CASE AUTH/3719/12/22

CHIESI/DIRECTOR v GSK

GSK promotional materials

CASE SUMMARY

This case concerned a banner advertisement that appeared on the Trelegy website, superiority claims for Trelegy, the use of data from a GSK network meta-analysis (NMA) and a claim for the Ellipta device. Chiesi also alleged GSK was in breach of an undertaking provided in a previous case.

Chiesi appealed five of the Panel's rulings of no breach of the Code relating to the alleged breach of undertaking and one iteration of a superiority claim for Trelegy.

The outcome under the 2021 Code was:

No Breach of Clause 2 [upheld at appeal]	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**
No Breach of Clause 3.3 [upheld at appeal]	**Requirement to comply with an undertaking**
No Breach of Clause 5.1 [upheld at appeal]	**Requirement to maintain high standards**
Breach of Clause 6.1 [Panel's no breach ruling overturned at appeal]	**Making a misleading claim**
Breach of Clause 6.2 [Panel's no breach ruling overturned at appeal]	**Making an unsubstantiated claim**

The Panel ruled breaches of the following Clauses of the 2021 Code in relation to an ambiguous superiority claim, the presentation of data from the NMA, and a claim for Ellipta which created a misleading impression:

Breach of Clause 5.1	**Failing to maintain high standards**
Breach of Clause 6.1 (x7)	**Making a misleading claim**
Breach of Clause 6.2 (x3)	**Making an unsubstantiated claim**
Breach of Clause 6.3	**Failing to ensure artwork conforms to the letter and spirit of the Code**
Breach of Clause 14.1 (x2)	**Making a misleading comparison**
Breach of Clause 14.4	**Implying that a medicine has some special merit**

The Panel did not consider that GSK's portrayal of data from its NMA was such that it had brought discredit upon, or reduced confidence in the pharmaceutical industry or that the banner advertisement was misleading or disparaging of another company's medicine. The Panel ruled no breach of the following Clauses of the 2021 Code:

No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**
No Breach of Clause 5.1	**Requirement to maintain high standards**
No Breach of Clause 6.1	**Requirement that information must be accurate, up-to-date and not misleading**
No Breach of Clause 6.6	**Requirement that another company's medicines must not be disparaged**

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 from Chiesi Limited about GSK UK Limited.

As the complaint concerned an alleged breach of undertaking that aspect of the complaint proceeded in the name of the Director.

COMPLAINT

Chiesi submitted that, in accordance with Paragraph 5.3 of the PMCPA's Constitution and Procedure, it recently completed formal inter-company dialogue with GSK. Also in accordance with the Constitution and Procedure, Chiesi offered inter-company dialogue at a senior level in an attempt to resolve several matters which included both informing GSK about an alleged breach of the Code as well as Chiesi's intention to make a formal complaint to the PMCPA if unresolved.

Chiesi therefore wished to escalate four separate matters to the PMCPA as a result of this unsuccessful inter-company dialogue:

1 **Banner Advertisement** (GSK website).

2 **Claim '*Only triple with 21st century molecules with in-class superiority*'** (GSK website).

3 **Use of data from a network meta-analysis (NMA) publication** (GSK website and LeavePiece).

4 **Ellipta claim** (GSK website).

1 Banner Advertisement

Chiesi submitted that the Trelegy landing page on the GSK Pro website contained a five-part banner advertisement which featured the pink coloured Fostair inhaler (together with two other inhalers) in close proximity to a bold, prominent headline of 'Climate Emergency'. It was Chiesi's assertion that this was both misleading as well as disparaging towards Fostair (Chiesi), Braltus (Teva) and Salamol (Teva) [brand identities of images used confirmed by GSK prior to formal inter-company dialogue].

During Chiesi's informal dialogue, GSK shared its perspective that a visitor to the website would never associate the inhalers with a climate emergency, the narrative on frame 4 provided sufficient context to justify the presence of the headline, and that the headline was only prominent in frame 4 (when the inhalers were in black and white). However, Chiesi did not agree for the following reasons:

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- Given the climate change/inhaler switch messages constantly in the news/social media, the various local and national recommendations related to inhaler prescribing interventions for environmental reasons, and the prominence of the capitalised headline "**CLIMATE EMERGENCY**" on all five frames (irrespective of the differences of the colouring on each frame), Chiesi strongly believed that a user of the website was very likely to associate the inhalers illustrated in the advertisement with the newspaper headline.
- Given the bold text in the newspaper headline, Chiesi asserted that the statement was prominent in all frames irrespective of whether the rest of the frame was black and white. Furthermore, Chiesi argued that it was likely that not all visitors to the website would sit through all 5 frames. In order to completely understand each image and its accompanying text a visitor to the website would need to spend approximately 30 seconds viewing the advertisement, and approximately 22 seconds if they were to only reach frame 4. However, browsing research suggested that only 4% of digital advertisements are viewed for more than 2 seconds. Therefore it was not unreasonable to assume that the majority of visitors would not remain on the advertisement for long enough to contextualise frame 4 and therefore would likely make conclusions from frames 1 and 2 alone, where the inhalers were in colour immediately adjacent to the bold, prominent headline without a visual partition. This assumption was also supported by the statement in Clause 12.1 supplementary information: "***the first part of an advertisement…..is often the only part of the advertisement that is seen by readers***".'

Without further context, which was not available on this frame, Chiesi strongly believed that this imagery was misleading and therefore in breach of Clause 6.1.

Chiesi also asserted that the inclusion of the pink coloured Fostair inhaler, and the notable absence of GSK inhalers, was intentional and disparaging to Fostair. During Chiesi's informal dialogue GSK indicated that the choice of Fostair (and other inhalers) was due to the UK market share of the respective inhalers, a position reiterated in the correspondence dated 4 November 2022. Although Chiesi accepted that Fostair was the UK market leader for the inhaled corticosteroid (ICS)/long acting beta agonist (LABA) class, it also noted GSK's avoidance in providing an explanation for why the market leaders for the short acting beta agonist (SABA) and long-acting muscarinic antagonist (LAMA) classes had not also been included within the imagery (Ventolin [GSK] and Spiriva [Boehringer Ingelheim], respectively). This was particularly pertinent as SABA's account for up to 70.2% of the total UK inhaler market (Wilkinson *et al*, 2021;), high SABA usage (≥3 canisters/year) was associated with sub-optimal asthma control

(Bloom *et al*. 2020;), and sub-optimal asthma control was associated with 3-fold larger total carbon footprint (and an 8-fold larger excess carbon footprint) compared to a well-controlled asthma patient (CARBON programme. Presentation ERS2021).

In correspondence dated December 2022, Chiesi noted that GSK referred to '***GSK has updated the SABA imagery to depict an inhaler more closely aligned to GSK's SABA***'. However, Chiesi disputed that GSK had made any changes to the imagery of the inhalers in the banner advertisement update (Original banner advertisement, Updated banner advertisement).

Given that GSK manufactured and marketed inhalers in all 3 categories of the inhalers illustrated in the advertisement (LAMA: Incruse; ICS/LABA: Seretide and Relvar; SABA: Ventolin), and none of which were depicted within the advertisement despite Ventolin being the UK SABA market leader, Chiesi asserted that GSK intentionally chose competitor inhalers for inclusion in the imagery to avoid the association between their products and the climate emergency described.

Chiesi also noted that GSK had chosen to include a global claim on the same page of the GSKPro website '***World's no.1 prescribed (COPD) triple therapy inhaler***', which it accepted was accurate based on global prescribing data, however, this was not accurate according to UK-based prescribing data which demonstrated 57.4% market share for Trimbow compared with 41% market share for Trelegy. Chiesi therefore questioned whether the use of global prescribing data on the same webpage as the banner advertisement, which used UK prescribing data, was misleading to a busy health professional.

Chiesi therefore believed that the choice of inhalers was intentionally misleading and disparaging to competitors and thus in breach of Clauses 6.1 and 6.6. Furthermore, this deliberate unfair practice was outwith the spirit of the Code and therefore in breach of Clause 5.1.

In correspondence dated November 2022, GSK acknowledged Chiesi's concern and proposed an update to the newspaper headline to read '**NHS DRIVE TO NET ZERO**'. Whilst Chiesi noted in its letter dated November 2022 that the updated headline might be reflective of the current position of the NHS and potentially more acceptable, it did not agree that this update alone, without further updates to the choice of inhalers illustrated within the advertisement (specifically to include GSK inhalers), satisfactorily addressed its concerns.

