CASE/0381/11/24 *NO BREACH OF THE CODE*

COMPLAINANT v CHIESI

Alleged misleading claim in an email regarding Trimbow

CASE SUMMARY

This case was in relation to an alleged misleading claim about exacerbation rates in a promotional email for Trimbow (beclometasone/formoterol/glycopyrronium). The complainant alleged the claim, which related to a secondary endpoint, would mislead clinicians as (1) there was no mention of what the primary endpoint, nor study design, was (2) the endpoint was not a key secondary endpoint and was not mentioned in either the abstract or clinical trial registration and (3) the inclusion criteria of the study was much narrower than Trimbow's licensed indication.

The outcome under the 2024 Code was:

No Breach of Clause 5.1	**Requirement to maintain high standards at all times**
No Breach of Clause 6.1	**Requirement that information/claims/comparisons must not be misleading**
No Breach of Clause 6.2	**Requirement that information/claims/comparisons must be capable of substantiation**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint was received about Chiesi Limited from an anonymous, contactable complainant who described themselves as a healthcare professional.

COMPLAINT

The complaint wording is reproduced below with some typographical errors corrected:

"Dear PMCPA,

In the following email there is the following statement:

Trimbow pMDI 87/5/9 demonstrated similar rates of moderate to severe exacerbations vs. multiple inhalers (Fostair pMDI 100/6 + Spiriva® HandiHaler® [RR 1.01])[10]*

The asterisk is to a much smaller statement that states:

*Secondary endpoint[10]

There does not appear to be a mention of what the primary endpoint, nor study design was of where this claim is made.

The study is [URL 1] and the NCT [National Clinical Trial] of the trial is [URL 2].

What is interesting is not only is this a secondary endpoint, it is not the key secondary endpoint - such a minor endpoint it isn't even mentioned in either the abstract or the clinical trial registration.; the inclusion criteria of the study was also much narrower than the licenced indication of the product. All together, these things is evidence that a clinician would be misled by this presentation of the data."

When writing to Chiesi, the PMCPA asked it to consider the requirements of Clauses 5.1, 6.1 and 6.2 of the 2024 Code.

CHIESI'S RESPONSE

The response from Chiesi is reproduced below:

"Thank you for your letter dated 3 December 2024 relating to a complaint you have received concerning a claim made in an email distributed by Chiesi on 29 November 2024 entitled '*Are your adult patients with moderate to severe COPD struggling with multiple inhalers? (Contains promotional content)*' (the **Email**).

We take alleged breaches of the ABPI Code of Practice (the **Code**) very seriously and have investigated the allegations made. Accordingly, we have set out below responses to the specific requests you made of Chiesi in your letter dated 3 December and responses to the allegations made by the complainant.

1. <u>Details of how the material at issue was used</u>

The Email was prepared and approved for the target audience of nurses in primary and secondary care. The Email was transmitted by [named publisher], a healthcare professional and marketing services group engaged by Chiesi to circulate promotional materials to specific audiences of healthcare professionals. Each of the recipients had opted in to receiving such materials via a registration form and stated their preferences as to content type, having expressed an interest in respiratory healthcare. A copy of the Email and registration form can be found at [copies provided].

The purpose of the promotional email was to inform the recipients that patients currently on multiple inhaler triple therapy (ICS/LABA + LAMA) who have symptoms that are not adequately treated, or who are struggling to manage multiple devices, may benefit from a change in their therapy. This was highlighted through the claim: '*Trimbow pMDI 87/5/9 demonstrated similar rates of moderate-to-severe exacerbations vs multiple inhalers (Fostair pMDI 100/6 + Spiriva® HandiHaler® [RR1.01]*' (the **Claim**).

The Claim is in line with the licensed indication for Trimbow (**Trimbow**) (see the Summary of Product Characteristics for Trimbow pMDI 87 micrograms/5 micrograms/ 9 micrograms pressurised inhalation solution , and the Summary of Product Characteristics for Trimbow NEXThaler 88 micrograms/5 micrograms/ 9 micrograms per actuation inhalation power

(the **SPCs**)). In particular, please note paragraphs 4.1 of each of the SPCs (Clinical Particulars, Therapeutic Indications, Chronic Obstructive Pulmonary Disease (COPD)), which state:

> '*Maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1)*.'

