for the use of search engine optimisation and meta data.

GlaxoSmithKline submitted that as the complainant had used the brand name Seretide and the acronym TORCH for the pivotal study relating to a GlaxoSmithKline product, it was not surprising that this was the first 'hit'.

When the search terms referred to above were entered into Google the following was displayed:

Seretide | Prescribing Seretide - Efficacy | Respiratory | GSK ...
hcp.gsk.co.uk/**pro**ducts/**seretide**/prescribing-**seretide**/efficacy.html
Seretide (salmeterol xinafoate/fluticasone propionate) efficacy information to support UK healthcare professionals in their daily practice. ... placebo (in a *post-hoc* analysis) (p<0.001). Read the TORCH study summary or the TORCH study in full ...

GlaxoSmithKline submitted that it was clear from the text highlighted in bold that this site was for health professionals who sought information about prescribing Seretide and was not one for the general public.

On opening up the website, the first page was displayed as follows:

> 'health.gsk. For UK Health Professionals.
>
> Not a Healthcare Professional? Visit our Public Site.'

GlaxoSmithKline submitted that once again it was made quite clear that the website was for UK health professional and that if the reader was not one, then they should visit the public site with the relevant URL provided.

Conversely, if the search terms Seretide and patients were entered into Google, the following was revealed https://www.google.co.uk/#q=patient+seretide. Here the first two entries were from the Medicines Compendium.com and related to the product information leaflet for the accuhaler and evohaler, the third entry from patientuk.com and the fourth from GlaxoSmithKline which stated the following:

> 'Seretide - | GSK Pharma UK | Public Site | (salmeterol ...
> public.gsk.co.uk/products/**seretide**.html.'

This website did not mention the TORCH data. GlaxoSmithKline therefore refuted a breach of Clause 23.1.

The content of the website

GlaxoSmithKline submitted that the complainant made no direct comment about the information contained on the Health.gsk website for health professionals but had drawn several yellow lines against those sections which he/she no doubt wished to bring to the PMCPA's attention.

These were the prescribing information for Seretide (which the Code required to be present for a health professional website), and brief information relating to TORCH, with the first statement being:

> 'TORCH was a 3 year study. The primary endpoint of the effect of Seretide 500 Accuhaler on all-cause mortality did not meet statistical significance; P=0.052'. This was then followed by the results of the two key secondary endpoints and a post hoc analysis and 'Read the TORCH study summary or the TORCH study in full.'

d) The responsible authorities seemed to have 'missed closer scrutiny' of the use of the TORCH study in promotion

GlaxoSmithKline was unclear what the complainant meant by 'responsible authorities'. Within the UK, however, the MHRA reviewed the TORCH study results in great detail as part of a regulatory submission. Following this review, the licence was broadened to allow for patients with an FEV1 <60% to be included and Section 5.1 of the Seretide SPC was updated with a new section relating to TORCH (both the design and the study results), which amounted to 30 lines of new text, as well as the inclusion of a tabulated summary of the results. Additionally, Seretide promotional materials were prevetted between 21 May and 3 September 2007 and all Seretide materials were submitted for an audit between July and November 2012. The MHRA's comments with respect to the TORCH data could be provided if required, but it did not criticise the use of secondary endpoints within the material.

GlaxoSmithKline therefore refuted the statement that the MHRA or indeed the PMCPA had not given close enough scrutiny to the TORCH data and its use in a promotional setting within the UK.

Overview and context of the publication

GlaxoSmithKline noted that the complainant stated that Gøtzsche 'Challenged both the design and analysis for the TORCH study and questioned the quality of the data derived'. GlaxoSmithKline noted that a similar publication by Gøtzsche appeared in the Journal of the Danish Medical Association in February 2014, where *inter alia*, he questioned whether Seretide should have been licensed for COPD. This article prompted a number of Danish health professionals to publish several articles refuting statements made by Gøtzsche; one of those health professionals was Professor Jørgen Vestbo, a member of the steering committee for the TORCH study at the time of its conduct and analysis and for which the original Danish version with accompanying English translation were provided.

GlaxoSmithKline noted that no complaint was ever made against GlaxoSmithKline Denmark about TORCH and the use of its secondary endpoints to the Ethical Board for the Danish Pharmaceutical Industry.