Furthermore, Chiesi noted that before completion of inter-company dialogue, GSK had not only updated the headline to read '**NHS DRIVE TO NET ZERO**', but that GSK had now also added a clear strapline '**INHALER CARBON FOOTPRINT IN THE SPOTLIGHT**' which was not discussed during the inter-company dialogue. Chiesi strongly believed that this was an intentional omission in the correspondence dated November 2022 and December 2022, as the strapline clearly now linked inhalers to the newspaper headline. This also strengthened Chiesi's assertion that there was an intentional link between the headline and the inhalers depicted in the image, which Chiesi asserted was both misleading and inaccurate given that pMDI inhalers contributed less than 0.05% to global emissions.

Chiesi provided an image summarising the intercompany dialogue.

2 *Claim 'Only choice with 21st century molecules with evidence of in-class superior components'*

Two pages on the GSK Trelegy website contained variations on the claim '***Only triple with 21st century molecules with in-class superiority***'. Chiesi did not believe that the second aspect of this claim '***evidence of in-class superior components***' could be substantiated, for the reasons set out below.

Chiesi asserted that the claim as it stood would be perceived by a busy health professional as though all three individual components had evidence of in-class superiority compared to the components contained within the two alternative triple therapies in the ICS/LABA/LAMA class (Trimbow and Trixeo), which could not be substantiated. This perception was backed up by the image immediately below the claim on the Trelegy molecules page with an illustration of the 24 hour action of each individual component.

In correspondence dated November 2022, GSK asserted that it was not appropriate to compare the individual components of Trelegy, as neither vilanterol nor fluticasone furoate were licensed as monotherapies in COPD[chronic obstructive pulmonary disease]. Whilst Chiesi accepted that neither vilanterol or fluticasone furoate were licensed as monotherapies, they strongly believed that the claim as it stood ('***evidence of in-class superior components***') would be perceived by a busy health professional as though all three individual components had evidence of in-class superiority which could not be substantiated.

In correspondence dated November 2022 GSK also asserted that there was no claim, or inference made, stating that any component of Trelegy was superior to either Trimbow or Trixeo. Chiesi, however, did not accept GSK's position that there was no indirect comparison with Trimbow or Trixeo. Given the claim started with '***only choice***' was on the Trelegy website, and was immediately adjacent to a prominent image of Trelegy Ellipta, which in turn was next to both Trimbow and Trixeo, then it would be considered 'in-class' for triple therapy. As such, then it was not unreasonable for a busy health professional with limited time, to assume that GSK referred to Trelegy's superiority over Trimbow and Trixeo which could not be substantiated by head-to-head studies.

Chiesi noted that, instead of comparing each individual component as would be reasonable, given the claim, GSK had, instead, chosen to compare various combinations of components (i.e., ICS/LABA, LABA/LAMA, LAMA). Whilst Chiesi maintained its position that the claim required substantiation of the superiority of each individual component, it also highlighted that only the ICS/LABA + LAMA component would be a viable licensed combination for the treatment of COPD, given that there was no ICS monotherapy licensed for COPD. Therefore, Chiesi asserted, similar to GSK's challenge, that it was not relevant to compare ICS monotherapy within the context of this claim, that it was also not relevant to compare LABA/LAMA combination therapy as LABA/LAMA + ICS was not a viable licensed combination for the treatment of COPD. GSK had chosen not to address this point raised in correspondence dated November 2022.

Notwithstanding the previous comments, Chiesi also highlighted a few areas of concern regarding the data GSK used to substantiate their ICS/LABA, LABA/LAMA and LAMA claims (Chiesi referred to a data summary table provided):

- **ICS/LABA component**: GSK had utilised Vestbo *et al* 2016 to substantiate the claim of superiority of FF/VIL, however, Chiesi questioned the relevance of this study to substantiate this claim for the following reasons:

- The study compared FF/VIL against standard of care, and demonstrated a significantly lower rate of moderate or severe exacerbations with FF/VIL when compared to standard of care. However, the publication did not declare any breakdown of what standard of care consisted of, therefore, Chiesi asserted that it could not be used to substantiate comparisons between any specific components of Trelegy, Trimbow or Trixeo.
- The study was carried out between March 2012 and October 2014, when the predominant competitor in the marketplace was Seretide (fluticasone propionate/salmeterol; neither molecule of which was part of Trelegy, Trimbow or Trixeo) and therefore Chiesi questioned the relevance to the combinations available on the marketplace today.

- **LABA/LAMA component**: GSK had utilised Maltais *et al* 2019 and Feldman *et al* 2017 to substantiate their claim of superiority of UMEC/VIL, however, Chiesi asserted that although superiority was demonstrated in Feldman *et al* 2017 for a secondary endpoint, only non-inferiority was demonstrated for the majority of primary endpoints. Furthermore, Maltais *et al* 2019 failed to meet non-inferiority in one of its co-primary endpoint (Chiesi referred to further details below and in its data summary table). Chiesi therefore strongly believed that these studies could not be used to demonstrate superiority of UMEC/VIL over GLY/FORM (the comparison of the LABA/LAMAs contained within Trelegy vs Trimbow/Trixeo):

    - Maltais *et al* 2019 was a randomized double-blinded non-inferiority study comparing UMEC/VIL and GLY/FORM, with superiority testing only to be carried out should non-inferiority be met. The study only met non-inferiority in one of its endpoints:

        - Non-inferiority was met for peak FEV_1 (superiority was not met).
        - Non-inferiority was not met for morning pre-dose trough FEV_1.
        - GLY/FORM had a faster onset of action versus UMEC/VIL ($p < 0.0001$).

    - Feldman *et al* 2017 was designed as a randomized, open-label cross-over non-inferiority study to compare UMEC/VIL and TIO/OLO in the Per Protocol (PP) population, with superiority testing only to be carried out should non-inferiority be met. The study met its primary endpoint of non-inferiority in the PP population:

        - Chiesi noted that superiority was met in trough FEV_1 in the intent-to-treat (ITT) population, however, given that this was a secondary endpoint, Chiesi questioned whether this study could be used to support a claim of superiority, especially in the absence of a clear reference to the primary endpoint.

- **LAMA component**: GSK had utilised Feldman *et al* 2016 to substantiate their claim of superiority of UMEC over other LAMAs, however, Chiesi asserted that there were no head-to-head studies of which Chiesi was aware comparing the two components of the current single inhaler triple therapies (ie UMEC vs GLY), and the indirect

evidence demonstrated pockets of superiority for both UMEC and GLY when compared to TIO[tiotripium]:

- Feldman *et al* 2016 demonstrated superiority of UMEC compared with TIO on trough FEV_1 at day 85, but non-inferior weighted mean FEV_1 over 0-24hrs post-dose at the same time point and no difference in patient reported outcomes. Similar safety profiles were observed between the two groups.
- Chapman *et al* 2014 demonstrated faster onset of action of GLY compared to TIO, significantly lower total COPD symptom score versus patients on TIO after 12 weeks ($p = 0.035$), and comparable efficacy in other endpoints (TDI focal score, SGRQ total score, rescue medication use, rate of COPD exacerbations and safety).

In correspondence dated December 2022 GSK drew attention to the substantiation provided immediately below the claim of '***in-class superior components***'. Whilst Chiesi acknowledged that there was some information provided below the claim to clarify the comparison was with ICS/LABA, LABA/LAMA and LAMA, Chiesi disputed that this information alone provided adequate substantiation of the claim for the following reasons:

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- The clarification text did not make clear the primary endpoint of each study, so the reader was not clear as to how superiority was demonstrated for each component.
- For the LABA/LAMA component, superiority was not demonstrated in a primary endpoint in either Maltais et al 2019 or Feldman et al 2017. Furthermore, as described above, in the case of Maltais et al 2019 one of the co-primary endpoints was also not met. This detail was not clear in the clarification text.
- Although Chiesi did acknowledge that GSK had included an asterisk to add a footnote to the clarification text to describe that one of the endpoints of Maltais et al 2019 was non-inferior, the same asterisk also referred to an improvement in trough FEV_1. Chiesi asserted that improvement (or superiority) was not a claim that could be made from Maltais et al 2019 given it did not meet its co-primary endpoint of non-inferiority with respect to trough FEV_1 (which had to be met according to the study protocol for superiority to be claimed).
- Similarly, although Chiesi acknowledged that the secondary endpoint in Feldman et al 2017 demonstrated superiority, the primary endpoint of non-inferiority had not been referred to in the clarification text to put the claim into context.
- Chiesi also questioned the readability of a footnote included within the clarification text, as well as the use of two single asterisks within the same claim which referenced two different pieces of additional information (i.e. ***'based on global date of first use***' and '***Anoro demonstrated improvement on the co-primary endpoint of trough FEV_1 while peak FEV_1 was similar***').
- Chiesi also noted that this asterisk and footnote had only been included on the GSKPro Trelegy molecules Page and not on the landing page.'