2. <u>Copy of the certificate approving the material at issue and details of the qualifications of the signatories</u>

A copy of the certificate approving the material is at [copy provided]. You will see that the material was certified by both a medical signatory [redacted] and a business signatory [redacted].

Details of the qualifications of each of those signatories are below: [details provided]

3. <u>Copy of the Trimbow summary of product characteristics</u>

As mentioned earlier, copies of the relevant SPCs are provided at [copy provided] and [copy provided].

4. <u>Copy of the documents referenced by the complainant</u>

A copy of the document referenced by the complaint, being the Lancet article *'Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a couple-blind, parallel group, randomised controlled trial'*, by Vestbo J, et al. Lancet. 2017; 389: 1919-1929, is at [copy provided], (the **TRINITY Study**).

A copy of the trial referred to by the Complaint, being *'Efficacy of Fixed Combination of Beclometasone + Formoterol + Glycopyrrolate in Chronic Obstructive Pulmonary Disease, Trial ID NCT01911364'* is at [copy provided], (the **Trial**).

5. <u>The complaint</u>

The complainant references the following text from the Email:

Trimbow pMDI 87/5/9 demonstrated similar rates of moderate to severe exacerbations vs. multiple inhalers (Fostair pMDI 100/6 + Spiriva® HandiHaler® [RR 1.01])[10]*

The complaint then goes on to state:

a. that the asterisk is to a *'much smaller statement noting the secondary endpoint'* and that there *'does not appear to be a mention of what the primary endpoint'* is;
b. the Email does not mention the *'study design'*;

c. *'it is not the key secondary endpoint – such a minor endpoint it isn't even mentioned in either the abstract or the clinical trial registration'*;
d. *'the inclusion criteria of the study was also much narrower than the licenced indication of the product'*.

Chiesi has considered each of those comments and reviewed the material at issue (being the Email, the TRINITY Study and the Trial) together with the SPCs and past cases considered by the Panel (detailed further below). We hereby address each of the comments as follows:

a. Primary endpoint and secondary endpoint

Before addressing the particular allegations in the complaint, it is important to provide the Panel with an overview of the primary and secondary endpoints set out in the TRINITY Study, and their relevance.

The primary endpoint of the TRINITY Study was the moderate-to-severe exacerbation rate for the comparison of Trimbow pMDI (beclometasone/formoterol/glycopyrronium) with tiotropium. A secondary endpoint of the TRINITY Study was the moderate-to-severe exacerbation rate for the comparison of Trimbow with Fostair (beclometasone/formoterol) plus tiotropium.

While the primary endpoint is not relevant to the Claim, data from a secondary endpoint within the TRINITY Study is relevant to the Claim and therefore referenced within the Email in order to substantiate it. We are of the view that it is clinically relevant and of critical importance to include this this data in order to inform those healthcare professionals looking to optimise patients' inhaler therapy from multiple inhalers to single inhaler triple therapy.

While the primary endpoint for the study was found to be statistically significant in favour of Trimbow over tiotropium (RR 0.80 [95% CI 0.69-0.92], p=0.0025) (see figure 2a of page 6 of the TRINITY Study), we strongly believe that it was not misleading to only reference results from a secondary endpoint of the study when making the Claim. This is especially relevant given that both the primary and secondary endpoints each refer to rates of moderate-to-severe exacerbations.

We are of the firm opinion that there is no ambiguity in the Claim as to what the comparators were or what the rate ratio was (1.01 - which clearly indicates that there were similar rates of moderate-to-severe exacerbations with Trimbow compared to multiple inhaler triple therapy), and maintain that it does not mislead as to its significance due to the clear statement within the Email that this was a secondary endpoint of the TRINITY Study.

We believe this approach is in line with the requirements of Clauses 6.1 and 6.2 of the Code that '*information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous',* they '*must not mislead directly or by implication*' and are '*capable of substantiation*' and therefore does not breach either of those clauses of the Code.