Summary

GlaxoSmithKline submitted that the complainant referred to the promotion of Seretide over the last six years in the UK and Europe but did not comment on any specific examples of promotional material which

he/she considered to be in breach of the Code. The complaint was based on an editorial by Gøtzsche which was very similar to the article published in a Danish journal earlier this year and for which the Danish affiliate was not found to be in breach of its local regulations.

GlaxoSmithKline therefore denied breaches of Clauses 2, 7.2, 7.4, 7.10, 9.1 and 23.1.

GlaxoSmithKline provided all Seretide materials that were in current use at the time of receipt of the letter on 8 August 2014. In addition, it had provided historical material relating to Seretide and the promotion of the TORCH clinical study which included the following 3 items:

COPD Secondary Care Campaign
Date of preparation November 2011

COPD Advertisement
Date of preparation February 2012

TORCH Leave piece
Date of preparation May 2011

GlaxoSmithKline explained that the TORCH study results first became available seven and a half years ago on 21 February 2007, so at this time, the results of this study would have been included in many promotional materials. However, the Code only required a pharmaceutical company to archive materials for three years after date of last use. In June 2010 GlaxoSmithKline introduced the electronic approval system called Zinc Maps, and a search of this database was undertaken on 18 August 2014. Several searches had been undertaken. Using the search term 'TORCH' in the section entitled 'Short description text' yielded five results – three of which related to clinical papers concerning the study and the other two, a leavepiece for general practitioners that was certified in both May and December 2011. As the complainant referred to 'Historical Journal Advertisements and promotional literature at booths and symposia', a search of all these items was undertaken. For advertisements 43 items were shown. Some referred to Avamys (fluticasone), others to the asthma indication and only one advertisement in February 2012 referred to TORCH. For exhibition panels, there were 12 items, most of which were very general in nature and none of them referred to TORCH.

The company trusted that the above material satisfied the need of the PMCPA to review all current Seretide promotional materials as well those that mentioned the TORCH study in the past.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedure such complaints were accepted and like all complaints, judged on the evidence provided by both parties. Complainants had the burden of proving their complaint on the balance of probabilities; as the complainant was anonymous and non-contactable it was not possible to ask the complainant for further information.

The Panel noted that GlaxoSmithKline had been asked to respond to Clause 7.10 in relation to an allegation that describing TORCH as a landmark study might have exaggerated its importance and thus not have encouraged the rational use of Seretide. The Panel noted GlaxoSmithKline's comments about this matter. The Panel did not consider that the complainant had made an allegation about the use of the term 'landmark' *per se*. The complainant referred to the perception that TORCH was a landmark study and then stated that 'it is probable that this promotion also shaped (rightly or wrongly) the perception of many UK HCPs and influenced key prescribing decisions ...'. In the Panel's view the complainant had not stated or inferred that the word 'landmark' contravened the Code. Indeed the complainant appeared to accept that the term may have 'rightly' influenced the perception of UK health professionals. The complainant bore the burden of proof. It was not possible to contact the complainant to clarify matters. The Panel therefore considered that there was no complaint in relation to the very narrow point about the principle of using the term 'landmark' to describe the TORCH study and thus it could not make a ruling about the use of the term landmark and Clause 7.10. The Panel noted that consideration of the term 'landmark' might nonetheless, be relevant when considering allegations about claims based on the secondary endpoints in materials within the scope of the complaint.

The Panel noted the complainant had not identified any specific materials other than pages from a website in relation to the allegation that the material therein was accessible to the general public. GlaxoSmithKline had been asked to provide all current Seretide material (including electronic material) and, if that did not encompass every secondary endpoint from the TORCH study which had been the subject of a promotional claim, it should also provide historical materials such that all such endpoints/claims were covered. GlaxoSmithKline explained that the TORCH study results first became available seven and a half years ago (21 February 2007) and its results would have been included in many promotional materials. The Code only required these to be archived for three years after the date of last use. The Panel noted that there was no such time limitation in relation to requests from the MHRA. In response to this complaint, GlaxoSmithKline provided *inter alia* all current Seretide materials. The company introduced an electronic approval system in June 2010. Relevant search terms had been used and according to GlaxoSmithKline all relevant materials were submitted.