Given the discussion above, Chiesi strongly believed that there was no substantative body of evidence to support the claim that Trelegy, or any molecule of which was superior to either Trimbow or Trixeo, and that this claim was misleading, not capable of substantiation and therefore in breach of Clauses 6.1 and 6.2.

Chiesi provided an image summarising the intercompany dialogue.

3 Misleading use of data from a network meta-analysis (NMA) publication

Two pages on the GSK Trelegy website, one video hosted on the GSK Trelegy website and one leavepiece contained variations of claims of '***superior lung function improvement***' or '***greater annualised moderate/severe exacerbation reduction***' vs '***other COPD single-inhaler triple therapies***'. These claims were referenced to a recently published network meta-analysis (NMA; Ismaila *et al*. 2022), within which Trelegy was compared indirectly with Trimbow and Trixeo, and reports on lung function and exacerbation endpoints at 12 and 24 week timepoints. Chiesi believed that these claims were an exaggeration of the evidence base, were misleading to health professionals and could not be substantiated for the reasons set out below.

*Claim 1: '**Greater annualised moderate/severe exacerbation reduction vs. other COPD single-inhaler Triple Therapies**'*

Ismaila *et al* 2022 demonstrated a significant reduction in exacerbation rate when Trelegy was compared to Trixeo (IRR 0.62 (95% CI 0.45, 0.86); p=0.0044), however, there was no statistically significant difference when compared to Trimbow (IRR 0.73 (95% CI: 0.51, 1.04); p=0.0774). The lack of statistical significance with Trimbow was acknowledged by GSK in correspondence dated November 2022. Despite the lack of clinical or statistical significance, claims on GSK materials included the broad claim: '***greater annualised moderate/severe exacerbation reduction vs. other COPD single-inhaler triple therapies***'.

Chiesi strongly believed that this claim implied that there was evidence to support an improvement in exacerbation rate with Trelegy compared to all triple combinations which was not the case from this NMA [network meta analysis], or in fact in any other published evidence. This was particularly pertinent given Trimbow 87/5/9 pMDI was the UK market leader amongst single-inhaler triple therapies and therefore Chiesi firmly believed this broad exaggerated claim to be misleading to health professionals, incapable of substantiation and therefore in breach of Clauses 6.1 and 6.2.

With regard to the imagery, Chiesi referred specifically to Clause 6.3 which stated that '***Graphs and tables must be presented in such a way as to give a clear, fair, balanced view of the matters with which they deal***' and Clause 6.3 supplementary information (SI) which required that '***differences which do not reach statistical significance must not be presented in such a way as to mislead***'. Chiesi also referred to the wording in Clause 14.1: '***A comparison is only permitted in promotional material if it is not misleading***' and Clause 14.1 SI: '***Critical references to another company's products are accurate, balanced, fair etc and can be substantiated, they are acceptable under the Code***'. Chiesi asserted that GSK had used imagery to illustrate this claim which included large prominent percentages illustrated in bold colours which mimicked the results of significance, therefore, increasing the likelihood that alongside the headline 'EXACERBATION REDUCTION' claim that the wrong conclusion may be drawn. Furthermore, the audio recording/subtitles on the video stated '***Trelegy showed a favourable 27% reduction***', further increasing the likelihood of the wrong conclusion being drawn.

In correspondence dated November 2022, GSK referred to three accommodations made in materials to highlight the differences in statistical significance between the Trixeo and Trimbow data. Whilst Chiesi acknowledged that GSK had made some accommodations in certain materials, it firmly believed that it was too small and often not immediately adjacent to the

pictorial of the percentage reduction in exacerbations to impact on the conclusion drawn by a busy health professional. Further details of the accommodations appear below:

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- **"Numerically" fewer is used with the font in bold**
    - Whilst Chiesi accepted that in some instances "numerically fewer" had been used, Chiesi asserted that this is not always the case.
- **P-value is stated**
    - Whilst Chiesi accepted that a p-value was stated somewhere on the same page as the claim, Chiesi also asserted that this was not always immediately adjacent to the claim. For example, the position of the claim on the GSK website was such that a healthcare professional would need to scroll down the page to see the statistical particulars as these were not adjacent to the claim and therefore the non-significant results would not be immediately apparent to the reader rendering the claim misleading.
- **Words "not-significant" stated in bold font**
    - Whilst Chiesi accepted that "non-significant" was sometimes stated, this was not always the case and not always in bold.'

Taking into account all of the above, Chiesi strongly asserted that use of the claim 'Greater annualised moderate/severe exacerbation reduction vs. other COPD single-inhaler triple therapies' did not reflect all the available evidence (Chiesi referred to 'exaggeration of available evidence' section for full details) in an accurate, balanced, fair and objective manner and was a misleading comparison of Trimbow and Trelegy and was in breach of Clauses 6.1, 6.2, 6.3 and 14.1 of the 2021 ABPI Code.

Chiesi provided an image summarising the intercompany dialogue.

*Claim 2: '**Lung function improvements and exacerbation reductions assessed in a network meta-analysis vs other single inhaler triple therapies**'*

Despite the absence of a significant difference in exacerbation reduction between Trelegy and Trimbow (as discussed above), a GSK leavepiece contained a general broad claim: '***Lung function improvements and exacerbation reductions*** assessed in a ***network meta-analysis vs. other single-inhaler triple therapies***'. Chiesi strongly believed that this claim implied that there was evidence to support an improvement in exacerbation rate *AND* lung function with Trelegy compared to all triple combinations.

In correspondence dated November 2022 Chiesi noted GSK's assertion that the claim related to the objective of the NMA (as opposed to the results) and highlighted additional wording used immediately below the claim, namely that '***Indirect comparison data, the limitations of these studies should be taken into account. While AEs across the respective single-inhaler Triple Therapy studies were similar in incidence and type across treatment arms, no formal evaluation through statistical analysis was undertaken***'.

Chiesi did not, however, agree that the most likely conclusion drawn by a busy health professional was that it was a statement of a study design, and it questioned the relevance of highlighting the lack of statistical evaluation of AEs [adverse events] when considering lung function and exacerbation specifically.

Chiesi noted that the claim was used in a series of four adjacently positioned claims, and the first three articulated significance-related claims. Chiesi strongly believed that by having this last claim, which was not associated with statistical significance, alongside the first three claims, it would not be unreasonable for a busy health professional to assume all four claims were supported by statistically significant data, and thereby would likely be misled by what was represented within the item at issue.

Chiesi also asserted that the use of the non-bold text for '***assessed in a***' enhanced the first half of the claim '***lung function improvements and exacerbation reductions***', and made it more likely for a busy health professional to assume that there were significant improvements in the NMA in both lung function AND exacerbation for Trelegy over all other single-inhaler triple therapies (ie Trimbow and Trixeo). However, as described above, and acknowledged by GSK in correspondence dated November 2022, Trelegy only demonstrated superiority over Trixeo in relation to exacerbation reduction (and not Trimbow).

Therefore, Chiesi strongly believed that the claim, as it stood, was not a fair, accurate and balanced representation of the data in the Ismaila 2022 NMA, nor of any other published evidence, and therefore a breach of Clauses 6.1, 6.2 and 14.1 of the 2021 ABPI Code.

Chiesi provided an image summarising the intercompany dialogue.

Exaggeration of available evidence

Chiesi asserted that not only was the data presented biased, but also that it was not a fair representation of the wider evidence base. There were five NMAs which had been used to compare triple therapies (Ferguson *et al* 2020, Bourdin *et al* 2021, Lee *et al* 2021, Rogliani *et al* 2022 and Ismaila *et al* 2022), and only the GSK NMA demonstrated any difference between the fixed triple therapies. Chiesi acknowledged that the other NMAs utilised difference methodologies, and that in some materials these alternative NMAs were referred to in footnotes, however, this did not negate the misleading nature of communicating data around this NMA which, according to Clause 6.1, '***must be based on an up-to-date evaluation of the evidence and reflect that evidence clearly***'.