The complainant comments that the asterisk referencing the secondary endpoint is to a *'much smaller statement noting the secondary endpoint'* and that there *'does not appear to be a mention of what the primary endpoint'* is.

In relation to those specific comments, we note that there is no requirement in the Code for companies to specifically state the primary endpoint of a study on occasions where a secondary endpoint is used, provided that the requirements of Clauses 6.1 and 6.2 are met. This concept is supported by past rulings and/or considerations of the Panel, examples of which are cited below. Case precedent also supports the use of a footnote to clarify that the Claim is based on a secondary endpoint.

In the cases cited below the Panel was of the opinion that the omission of the primary endpoint was not necessarily misleading, and that it was not unacceptable to clarify a secondary endpoint by use of a footnote (or without qualification (i.e. no footnote at all)) provided the primary endpoint was met, which it was:

- **AUTH/3686/8/22 – Complainant v Eli Lilly** : Regarding the absence of a primary endpoint, the Panel concluded no breach of Clause 6.1 on the basis that the complainant had failed to establish that the reference to a secondary endpoint of a trial, without stating what the primary endpoints of that study were, was misleading, and '*that the complainant had not stated why the omission of the primary endpoint, in the particular circumstances of this case, was misleading. The Panel therefore ruled no breach of Clause 6.1 in this regard.'* Please see the penultimate paragraph of that case.

- **AUTH/3665/6/22 – Anonymous Health Professional v Novartis :** Regarding the use of a footnote, the Panel stated: '*Since the primary endpoint was met, and that it was not unacceptable to use a secondary analysis to support a claim as long as it was not misleading, stating the fact this is a secondary analysis in the footnote was not unacceptable, and would not be qualifying the claim or materially changing the way a health professional interprets the information*.' Regarding the absence of a primary endpoint, the Panel concluded that *'the complainant had not established … that the omission of the primary endpoint and the failure to make it clear that the quality of life data was derived from a secondary endpoint and post hoc analysis was misleading and contrary to the requirements of Clause 6.1. No breach of Clause 6.1 was ruled.'*

- **AUTH/3635/4/22 – Complainant v Novartis :** Regarding the reference to a secondary endpoint '*The Panel noted that it was not unacceptable to use secondary endpoints without qualification to substantiate claims, whether such use was acceptable would be decided on a case-by-case basis bearing in mind amongst other things the quality standards in Clause 6*.' The Panel then went on to rule that *'The complainant had not established why the reference to quality of life in the second claim in question required qualification of its trial endpoint status as alleged and thus no breach of Clauses 6.1, 5.1 and 2.'*

In relation to the complainant's comment that 'the asterisk is to a much smaller statement', we note that it is not a requirement of the Code that the secondary endpoint be qualified, but nonetheless we assert that the statement is in a standard font size for any footnote and is in fact placed ahead of other references and footnotes in an effort to draw the

readers' attention to it. We strongly dispute the inference made by the complainant that the reference is not sufficiently clear.

In light of the above, it is therefore our firm view that:

- the absence of a primary end point reference, but the inclusion of a secondary endpoint reference, and denoting its status as such by use of an asterisk in the Email at issue is not misleading, as alleged by the complainant or at all;
- the Claim is accurate, balanced, fair, objective and unambiguous, clearly reflecting the appropriate evidence, and does not mislead the reader; and

therefore the Claim and its presentation in the Email is not in breach of Clauses 6.1 and 6.2 of the Code.

b. Study Design

We note that the complainant states that the Email does *'not mention study design'* alongside the Claim. Noting the requirements of Clauses 6.1 and 6.2 that claims must be '*accurate, balanced, fair, objective and unambiguous… and reflect evidence clearly', 'must not mislead either directly or by implication*' and *'be capable of substantiation'* we are of the opinion that there is no requirement to refer to study design for claims, provided the requirements of Clauses 6.1 and 6.2 are met.

As expressed in paragraph 5a. above, we firmly believe that the claim contained within the Email is capable of substantiation, that it does not mislead, and is therefore in line with the requirements set out in the Code.