The Panel noted that the complainant referred to Case AUTH/2006/5/07 and noted GlaxoSmithKline's submission on this point. The Panel noted that Case AUTH/2006/5/07 concerned the graphical depiction of the non-statistically significant 16% reduction in mortality on an exhibition stand. The Panel in Case AUTH/2006/5/07 had considered that overall the

exhibition panel did not make it sufficiently clear that the mortality data depicted was not statistically significant, particularly given the description of TORCH as a landmark study. The Panel considered that on glancing at the exhibition panel delegates would be struck by the prominent subheading 'Primary outcome - Seretide 500 Accuhaler survival result'. The results were then depicted in the graph which showed a visual difference between Seretide and the control group alongside an emboldened arrow and '16.5%' which was in a larger, bolder typeface than the explanatory text immediately beneath. A delegate who did not take the time to read the entire exhibition panel would be left with the impression that the 16.5% risk reduction was statistically significant. The Panel considered that graph was misleading and that its content could not be qualified by the text below. Breaches of the Code were ruled. The Panel noted that the issue in Case AUTH/2006/5/07 was different to that presently before the Panel, Case AUTH/2726/8/14.

The Panel noted that at its inception the TORCH study (Calverley *et al* 2007) was the largest ever multicentre, long-term chronic obstructive pulmonary disease study and the first to investigate the effect of the salmeterol/fluticasone propionate combination and its components on chronic obstructive pulmonary disease mortality. It was a prospective randomized double-blind trial comparing a combination regimen of salmeterol and fluticasone in a single inhaler with placebo, salmeterol alone or fluticasone propionate alone for three years. The primary endpoint was the time to death from any cause for the comparison between the combination regimen and placebo. Key secondary endpoints included the reduction in COPD morbidity and the difference in QoL, each between the combination regimen and placebo. Other endpoints included the difference in composite endpoint made up of overall mortality and COPD admissions, COPD-related mortality, clinic post-bronchodilator FEV1, other COPD exacerbation endpoints, health status and health utilisation. The reduction in death from all causes amongst COPD patients in the combination therapy group as compared to placebo did not reach the predetermined level of statistical significance. Treatment with the combination regimen resulted in significantly fewer exacerbations compared with placebo including those exacerbations requiring hospitalization. The combination regimen was also significantly better than each of its components alone in preventing exacerbations and these benefits were accompanied by sustained improvements in health status and FEV1. The study authors noted that the greater number of patients withdrawing from the placebo group was likely to have resulted in an underestimation of the effect of the combination regimen on all the secondary outcomes. The study authors also noted that the size of the TORCH study was modest compared with studies of mortality associated with other major chronic illnesses such as cardiovascular disease and thus the results of the mortality analysis should be viewed in this context.

The Panel noted that there was a *post-hoc* analysis of the TORCH study secondary endpoint data which was referred to in some of the materials provided by GlaxoSmithKline.

The Panel noted the allegation that in a promotional setting, it was misleading to make claims based on secondary endpoints from a study that did not meet its pre-defined primary endpoint. The Panel considered that, in principle, when a primary endpoint failed to achieve statistical significance it was not necessarily unreasonable to refer to secondary endpoint data so long as this was placed within the context of the overall study findings. The nature of the material might also be relevant.

The Panel examined the materials provided and only considered those items which referred to the secondary endpoint data from the TORCH study including the *post-hoc* analysis as these were the only items covered by the complaint.

The Panel examined the material published at Seretide.co.uk. The Panel noted that the 'Efficacy and Clinical Evidence' page (UK/SFC/005c/13) summarized clinical data from five studies including the TORCH study. Each reference to the TORCH secondary endpoint data was preceded by the statement 'The primary endpoint of the effect of Seretide 500 Accuhaler on all-adverse mortality did not meet statistical significance p=0.052'. The Panel considered that the secondary endpoint data was placed within the context of the study. No breach of Clauses 7.2 and 7.4 were ruled.