Chiesi also noted that during the narration in a Trelegy video hosted on the GSKpro website, as well as the language used during GSK symposiums when this data was discussed, named professor made strong, broad statements such as '***Meta-analysis is now widely recognised as a useful tool by national and international policy making bodies and by guideline developers……such a comparison would be important to us as clinicians as this provides insights that could inform our treatment decisions within the single inhaler triple therapy class for COPD patients***', '***This analysis shows that Trelegy could offer favourable benefits versus other single inhaler triple therapies with regards to exacerbation reduction and lung function improvement. These are important results to take into consideration when selecting triple therapy for your patients with COPD***' and '***This NMA will help clinicians in their choice of triple therapy for the optimal management of their patients with COPD***'. Given the concerns raised above, Chiesi strongly believed that

this narrative was over-emphasising the importance of this NMA, especially given that it did not reflect all of the evidence in an accurate, balanced, fair and objective manner.

In correspondence dated November 2022, GSK disagreed that Ismaila *et al* 2022 was not a fair representation of the wider evidence base, and asserted that this NMA was aligned with the body of existing evidence. Chiesi, however, strongly disagreed for the following reasons:

- GSK had omitted to respond directly to Chiesi's assertion that there were five NMAs which had been used to compare triple therapies (Ferguson *et al* 2020, Bourdin *et al* 2021, Lees *et al* 2021, Rogliani *et al* 2022 and Ismaila *et al* 2022), and only the GSK-sponsored NMA demonstrated any difference between the fixed triple therapies.
    - In correspondence dated December 2022 GSK referred to a footnote included on certain materials relating to the data from the NMA: '***other NMAs exist which differ in their methodology and study inclusion which do not show any statistical significance between different SITTs***'. However, Chiesi noted that the footnote was not incorporated on every material, and never immediately adjacent to the claim. Given the Code requirement in Clause 6.1 that '***claims should not be qualified by the use of footnotes and the like***', Chiesi strongly believed that the inclusion of this footnote in certain materials did not mitigate the requirement to accurately reflect the evidence base.

- There was no head-to-head data backing up superiority of <u>each</u> of the components as discussed earlier in Chiesi's response (as part of the claim around '***in-class superiority***') predominantly due to the absence of each component being licensed for COPD as a monotherapy.
- The only component available as monotherapy for COPD was the LAMA component, however, no head-to-head studies existed between glycopyrronium and umeclidinium. Furthermore, as discussed earlier in Chiesi's response (as part of the claim around '***in-class superiority***'), indirect evidence comparing both LAMAs against tiotropium demonstrated pockets of superiority for both umeclidinium and glycopyrronium over tiotropium, and therefore could not substantiate a claim of superiority of umeclidinium versus glycopyrronium.
- Chiesi disagreed with GSK that the comparisons of all the combinations of the components licensed for COPD were capable of substantiating a claim of superiority (Chiesi referred to the discussion as part of the claim around '***in-class superiority***' for further details).
- Chiesi was aware of no evidence, published or otherwise, that described a significant improvement in exacerbation for any molecule within Trelegy, or combination thereof, compared to Trimbow or Trixeo.

In correspondence dated November 2022, GSK asserted that the narration provided by [named professor] in the NMA video '***accurately contextualises the relevance of the NMA***'. Chiesi, however, did not agree, as there were statements such as '***Trelegy could offer favourable benefits versus other single inhaler triple therapies with regards to exacerbation reduction and lung function improvement. These are important results to take into consideration when selecting triple therapy for your patients with COPD***', with no corresponding discussion of the four NMAs which did not demonstrate any difference between the fixed therapies.

Taking into account all of the above, Chiesi strongly believed that the claims made by GSK when communicating the Ismaila NMA were not a fair and accurate representation of the body of existing evidence, and therefore were in breach of Clause 6.1.

It was also of concern to Chiesi that this was the second instance of which it was aware relating to misleading Trelegy claims which did not accurately reflect the evidence base. In the first instance (Case AUTH/3260/10/19), the Panel found GSK in breach of Clauses 7.2, 7.3 and 7.4 (2019 ABPI Code; equivalent to Clauses 6.1, 6.2 and 14.1 of 2021 ABPI Code) for making a general claim of '***Improvements in QoL vs ICS/LABA***', implying evidence compared to all ICS/LABA combinations for COPD when the evidence base was very specific (Trelegy vs Symbicort). In accordance with the PMCPA Constitution and Procedure (Clause 7.1 of the 2021 Code), GSK signed an undertaking at the time that, *inter alia*, included taking all possible steps to avoid a similar breach of the Code in the future. Chiesi asserted that this error would be considered a breach of this undertaking, and was therefore also in breach of Clause 3.3. A breach of undertaking reflected a lack of high standards and brings discredit upon the industry and thus additional breaches of Clauses 5.1 and 2 were cited.

Chiesi provided an image summarising the intercompany dialogue.

Chiesi raised its significant concerns regarding the reliability and robustness of the NMA analysis (peer reviewed and published in Ismaila *et al* 2022), which it believed called into question the reliability of the result and thereby of its use in any promotional materials by GSK. This was particularly relevant when considering whether the NMA was a fair reflection of the wider evidence base, especially given the availability of four alternative NMAs which did not demonstrate any significant difference between the fixed triple therapies. These concerns are summarised below:

- The PRISMA flow chart for the study demonstrated that after an abstract search GSK added 13 records retrospectively, including 11 GSK CSRs[Clinical Study Report], whereas neither AstraZeneca nor Chiesi were approached to similarly include additional CSR datasets. Chiesi, therefore, asserted that the addition of GSK records fundamentally biased the results of the NMA:

    - In correspondence dated December 2022, GSK stated that the CSRs were not included in the NMA, however, the PRISMA diagram clearly stated inclusion at the eligibility stage. Furthermore, in the results section Ismaila *et al* 2022 described that '***in total, 93 publications (80 journal articles, 11 clinical study reports, and two trial records) reporting on 31 different trials were included in the SLR. Following a feasibility assessment, a total of 23 trials identified from the SLR and internet searches were included in the NMA***', and the CSRs were not specifically listed in the 'not relevant' box of excluded trials. It therefore remained Chiesi's assertion that data from these CSRs were included in the NMA (possibly by addition of data to the relevant trial publication as opposed to relying on data included only within the publication as would be the case with competitor studies) thereby creating a bias in the results.

- The analysis included three Chiesi studies with Trimbow which all had endpoints at 12, 26 and 52 weeks. However, all three studies were disconnected by GSK from the

network except at 12 weeks. With such a significant proportion of the data missing from the analysis comparing Trelegy to Trimbow, this called into question the robustness of this analysis, in particular, for drawing conclusions which informed promotional claims which, in this regard, would be misleading to a busy health professional.

- The analysis utilised a frequentist weighted regression-based approach following Rucker, and although it used both a fixed effect and random effects model (as described on the ATS posters 478 and 649, it only reported on the fixed effects model. It was Chiesi's understanding that a fixed effect model should only be used to compare studies with similar study designs and patient populations, which was not the case between the triple studies, whereas a random effects model should be used to account for differences between study design. In particular, GSK studies had a much more severe patient population at baseline which would have created a more favourable platform to demonstrate a greater degree of clinical improvement than in a less severe population, and therefore biasing the results accordingly. Therefore, the choice to only communicate the results from the fixed effects model was misleading.

In correspondence dated November 2022 GSK articulated their choice for choosing a fixed effects model was due to several large studies informing the network. Chiesi questioned whether 2 large studies by AstraZeneca [ETHOS; Trixeo] and GSK [IMPACT; Trelegy], and not Chiesi [Trimbow], were sufficient justification to drive a model intended to compare Trelegy versus both Trixeo and Trimbow. GSK, however, omitted to address why the results of the random effects model were not reported, or how the random effect model accounted for the differing study designs and patient populations between the different triple therapy studies. In particular, the more severe patient population at baseline in the GSK studies would have created a more favourable platform on which to demonstrate a greater degree of clinical improvement than a less severe population, and therefore biased the results accordingly.

4 Ellipta claim

Two pages on the GSKpro website contained a claim '***Don't settle for a MDI, when you can give the preferred, easy-to-use Ellipta device***'.