We maintain that absence of the study design from the Email is not in breach of Clauses 6.1 or 6.2 of the Code.

c. Alleged absence of the secondary endpoint from the abstract of the TRINITY Study

The complainant contends that the secondary endpoint referenced in the Email was '*not the key secondary endpoint – such a minor endpoint it isn't even mentioned in either the abstract or the clinical trial registration*' (the 'abstract' referenced being the abstract of the TRINITY Study).

We dispute this allegation and take this opportunity to highlight that the following statement was included in the abstract of the TRINITY Study, with the relevant part underlined: '*Moderate-to-severe exacerbation rates were 0·46 (95% CI 0·41-0·51) for fixed triple, 0·57 (0·52-0·63) for tiotropium, and 0·45 (0·39-0·52) for open triple.'* This was included in both the Findings in the abstract (page 1, Findings paragraph, line 3), and the main Results (page 6, Results paragraph, line 22 and figure 2).

It is well understood amongst healthcare professionals that 'open triple' refers to use of multiple inhalers, and therefore we maintain that this secondary endpoint is clearly referred to in the TRINITY Study, being capable of identification and comprehension by healthcare professionals reading the TRINITY Study.

On this basis, it is our firm position that there has been no breach of Clauses 6.1 or 6.2 of the Code.

d. The inclusion criteria of the study was narrower than the licenced indication

In response to the allegation that the inclusion criteria for the TRINITY Study was '*much narrower than the licensed indication of the product*', we would like to highlight that the TRINITY Study is a key registration trial for the use of Trimbow in moderate-to-severe COPD patients (see full indication in section 4.1 of the SPCs).

We assert that the Claim accords fully with the licensed indication of Trimbow and, as such, this allegation is unfounded in circumstances where both the MHRA and the EMA exercised their regulatory powers to grant a licence on the basis of the TRINITY Study (a key registration trial).

6. <u>Conclusion</u>

In reliance upon the facts and matters set out above, we strongly deny all of the allegations raised by the complainant and respectfully submit that:

- the Email and the Claim made therein would not mislead healthcare professionals as to the significance of the secondary endpoint as alleged by the complainant or at all;
- the Claim is accurate, balanced, fair, objective and unambiguous, clearly reflecting the appropriate evidence;
- high standards have been maintained at all times; and
- accordingly, there has been no breach of Clauses 5.1, 6.1 and 6.2."

PANEL RULING

This case concerned a promotional email for Trimbow (beclometasone/formoterol/ glycopyrronium) which included the following claim highlighted by the complainant:

> *"Trimbow pMDI 87/5/9 demonstrated similar rates of moderate to severe exacerbations vs. multiple inhalers (Fostair pMDI 100/6 + Spiriva® HandiHaler® [RR 1.01])[10]*"*

The claim was referenced to the TRINITY Study (Vestbo et al., 2017), and the asterisk (*) linked to a small footnote reading "secondary endpoint".

The promotional email featured the subject line "*Chiesi Ltd: Are your adult patients with moderate to severe COPD [Chronic Obstructive Pulmonary Disease] struggling with multiple inhalers? (Contains promotional content)*" and featured the brand logo and indication for Trimbow at the top. Immediately beneath was a prominent heading which stated "*Do you see adult patients with moderate to severe COPD who struggle with multiple inhalers?*". This was followed by an image and description of a fictional patient, and a section titled "*How can inhaler choice impact your patients?*" which included information from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) along with information relating to multiple versus single

inhaler therapy. The claim in question appeared towards the end of the email, and was the last in a list of three boxed claims that appeared under an overarching statement that "*Trimbow is the only ICS/LABA/LAMA combination available as a pMDI [pressurised metered-dose inhaler] or NEXThaler (DPI [dry powder inhaler]) for your adult patients with moderate to severe COPD not adequately treated with ICS/LABA + LAMA via multiple inhalers*" and an image of the Trimbow inhalers.