In relation to the 'Seretide campaign' materials the Panel noted that the Seretide TR Campaign pilot (UK/SFC/0025/14(1)) appeared to be a 24-page slide deck. Slide 12 onwards referred to Seretide in COPD. Slides 14 and 15 each headed '... And benefit over the long term' discussed the clinical benefits of Seretide 500 Accuhaler over three years with reference to the secondary endpoints of the TORCH study. Slide 16 introduced the TORCH study and made it clear that the primary endpoint did not achieve statistical significance. More detailed information about the TORCH study appeared at Slide 17. The Panel was concerned that the information about the primary endpoint of the TORCH study appeared after the slides discussing the secondary endpoint data. The Panel considered that the secondary endpoint data on Slides 14 and 15 could not take the benefit of the subsequent qualification about the non-statistically significant primary endpoint on Slides 16 and 17 and thus had not been placed within the context of the TORCH study. The slide deck was misleading. The misleading impression was incapable of substantiation. A breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that 'Seretide COPD slides for RVT' (UK/SFC/0389h/13) referred to Seretide in COPD in relation to NICE guidelines, clinical benefits and appropriate prescribing. Slide 4 'Seretide in COPD: Clinical benefits' included 'TORCH was a 3-year study. The primary endpoint of effect of Seretide 500 Accuhaler on all cause mortality did not meet statistical significance (p=0.052)' and discussed secondary endpoint data. Subsequent slides referenced the TORCH study in relation to health related quality of life score, three-year outcome data, and long-term benefits. It appeared that a reference to the TORCH study on the summary

Slide 13 in relation to rate of exacerbations was incorrectly referenced to Vestbo *et al* 2003. In addition, it appeared that a claim about the *post-hoc* analysis and lung function decline had been incorrectly referenced to Briggs *et al* 2010, a health economic analysis. The Panel noted that with the exception of Slide 4, none of the other slides which discussed clinical secondary endpoint data from the TORCH study had placed such data within the context of the non-statistically significant primary endpoint. The slide deck was misleading in this regard. The misleading impression was incapable of substantiation. A breach of Clauses 7.2 and 7.4 was ruled. The Panel considered that the referencing of this slide deck was confusing. Each slide had details of the referencing but the same number did not link to the same study consistently. For example, reference 1 was sometimes a reference to TORCH and in other slides was a reference to Vestbo.

The Panel noted that the COPD Cost-Effectiveness Slides (UK/SFC/0229/11(2)) was a presentation which discussed a multinational economic analysis of the TORCH study, (Briggs *et al* 2010) based on health outcome data including cost and EQ-5D utility data. The presentation did not appear to have any mention of clinical data from TORCH. The TORCH study was referred to on Slide 13. The Panel considered that whilst it would have been helpful to provide additional relevant information about the TORCH study on Slide 13, the failure to do so did not render that slide misleading or incapable of substantiation. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel then examined the historical material. The Panel noted that the historical material was certified between November 2011 and August 2013. It noted that the applicable Code would be the 2011 Code, or either of the 2012 Codes (first and second editions). The requirements of Clauses 7.2 and 7.4 were the same in all three Codes and the same in the 2014 Code.

The Secondary Care Campaign Detail Aid (ref UK/SFC/0207/11) included the statement 'TORCH was a three-year study. The primary endpoint of the effect of Seretide on mortality did not meet statistical significance p=0.052' at the beginning of every page which discussed the secondary endpoint data. The data had been placed in the context of the non-statistically significant primary endpoint. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that items UK/SFC/0150a/11 and UK/SFC/0150/11 were each designed to be made into cubes the sides of which discussed the TORCH study. The Panel did not have the final items. It was made clear on the Results 'All-cause Mortality' sections and Conclusion sections that the primary endpoint did not achieve statistical significance. No breach of Clauses 7.2 and 7.4 was ruled in relation to each item. This ruling also applied to the one page item, item UK/SFC/0040a/12, which was described as 'Seretide COPD DXS click – through content'. Again, the Panel did not have the final item or information about its use. In the absence of detailed allegations, the Panel made its ruling on the single page which discussed the non-statistical primary endpoint finding at the outset before the reference to secondary endpoint data. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel then examined the Primary Care Campaign iPad 2012 UK/SFC/0129/12(1). The Panel had no information about how it was used. The Panel accepted it was unlikely that all 77 pages would be displayed during a representative detail. Three pages headed '… and benefit over the long-term' discussed secondary endpoint data from the TORCH study in relation to lung function, rate of exacerbations and improvements in qualify of life. A highlighted box on the right of the first two of the three pages read 'TORCH study'. This appeared to be the first mention of the TORCH study. It was unclear whether this was a link to the TORCH study or information about it. No print out of any link had been provided with these 2 pages. In any event, in the Panel's view, any qualification necessary to ensure that a claim complied with the Code should be an integral part of the claim or within the visual field of the claim in question and not relegated to a link or footnote etc. A fourth page headed 'Seretide 500 Accuhaler improves QoL [quality of life] total score over 3 years' featured a graph showing the change from baseline in SGRQ total score over three years referenced to Calvery *et al*, 2007 (TORCH). There was no highlighted box referring to the TORCH study. The Panel considered that overall the secondary endpoint data was not sufficiently qualified by a reference to the primary endpoint. There was no reference to the primary endpoint data. The material was misleading. The misleading impression was incapable of substantiation. A breach of Clauses 7.2 and 7.4 was ruled.