Chiesi asserted that this claim was not accurate and substantiable for the following three reasons:

a) Chiesi asserted that the use of the word '***the***' could not be substantiated by the weight of the evidence and did not relate to a clear fact about a medicine:

   - Chiesi specifically referred to Clause 14.4 and its supplementary information referred to the requirement that '***superlatives must not be used except in those limited circumstances where they relate to a clear fact about a medicine***' and for the word '***the***' to be substantiable in order for its use to be acceptable.
   - Divergent data was fairly common in relation to patient preference studies, as they were heavily influenced by the set up of the study, the patient population chosen, the exact devices chosen, as well as the exact questions asked. With this in mind, Chiesi strongly believed that such studies could never be used to imply a special merit, quality or property of a single device.

Therefore, Chiesi asserted that patient preference studies should never be used to back up a claim including the word '***the***'.

Chiesi provided an image summarising the intercompany dialogue.

b) Chiesi asserted the weight of the evidence did not back up the broad claim of '**preferred**' when making a comparison between the Ellipta device and pMDIs [pressurised metered dose inhaler]:

- Chiesi specifically referred to Clause 6.1 which required '***information, claims and comparisons must be an accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly***'.
- Chiesi noted that GSK had chosen to use a study published in 2016 by Palen *et al* to substantiate the claim, which was a patient preference study comparing the use of Ellipta with other DPIs [dry powder inhaler] and a placebo pMDI. However, Chiesi asserted that this patient preference study was not genereralisable to the pMDI choice available in the marketplace today. In particular, the pMDI used within the study required shaking before use and did not have a dose counter; both were factors which influenced ease of use and patient preference, but neither of which was true for many pMDIs on the marketplace today.
- In contrast to this study, Chiesi noted there were other studies which showed patient preference for pMDIs:
    - Ohbayashi *et al* 2021, where Flutiform pMDI demonstrated a significantly higher satisfaction and preference levels than Relvar Ellipta in elderly asthmatic patients (average 74 years). This was especially relevant as COPD was usually considered a disease of the elderly, however, the average age of patients included in Palen *et al* 2016 was 41 years for the pMDI vs Ellipta arm which was significantly lower than the age of the average COPD patient.
    - Ciciliani *et al* 2019, which also demonstrated a significantly higher patient satisfaction with the pMDI device compared to the Ellipta device ($p<0.001$). This was especially evident in the elderly population, with an average age of 77.
    - Chiesi asserted that the age of the patient was more relevant than whether a patient had asthma or COPD, as manual dexterity deteriorates with age (Carment *et al* 2018) and therefore any patient preference study between devices should be relevant to the age group where the device was to be utilised.
- Given the above contrasting evidence, Chiesi strongly believed that the weight of the evidence did not substantiate the broad claim of '***preferred***'.
- Chiesi also questioned whether the term '***preferred***' could be used in a promotional claim when Trelegy Ellipta was not the market leader for triple therapy (British Pharmaceutical Index market share data indicated the overall market share for Trimbow pMDI was 57.4% and Trelegy Ellipta is 41%), which suggested that the device was not the preferred option within the marketplace.

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Chiesi provided an image summarising the intercompany dialogue.

c) Chiesi asserted that the initial part of the claim, '***don't settle for a MDI***', could be viewed as disparaging to pMDIs, and such a recommendation could not be substantiated (either by clinical guidance, efficacy and/or safety data):

   - Chiesi specifically referred to Clause 6.1 as above.
   - Chiesi also highlighted that not all patients could generate the required level of inspiratory flow to activate a DPI (Usmani *et al* 2019), and therefore discouraging pMDI use might have a patient safety implication.

Taking into account the points above, Chiesi believed this claim was in breach of Clause 6.1 and 14.4 of the Code.

When writing to GSK, the Authority asked it to consider the requirements of Clauses 2, 3.3, 5.1, 6.1, 6.2, 6.3, 6.6, 14.1 of the 2021 Code, Clauses set out and cited by Chiesi in its complaint.

RESPONSE

GSK submitted that it believed that various elements of the complaint had been resolved during inter-company dialogue and so was surprised to see it form part of this formal PMCPA complaint and asked the Panel to consider whether it should be set aside as resolved rather than be ruled upon.

1 Banner Advertisement

Background

This was a 5-frame rotating image (copies of the original visual that was the subject of ICD and an updated version were provided) designed to illustrate the profile of a typical COPD patient, including highlighting the well-known position that there was a need for us all to reduce our environmental impact.

The NHS Sustainable Development Unit (SDU) first formally reported on the carbon footprint of the NHS in 2016 with a recognition that inhalers formed a significant part of emissions from the procurement of goods and services analysis. As part of the Environmental Audit Committee F-gas inquiry 2017-18, the SDU confirmed that Metered Dose Inhalers (MDIs) made up approximately 3.5% of NHS emissions. In response, the government agreed that low global warming potential (GWP) inhalers should be promoted in the NHS. The launch of the Delivering a 'Net Zero' National Health Service report in 2020, the new Greener NHS National Programme, had taken over the work of the SDU and section 3.4.1 of the report was dedicated to the NHS strategy on low carbon inhalers. Indeed, there was an NHS England financial incentive specifically to reduce the number of MDIs prescribed as a proportion of all inhalers in BNF Chapter 3, excluding salbutamol, which specifically stated '*This indicator recognises PCNs for a reduction in the number of MDI prescriptions, as a percentage of all non-salbutamol inhaler prescriptions*'.

The advertisement in question aligned with this approach.

To find resolution during inter-company dialogue, GSK agreed to change both the 'Climate Emergency' headline and the visual to include clear display of GSK's short-acting bronchodilator (SABA) which it believed had brought the matter to a close. Therefore, Chiesi's continued complaint about the original headline 'Climate Emergency' would appear to be unfounded as it agreed the change 'NHS DRIVE TO NET ZERO' '*is acceptable*' in inter-company dialogue letter dated November 2022.

However, in this current formal complaint to the PMCPA Chiesi now said the subheading 'Inhaler carbon footprint in the spotlight' clearly linked inhalers to the headline. As outlined above and further below, inhalers were clearly linked to the NHS drive to net zero and, as such, GSK did not believe the statement was misleading or inaccurate.

The purpose of the advertisement was to show visitors to the website an array of devices typically being used by an individual COPD patient. It was not intended to represent all possible devices but chose a typical patient sitting at their table with several different inhalers representing the various medications a patient might be using to control their COPD. The purpose was to show a patient who could potentially be prescribed Trelegy (COPD inadequately controlled on dual therapy, and therefore simplify their treatment regimen by reducing the number of inhalers required to be taken as maintenance therapy and, at the same time, reduce the carbon footprint by moving away from a higher global warming potential inhaler (pressurised metered dose inhalers – pMDI) to one with lower global warming potential inhaler (Trelegy) which was a dry powder inhaler (DPI). It was accepted that DPIs had lower global warming potential (ie, were 'greener' or 'lower carbon') than pMDIs (British Thoracic Society position paper on environment and lung health).

The National Institute for Health and Care Excellence (NICE) and the NHS advocated changing to lower carbon inhalers where appropriate. The patient image in the advertisement had three inhalers; an ICS/LABA inhaled corticosteroid/long acting beta agonist (ICS/LABA), a long-acting muscarinic antagonist (LAMA) and a short-acting beta agonist (SABA). Chiesi was concerned that the ICS/LABA was recognisable as Fostair and was therefore being disparaged as it was in association with a headline referring to the climate impact of inhalers which they believed was misleading and inaccurate. Chiesi appeared to assert that pMDIs had a negligible impact on the environment when this was in direct contrast to the government and the NHS plan which made clear that *a 'shift to lower carbon inhalers will deliver a reduction in 4%'* – the greatest impact a single change would make to the NHS carbon footprint.

NICE published a decision aid in 2019 'to encourage the use of greener inhalers'. This marked the first time that health professionals were directly encouraged to speak with patients about the carbon footprint of inhalers when considering their treatment options. Thus, clearly it was neither misleading nor inaccurate to link inhalers to climate change or the NHS drive to net zero as it was a widely accepted connection that both NICE and NHS wished to support clinicians to tackle and, as such, GSK denied breaching Clauses 6.1 and 6.6.

<u>Fostair was a pMDI – a higher carbon inhaler than dry powder inhalers</u>

Using a pink MDI in the visual was not an attempt to disparage Fostair, but illustrated the market-leading ICS/LABA, alongside a commonly prescribed LAMA dry powder inhaler and a blue reliever MDI. Fostair was a pMDI and was therefore a higher carbon inhaler than a dry powder inhaler and therefore it was not disparaging to include it in the visual as changing away from pMDIs where clinically appropriate was entirely in line with NHS and NICE guidance.