Chiesi submitted the email was for the target audience of nurses in primary and secondary care to inform them that COPD patients currently on multiple inhaler triple therapy (inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) + long-acting muscarinic antagonist (LAMA)) who have symptoms that are not adequately treated, or who are struggling to manage multiple devices, may benefit from a change in their therapy [to a single inhaler].

The complainant alleged that the claim in question, which related to a secondary endpoint, was misleading due to the cumulative effect of the following:

1. there was no mention of what the primary endpoint, nor study design, was
2. the endpoint referred to was not a key secondary endpoint and was not mentioned in either the abstract or clinical trial registration
3. the inclusion criteria of the study was much narrower than Trimbow's licensed indication.

The Panel considered each aspect in turn.

1) <u>No mention of primary endpoint and study design</u>

The Panel noted the claim in question referenced the published TRINITY study (Vestbo et al, 2017), a 52-week double-blind, parallel-group, randomised, controlled trial in adult patients with moderate-to-severe COPD. Eligible patients had a post-bronchodilator forced expiratory volume in 1s (FEV1) of less than 50%, at least one moderate-to-severe COPD exacerbation in the previous 12 months, and a COPD Assessment Test total score of at least 10.

Patients were randomised to receive one of three treatment arms: tiotropium, "fixed triple" (beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide), or "open triple" (beclomethasone dipropionate/formoterol fumarate plus tiotropium).

The primary endpoint was the annual rate of moderate-to-severe COPD exacerbations for fixed triple therapy versus tiotropium, which was reportedly met, with the fixed triple superior to tiotropium with an adjusted rate ratio of 0.80 (95% CI 0.69-0.92; p=0.0025).

The secondary efficacy endpoint relevant to the claim was the rate of severe and moderate COPD exacerbations throughout 52 weeks of treatment, with the comparison of fixed triple versus open triple being prespecified. The Panel noted that the rates of moderate-to-severe COPD exacerbations were 0.46 per patient per year for the fixed triple, 0.57 for tiotropium, and 0.45 for the open triple. The adjusted rate ratio (RR) between fixed and open triple was 1.01.

The Panel noted Chiesi's submission that there was no requirement in the Code for companies to specifically state the primary endpoint of a study on occasions where a secondary endpoint was used, nor refer to study design for claims, provided that the requirements of Clauses 6.1 and 6.2 were met.

The Panel considered that it was not necessarily unacceptable to promote on the basis of secondary endpoint data; its acceptability depended on a number of factors including the context and nature of the trial, along with the manner in which it was presented. Whether the endpoint was met might be relevant.

The Panel took into account that the intent of the email was to communicate that some patients with moderate to severe COPD on multiple inhalers could benefit from switching therapy to a single inhaler. In this context, the Panel considered that the claim relating to fixed versus open triple was consistent with the findings of a prespecified TRINITY study secondary endpoint. The Panel noted that the primary endpoint, which was not directly relevant to the claim, had also achieved statistical significance.

While the Panel considered it may have been helpful to include details of the study design and primary endpoint in the promotional email, the complainant had not stated why the omission of this information, in the particular circumstances of this case, was misleading. It was not for the Panel to infer reasons on behalf of the complainant.

2) Endpoint not mentioned in abstract or clinical trial

The complainant alleged that the endpoint used to support the claim in question was not a key secondary endpoint and was such a minor endpoint that "*[the endpoint] isn't even mentioned in either the abstract or the clinical trial registration"*.

The Panel noted the methods section of the abstract of the TRINITY study described the study design along with the primary endpoint and stated that the ***key*** secondary endpoint was change from baseline in pre-dose FEV1 at week 52 *(emphasis added by Panel)*. The results section of the abstract reported findings for each of these endpoints and further reported *"Moderate-to-severe exacerbation rates were 0.46 (95% CI 0.41-0.51) for fixed triple, 0.57 (0.52-0.63) for tiotropium and 0.45 (0.39-0.52) for open triple"*.

The Panel noted that although the comparison for moderate-to-severe exacerbation rates, which underpinned the claim at issue, was not labelled in the abstract as a secondary endpoint, it was nevertheless clearly included. The full published study showed the findings graphically and included an adjusted rate ratio between the fixed and open triple: *"RR 1.01 (95% CI 0.85-1.21); p=0.89"*, as referred to in the claim in question.