The Panel examined the Secondary Care Campaign iPad 2012 (UK/SFC/0131/12(1)). The Panel noted the large number of pages but had no information about how representatives were directed to use the material. This was especially important given that there would be insufficient time to discuss all of the material with a health professional during an average detail. The material began with a detailed introductory section titled 'How good could Seretide make your patients feel?' which comprised 6 sections. Some of this material appeared to be similar to that referred to above. There were 10 detailed specialist modules including exacerbations, long-term efficacy, lung function and Seretide use. It was unclear whether all of the specialist modules such as 'Seretide or Symbicort' had been provided by GlaxoSmithKline. The Panel noted that sometimes the material referred to the non-statistically significant primary endpoint when discussing secondary endpoint data and sometimes it did not. The material was inconsistent in this regard and the reason for this inconsistency was unclear. The Panel noted that site architecture might be an important factor. The Panel noted a pop-up box headed 'Towards a Revolution in COPD health (TORCH) was a 3-year randomised multi-centred trial' gave detailed information about the study including, in bold, the primary non-significant outcome. To which pages the pop-up box was linked was unclear. However, the Panel noted its comments above about the use of pop up boxes. The Panel noted that two pages headed '… and benefit over the long-term' in the introductory

section discussed the reduced rate of lung function decline and reduced rate of moderate/severe exacerbations with reference to the TORCH study. A highlighted box 'TORCH study' appeared on the right-hand side. It was unclear whether this was a link to further information about the study and in this regard the Panel noted its comments above about pertinent information necessary for Code compliance appearing in a pop-up box alone. A further page in the introductory section also headed 'and benefits over the long-term' discussed data SGRQ from TORCH with no reference to the primary endpoint or highlighted TORCH tab. A subsequent page in the introductory section was headed 'Seretide 500 Accuhaler improves QoL total score over 3 years' and featured a graph adapted from the TORCH study. The study's primary endpoint result was not referred to. The Panel considered that the failure to refer to the non statistically significant primary end point was such that pages identified above in the introductory section of the secondary care ipad detail aid were misleading. The misleading impression was incapable of substantiation in relation to its reference to secondary endpoint data. A breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that site architecture was more difficult to decipher in the balance of the secondary care campaign ipad material which comprised the specialist modules. Most pages discussing TORCH secondary endpoint data featured the primary endpoint as a prominent and integral part of the page. In the absence of any detailed allegation from the complainant in relation to the secondary care campaign ipad 2012 detail and its layout and noting the complainant bore the burden of proof, the Panel considered the specialist modules provided were not misleading or incapable of substantiation in relation to secondary endpoint data and ruled no breach of Clauses 7.2 and 7.4.

With regard to the allegation that GlaxoSmithKline promotional material based on secondary endpoints from the TORCH study were accessible to the public, the Panel noted GlaxoSmithKline's response and in particular that the complainant's search terms had included 'healthcare professional'. The search had taken the complainant to the section on the GlaxoSmithKline website which stated, *inter alia*, 'For UK Healthcare Professionals, Not a Healthcare Professional? Visit our Public Site'. The Panel noted the supplementary information to Clause 25.1 'Access' which stated that a company website or sponsored website with unrestricted access must provide information to the public as well as health professionals with the sections for each target audience clearly separated and the intended audience identified. That a search including the terms 'health professional, Seretide and TORCH study' identified a promotional site for Seretide did not, in the Panel's view, mean that the site was therefore promoting Seretide to the public. Access to such sites did not have to be restricted to health professionals so long as the requirements in the supplementary information to Clause 25 were met. No breach of Clause 23.1 was ruled.

The Panel noted its rulings of breaches of the Code above. There did not appear to have been a consistent approach in relation to the certification of material which discussed secondary endpoint data from TORCH. Some material was qualified in relation to the non-statistically significant primary endpoint and some was not. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 and no breach was ruled accordingly.

Complaint received **7 August 2014**

Case completed **11 December 2014**