Chiesi believed there were deliberately no GSK inhalers in the picture, but the purpose of the advertisement was to encourage changing to a GSK inhaler, Trelegy. Having chosen the market leading ICS/LABA (Fostair) as it was an MDI, there would be no sense in showing a GSK ICS/LABA as no patient would be on more than one ICS/LABA and the visual was to represent one patient, not the availability of all types of inhalers. Chiesi appeared concerned that market leaders of all classes were not depicted, but again this was to illustrate one individual patient – who would not automatically be prescribed the market leader for every category of inhaler. GSK wanted to reflect that many patients were on a mixture of device types including both MDIs and DPIs, and therefore chose to depict both in the advertisement. The most prescribed combination was Fostair (ICS/LABA MDI) with Spiriva (LAMA soft mist inhaler). The second most common was Fostair with Braltus (LAMA DPI) which was the combination depicted. It was not unreasonable to have the patient on the market-leading ICS/LABA with a commonly prescribed LAMA, and a SABA, as was the case for many individual patients.

The blue reliever MDI was chosen to represent a salbutamol MDI, which could be Ventolin (a GSK product, or one of the numerous branded or unbranded generic alternatives, many of which looked like the originator. The picture was clearly drawn and stylised, not a photograph, and was not intended to exactly replicate a particular inhaler but gave the busy reader the visual impact of a patient having their inhalers in front of them, to reinforce the possibility of simplifying treatment. The original visual had one spacer in it but GSK added its Volumatic spacer to appease Chiesi during inter-company dialogue and it had hoped the updated visual had satisfied their requests.

GSK denied that the choice of inhalers was *'intentionally misleading and disparaging to competitors*' but represented a not unreasonable selection of inhalers for a COPD patient. As such, GSK denied breaches of Clauses 6.1 and 6.6. As GSK did not believe it had engaged in '*deliberate unfair practice*' that was *'outwith the spirit of the Code*', it also denied a breach of Clause 5.1.

Unclear complaint

Within the complaint about the Banner advertisement, Chiesi referred to a claim on the same page of the GSKPro website, '*World's No.1 prescribed COPD triple therapy inhaler*' which it accepted was accurate. GSK was unclear exactly what Chiesi's complaint was or how health professionals would be misled, and no clause was cited in relation to it. Chiesi confirmed it accepted the accuracy of the claim, and it was abundantly clear within the claim that it referred to global prescription data not UK-specific data. The banner advertisement discussed above was separated from the '*World's No.1 prescribed COPD triple therapy inhaler*' claim by the indication statement and three boxes containing text, icons and links to further information. The banner advertisement itself made no claim regarding market share and referred to the use of UK data when highlighting the need for most patients on triple therapy having to manage once and twice daily inhalers concurrently. GSK did not believe any UK health professional would be misled in any way.

2 'Only choice with 21st century molecules with evidence of in-class superior components' [sic] and 'Only triple with 21st century molecules with in-class superiority' [sic]

Both claims alleged by Chiesi were incorrectly cited. The first claim was '*Only choice with 21st century molecules and evidence of in-class superior components*' ('and' not 'with'), and the second was '*The only choice with 21st century molecules & evidence of in-class superior components*' ('choice' not 'triple'; 'superior components' not 'superiority') as could be seen on the relevant Chiesi and GSK Enclosures. Immediately underneath both was text to elucidate the component comparisons (which were for the relevant COPD licenced ICS/LABA, long-acting muscarinic antagonist/long-acting beta agonist (LAMA/LABA), and LAMA components of Trelegy (Relvar, Anoro and Incruse).

Chiesi asserted that the claim '*evidence of in-class superior components'* was misleading and could not be substantiated as it believed a busy health professional would assume this meant that the superiority for each component was over the specific components of the two other single inhaler triple therapies available (Trimbow) and Trixeo. This was not what the claims said – there was no mention of Trimbow or Trixeo or their specific components – it simply asserted that components of Trelegy had shown superiority over other members of the same class, not specifically those contained in Trimbow or Trixeo and went on to outline those comparisons immediately below. Triple inhaler therapy could be delivered by single inhalers (60% market share) or using multiple inhalers (40% market share). Trelegy competed with both single and multiple inhaler triple therapy, not only Trimbow or Trixeo.

Chiesi claimed this '*perception is backed up by the image immediately below the claim on the Trelegy molecules page with an illustration of the 24-hour action of each individual component*' but did not explain how this backed up its alleged perception. The image of the 24-hour duration of action of each of the molecules contained in Trelegy gave non-comparative, topline information about their pharmacodynamic action and also clearly identified that both fluticasone furoate and vilanterol were not licensed as individual components in COPD. This reinforced GSK's position that the comparisons of in-class superior components related to the licensed use of GSK medicines, ie, the GSK ICS/LABA (marketed as Relvar) had shown superiority over another ICS/LABA, the GSK LAMA/LABA (marketed as Anoro) had shown superiority versus another LAMA/LABA, and the GSK LAMA (marketed as Incruse) had shown superiority over another LAMA.

Thus, each of the components of Trelegy that were authorised for COPD had evidence of in-class superiority as outlined immediately below the claim where the three component classes (ICS/LABA, LABA/LAMA and LAMA) were listed:

> *'ICS/LABA: Relvar (fluticasone furoate/vilanterol) vs twice daily ICS/LABA LABA/LAMA: Anoro ▼Ellipta (umeclidinium bromide/vilanterol) vs Spiolto & improvements vs Bevespi* LAMA: Incruse▼Ellipta (umeclidinium bromide) vs Spiriva *Anoro demonstrated improvement on the co-primary endpoint of trough FEV1 while peak FEV1 was similar.'*

Chiesi '*acknowledge that there is some information provided below the claim to clarify the comparison is with ICS/LABA, LAMA/LABA AND LAMA*' thus agreeing that the claim was clear what the comparisons were, but went on to say '*Chiesi dispute that this information alone provides adequate substantiation of the claim for the following reasons:*'. Thus it appeared Chiesi accepted the claim was clear about what the comparisons were but that they were not adequately substantiated in the material itself and alleged breaches of Clauses 6.1 and 6.2. GSK believed the claim was accurate, balanced, fair, objective, unambiguous and not misleading in accordance with Clause 6.1. GSK noted that Clause 6.2 required that '*Any*

information, claim or comparison must be capable of substantiation' (GSK's emphasis). It did not mandate that the substantiation formed part of the material.

ICS/LABA (Relvar, the fluticasone furoate/vilanterol component of Trelegy demonstrated significant reduction in the mean rate of moderate/severe exacerbations (P=0.047) vs twice daily ICS/LABAs (GP choice) as acknowledged by Chiesi. As the publication Vestbo *et al* did not itemise which ICS/LABAs were used, Chiesi asserted it could not be used to substantiate comparisons between specific components of Trelegy, Trimbow or Trixeo and as the market leader at the time of the study was Seretide (fluticasone propionate/salmeterol) whose molecules were not included in Trelegy, Trimbow or Trixeo, they *'question the relevance'.* As mentioned above, the claim was not saying the superiority was specifically versus Trimbow or Trixeo components. The evidence clearly demonstrated in-class superiority of the ICS/LABA component of Trelegy over other members of the same class. Even if every patient had been on Seretide in the study, the claim would still be true as the claim was that the components of Trelegy having in-class superiority, not that they specifically had in class superiority over Trimbow or Trixeo components.

LABA/LAMA (Anoro, the umeclidinium bromide/vilanterol component of Trelegy (SPC, Enclosure 17)) demonstrated superiority versus another member of the same class, TIO/OLO, as acknowledged by Chiesi. However, Chiesi implied this data could not be used as it was a secondary endpoint. There was no restriction on the use of secondary endpoints or the requirement to include the primary endpoint unless it would be misleading not to do so. However, the conclusion of the Feldman 2017 study at issue stated, *'…superiority was observed for the primary end point of trough FEV1 at week 8 with UMEC/VI compared with TIO/OLO in patients with symptomatic COPD.'* which substantiated the claim relating to LABA/LAMA superiority and showed it was a primary endpoint, rebutting Chiesi's claims.

The other study used in the claim was Maltais *et al* which Chiesi appeared to misunderstand as it stated that the study '*failed to meet one of its primary endpoints*' and '*the study only met non-inferiority in one of its endpoints'* and that this was the reason this study *'cannot be used to demonstrate superiority of UMEC/VIL over GLY/FORM'.* This AstraZeneca study was a non-inferiority study looking to confirm non-inferiority of GLY/FORM (AstraZeneca's Bevespi) over UMEC/VIL not the other way round. The study failing to meet a primary endpoint was a reflection of GLY/FORM not performing as well as UMEC/VIL and did not mean that UMEC/VIL could not claim superiority if that had been shown.