In relation to the ClinicalTrials.gov registry entry, the Panel noted this outlined the TRINITY study and included headings such as *Study Overview*, *Participation Criteria*, and *Study Plan,* amongst others. The study plan section included design details and what the study was measuring, with the COPD exacerbation rate listed as the primary outcome measure and the pre-dose morning FEV1 listed as the secondary outcome measure. There was no reference to other prespecified secondary endpoints, including that relating to the claim at issue.

The Panel concluded that while the specific prespecified secondary endpoint underpinning the claim *"Trimbow pMDI 87/5/9 demonstrated similar rates of moderate to severe exacerbations vs. multiple inhalers (Fostair pMDI 100/6 + Spiriva® HandiHaler® [RR 1.01])[10]*"* did not appear within the registry, the exacerbation rates were reported within the abstract and the adjusted rate ratio was presented within the full published TRINITY study. The complainant had not established that the absence of endpoint data in the clinical trial registration or abstract meant

that a clinician would be misled. The Panel considered that the complainant had failed to discharge the burden of proof in relation to this aspect of their allegation.

3) Inclusion criteria of study were narrower than the licensed indication for Trimbow

The complainant alleged that the inclusion criteria of the TRINITY study were much narrower than Trimbow's licensed indication.

Chiesi submitted that the TRINITY study was a key registration trial for the use of Trimbow in moderate-to-severe COPD patients and that the claim in question accorded fully with the licensed indication of Trimbow.

The Summary of Product Characteristics (SPC) for Trimbow pMDI stated in Section 4.1, Therapeutic Indications:

> *"Chronic obstructive pulmonary disease (COPD)*
>
> *Maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist for effects on symptoms control and prevention of exacerbations see section 5.1)"*

Section 5.1, Pharmacodynamic Properties, described the TRINITY study as part of the clinical efficacy data.

The Panel noted its comments above regarding the population of the TRINITY study in that it included COPD patients with a post-bronchodilator forced expiratory volume in 1s (FEV1) of less than 50%, at least one moderate-to-severe COPD exacerbation in the previous 12 months, and a COPD Assessment Test total score of at least 10. Further to this, the Panel noted that patients also had to have used an inhaled corticosteroid plus long-acting beta2-agonist, or inhaled corticosteroid plus long-acting muscarinic antagonist, or inhaled long-acting beta2-agonist plus long-acting muscarinic antagonist, or long-acting muscarinic antagonist monotherapy for at least 2 months before screening.

While the inclusion criteria for the TRINITY study appeared to represent a subgroup of adults with moderate-to-severe COPD, as defined in Section 4.1 of the Trimbow SPC, the Panel considered it had not been established that the inclusion criteria for the study was "much narrower" than the licensed indication for Trimbow, nor how this rendered the claim misleading in the particular circumstances of this case. It was not for the Panel to infer reasons on behalf of the complainant.

Misleading presentation of the data (Clause 6.1, 6.2 and 5.1)

The complainant alleged that, *"all together",* aspects 1-3 above constituted *"evidence that a clinician would be misled by this presentation of the data"*. The Panel noted its comments for each point above and took into account the broader context that the focus of the promotional email was on switching from multiple inhalers to single inhaler therapy, rather than a review of the TRINITY study.

Within the context of the email as a whole, the Panel considered the complainant had failed to establish why the inclusion of the claim *"Trimbow pMDI 87/5/9 demonstrated similar rates of moderate to severe exacerbations vs multiple inhalers (…[RR 1.01])"* meant that a clinician would be misled. The Panel, therefore, on the evidence before it, ruled **no breach of Clauses 6.1 and 6.2**.

Given its rulings of no breaches of the Code above, and without any further allegations or evidence, the Panel considered that the complainant had not established that Chiesi had failed to maintain high standards. The Panel ruled **no breach of Clause 5.1**.

Complaint received **29 November 2024**

Case completed **5 December 2025**