Thus, GLY/FORM failing to meet a non-inferiority endpoint showed superiority of UMEC/VIL over GLY/FORM as per the CHMP guideline 'Points to consider on switching between superiority and non-inferiority'. *'If the 95% confidence interval for the treatment effect not only lies entirely above -Δ but al*so above zero then there is evidence of superiority in terms of statistical significance at the 5% level ($p<0.05$)' which was the case here.

As stated in the Maltais results section, *'For the change from baseline in morning pre-dose trough FEV1, the treatment difference for GFF MDI versus UV DPI in the PP analysis set was − 87.2 mL (97.5% CI − 117.0, − 57.4; Table 2); non-inferiority was not demonstrated as the 97.5% CI was below the margin of − 50 mL. Findings for trough FEV1 in the full analysis set were consistent with those for the PP analysis set'.*

GSK therefore believed both Feldman (2017) and Maltais supported the contention that UMEC/VI had shown superiority versus other members of the LABA/LAMA class and denied breaches of Clauses 6.1 and 6.2.

LAMA component (Incruse, the umeclidinium component of Trelegy had been shown to be superior to a member of the LAMA class, tiotropium, as stated in the conclusion of the study, Feldman 2016, *'UMEC 62.5 µg demonstrated superior efficacy to TIO 18 µg on the primary end point of trough FEV1 at day 85.'*. The claim made clear which LAMA was the comparator (Spiriva (TIO)) so GSK did not believe a reader would be mistaken into thinking the claim related to GLY (the LAMA component of Trimbow and Trixeo) as Spiriva was the most prescribed LAMA and well known to the health professional audience as it had been available for two decades.

The claim clearly stated that (and was capable of substantiation) Trelegy was the only triple inhaler to have both attributes of being compiled of 21st century molecules (as agreed by Chiesi in inter-company dialogue and not in dispute here) and to have evidence of superiority for all its COPD licensed components (ICS/LABA, LAMA/LABA and LAMA). The claim did not state or imply that individual Trelegy components were superior to individual Trixeo or Trimbow components.

As such, GSK did not believe it had been misleading breaching Clause 6.1 and the claim was capable of substantiation in accordance with Clause 6.2.

3 Misleading use of data from a network analysis (NMA)

GSK submitted that there were no head-to-head comparisons of Single Inhaler Triple Therapy (SITT) for COPD. NMAs allowed comparison of different therapies in the absence of head-to-head studies and 5 had been done in this area. However, there were differences in how NMAs were carried out which could impact their applicability and relevance (GSK provided a summary table comparing different network meta-analyses, their funding souce, the number of studies included, assumptions made and studies missing from the analysis).

The GSK NMA was the largest, most robust NMA to date and included all relevant studies that fitted the inclusion criteria and reflected the licensed indication for Trelegy. The methodology was in line with the Cochrane principles for NMAs. Contrary to Chiesi's assertion, GSK could confirm that no Clinical Study Report data were used in any of the final analyses as per the author's email.

The four other NMAs were unable to find a statistically significant difference between the single inhaler triple therapies, but their methods had limitations that might have made them less likely to be able to differentiate and it was essentially due to 2 reasons:

'1 Excluding key trials - therefore the NMA is not an accurate presentation of the available data **and/or**

2 Making invalid assumptions e.g., assuming all ICS/LABAs and/or LAMA/LABAs are the same. This would impact the analysis as then you are only able to detect the incremental benefit of one different component rather than all 3 as you're essentially

> assuming that 2 thirds of the drugs are comparable, and the clinical efficacy difference sits with only one component of the triple therapy.'

Ferguson *et al* and Woo Lee *et al* omitted ETHOS (n= 8573) which was an AstraZeneca Trixeo phase 3 registration study from their networks. The recent Rogliani *et al* NMA had very narrow inclusion criteria and therefore only included 4 studies forming a very small network and omitting FULFIL (n= 1,810) a GSK Trelegy phase 3 study from its analysis. It was important to include the most up-to-date available body of evidence within an NMA to ensure that the analysis was robust, and the results provided were a more accurate representation of clinical studies.

Bourdin *et al* (the updated version of Ferguson *et al* to include ETHOS) was the only other NMA that had a large body of evidence but, as stated in their manuscript, one of their limitations was that they assumed all LABA/LAMA's had the same efficacy, an assumption they had based on previous NMA's not RCTs [randomised controlled trials]. Whereas GSK knew from head-to-head RCTs that this was not the case and there were intraclass efficacy differences between LABA/LAMA's as discussed above and shown below:

> Umeclidinium/Vilanterol had shown superior efficacy in improving lung function in three head-to-head studies vs other LABA/LAMA's:
>
> - *'…superiority was observed for the primary end point of trough FEV_1 at week 8 with UMEC/VI compared with TIO/OLO in patients with symptomatic COPD.'* as discussed above (Feldman GJ *et al* 2017)
> - UMEC/VI was superior to GLY/FORM as discussed above (Maltais F *et al*. Adv Ther. 2019)
> - UMEC/VI was superior to IND/GLY as IND/GLY failed to achieve non-inferiority Kerwin *et al*, Lung 2017).

This was further reinforced by the Ismaila LAMA/LABA NMA, which showed favourable long-term efficacy with UMEC/VI. There were significantly greater improvements in trough FEV_1 vs most other dual comparator therapies at 12 weeks (8 out of the 11 comparators), and all dual comparators at 24 weeks. This NMA used the same methodology as the Single inhaler triple therapy NMA. The LAMA/LABA dual Ismaila NMA showed significant efficacy improvements for UMEC/VI versus comparators and these results were further reinforced by head-to-head RCTs confirming the same. The same methodology was used in the triple Ismaila NMA therefore, GSK was confident that the methodology used in the Ismaila triple therapy NMA was robust.

Assuming all LAMA/LABAs were the same would impact the analysis as it was then only possible to detect the incremental benefit of the two different components rather than all 3 as an assumption had been made that one third of the molecules comparable and the clinical efficacy difference sat with only two of the components of the triple therapy. Even though this assumption had been made, there was still a trend that Trelegy showed numerical improvements in both Ferguson and Bourdin who both used this assumption.

Thus, GSK had used the NMA that included the most studies, most patients and it found a significant difference in favour of Trelegy compared to Trixeo (BUD/GLY/FOR) and a numerical improvement in favour of Trelegy vs Trimbow (BDP/GLY/FOR).

All materials were clear that there were no head-to-head clinical trials, and the claims and information were based on an NMA. For further transparency, GSK also included the fact that other NMAs existed that did not find a difference.

Claim 1: 'Greater annualised moderate/severe exacerbation reduction vs other COPD single inhaler triple therapies'

Chiesi's complaint about the claim above related specifically to pages of a website and a video. In addition, Chiesi complained about the data in a leavepiece which contained NMA data beneath the heading 'EXACERBATION REDUCTION VS. OTHER SINGLE-INHALER TRIPLE THERAPIES' on the last frame. The leavepiece was approved for, and used solely at, ERS (European Respiratory Society) 2022 conference in Barcelona in August and GSK assured Chiesi it had no intention of re-issuing the leavepiece again during inter-company dialogue so it believed it should not be considered during the Panel's deliberations.

Website pages and video

Similarly, GSK regretted not resolving this at inter-company dialogue and conceded that the headline claim *'Greater annualised moderate/severe exacerbation reduction vs other COPD single inhaler triple therapies'* should have been worded more clearly as improvement was significant for comparison to Trixeo (BUD/GLY/FOR) but that the improvement seen vs Trimbow (BDP/GLY/FOR), although numerically in favour of Trelegy, was not significant.

Claim 2 'Lung function improvement and exacerbation reductions assessed in a network meta-analysis vs other single inhaler triple therapies.'

Leavepiece (resolved during inter-company dialogue)

This sentence and Chiesi's concerns about the ERS leavepiece that contained it were resolved during inter-company dialogue where GSK committed not to use the item in future so it believed this should not be considered by the Panel. It had been created solely for use at ERS and had not been distributed since then and had been withdrawn from use. However, should the Panel wish to consider this point, GSK reiterated that the statement was not a claim *per se*, but making clear that Trelegy had been the subject of a network meta-analysis and it did not believe '*assessed in a'* made it more likely a health professional would assume there were significant improvements in both lung function and exacerbations versus all other single inhaler therapies as it did not say or imply that.

Trelegy website

The claim *'Superior lung function improvement*' versus *'other COPD single-inhaler triple therapies*' on Trelegy GSKPro website, was cited as a breach but Chiesi did not elaborate further as to its rationale. To avoid any confusion, GSK considered this claim fully substantiated by the graphical representation of the Ismaila NMA showing statistically significant mean trough FEV1 differences in favour of Trelegy versus Trimbow (p,0.0001) and Trixeo (p=0.0031) the only other single-inhaler triple therapies; it was contextualised by inclusion of a study descriptor immediately beneath the claim, an explanatory video on the NMA methodology, hierarchy of evidence and Ismaila resulted by [named professor] and by the addition of disclaimers to maximise transparency, eg '*No head to head randomised clinical trials exist for single inhaler triple therapies*' and '*Other NMAs exist which differ in their methodology and study inclusion*

which do not show any statistical differences between different SITTs' in bold text on the same page as the claim.

Chiesi asserted a breach of Clauses 6.1, 6.2 and 14.1 but made no argument for a breach of Clause 14.1. As such, GSK refuted allegations of being misleading (Clause 6.1), capable of substantiation (Clause 6.2) or being an inappropriate comparison (Clause 14.1).

Exaggeration of available evidence

As outlined above, use of Ismaila 2022 was appropriate as it was the largest, most robust NMA available in this area. This NMA was one of two NMA's conducted by Ismaila *et al*, with the other being a LAMA/LABA NMA and both used the same methodology which was in accordance with that described by Cochrane for NMAs. The results of the LAMA/LABA Ismaila NMA were consistent with the head-to-head studies between LAMA/LABA. Therefore, GSK was confident that the methodology used was robust. The four other NMAs either did not analyse the most up-to-date body of evidence either because the analysis was done before the results of key clinical trials were published or due to narrow inclusion criteria. Or in the case of some of these NMAs, the assumptions made that drive the analysis were not consistent with the results of head-to-head studies thereby producing less accurate results. It had been shown in a number of RCTs that there were efficacy differences within the LAMA/LABA group and therefore grouping them together was not appropriate.

The wording highlighted by Chiesi as problematic in the video

At 1 minute 9 seconds,[named professor] said that 'T*here are no head-to-head trials to compare the relative benefits of these treatments*', and this was shown as subtitles on the video for the audience to read making the context very clear. Chiesi complained that [named professor] made '*strong broad statements*' such as '*Meta-analysis is now widely recognised as a useful tool by national and international policy making bodies and by guideline developers*' which it asserted over-emphasised the importance of this NMA, but this was a statement of fact that could be supported by Antoniou *et al* and Laws *et al*. Chiesi was similarly concerned when [named professor] said '*Such a comparison would be important to us as clinicians, as this provides insights that could inform our treatment decisions within the single inhaler triple therapy class for COPD patients'*. [Named professor] had stated that the NMA did provide 'insights' into the efficacy comparisons of single inhaler triple therapy and that the information 'could' help inform clinicians with their treatment decisions, there was no obligation placed on the audience that they 'must' use these data to inform their decision, but clearly the information could inform them.

[Named professor] then went on to present the design of the NMA from 1 minute 51 seconds to 2 minutes 40 seconds to ensure that the data of the NMA was presented in the context that it was an indirect comparison and not a head-to-head study.

From 4 minute 22 seconds to 6 minute 55 seconds [named professor] presented the results of the NMA. First the forest plot showing the '*comparative effectiveness of Trelegy Ellipta vs other therapies on annualised moderate and severe exacerbations*' analysis from all studies in the NMA was displayed on the screen showing that Trelegy demonstrated statistically significant greater improvements in the annual rate of combined moderate and severe exacerbations versus 11 out of 18 comparators including Trixeo. Of the remaining 7 comparators, while statistical significance was not demonstrated, the point estimate of the IRR numerically favoured

Trelegy in 6 comparisons, including the comparison with Trimbow (ref BDP/FOR/GLY), IRR (95% CI) 0.73 (0.51, 1.04), p=0.0774.

There was also one comparison where the point estimate was exactly 1.00. In total, therefore, 17 of the 18 comparisons for this endpoint were numerically favourable to Trelegy, with 11 of these being statistically significant. Those comparators where statistical significance was not demonstrated, including versus Trimbow (ref BDP/FOR/GLY) were clearly graphically shown on the forest plot with confidence intervals crossing the IRR value of 0, with accompanying labels showing the p-values.

The second Forest plot illustrated the results of the '*mean change in baseline from trough FEV1 of Trelegy Ellipta vs comparators at 24 weeks*'. Trelegy showed statistical significance versus 7 of the 8 comparators including both Trimbow and Trixeo and a numerical improvement was shown in the one remaining comparator. Again the p-values of all the comparisons were shown next to each comparator on the forest plot which, in itself, clearly showed which comparators showed statistical significance by showing which crossed the IRR value of 1.0.

The third forest plot displayed the results of 'm*ean change in baseline from trough FEV1 of Trelegy Ellipta vs comparators at 12 weeks*'. Trelegy showed statistically significant improvements in FEV1 at 12 weeks versus 11 of the 14 comparators including Trimbow with a 46ml improvement (46.7 (15.12-78.20) p=0.0037). The accompanying narration by [named professor] said '*versus the other single inhaler triple therapy Trimbow BDP/FOR/GLY, Trelegy FF/UMEC/VI showed a favourable 27% reduction in the incident rate ratio, but this was not statistically significant*', the narration was also subtitled and could be read from the screen. Of the remaining 3 comparators, one showed a numerical improvement with Trelegy and the other showed a numerical improvement with the comparators.

The disclaimer *'Other NMA's exist which differ in their methodology and study inclusion which do not show any statistical differences between SITTs*' was displayed next to each forest plot referred to above, further reiterating to the watching health professional that this was one of a number of NMAs comparing triple therapies.

At 6 minute 55 seconds, [named professor] verbalised '*This analysis shows that FF/UMEC/VI could offer favourable benefits versus other single inhaler triple therapies with regards to exacerbation reduction and lung function improvements. These are important results to take into consideration when selecting triple therapy for your patients with COPD*'. [Named professor] did not guarantee that Trelegy would offer favourable benefits but used the conditional 'could' as it reflected the statistically significant findings versus Trixeo and the results that favoured Trelegy when compared to Trimbow. GSK believed these were important results to '*take into consideration*' when selecting triple therapy along with all the other considerations that needed to be allowed for with each individual patient.

[Named professor] also discussed the limitations of the NMA ensuring that the audience was able to interpret the data in the context of the limitations associated with conducting an NMA. [Named professor] then went on to talk about how the study addressed these limitations. At 8 minutes and 1 second [named professor] stated '*In the absence of head-to-head randomised control trials, this analysis gives us useful insights which will help clinicians in their choice of triple therapy for the optimal management of their patients with COPD*'. This was not over-emphasising the importance of this NMA as alleged by Chiesi but indicating that it was something that 'will help' as it was a robust, up-to-date NMA that used accepted methodology

and did not ignore known differences between medicines that had been shown in head-to-head clinical trials.

Based on the above, GSK did not believe the video narrated by [named professor] over-emphasised the importance of the NMA and GSK believed the video did, in fact, reflect the evidence in an accurate, fair, balanced and objective manner.

GSK believed that the claims made from Ismaila were a fair and accurate representation of the body of evidence on the specific topic of how Trelegy compared to other inhaled therapies in COPD and, as such, GSK refuted breaching Clause 6.1.

Breach of undertaking

GSK was committed to complying with undertakings given on case rulings. Chiesi asserted that GSK had breached the undertaking given in Case AUTH/3260/10/19 where GSK made the claim for Trelegy 'Improvements in QoL vs ICS/LABA' and Chiesi summarised the case to state that the evidence was specific only to Symbicort which was inaccurate as there were also data versus Relvar and indirect data versus Fostair.

This case was different in that it did not relate to QoL[Quality of Life], or to comparison with ICS/LABA and, as such, GSK did not believe it was a breach of undertaking and refuted the allegation of breaching Clause 3.3 and the subsequent claim of lack of high standards (Clause 5.1) and bringing discredit upon the industry (Clause 2).

4 Ellipta claim 'Don't' settle for a MDI when you can give the preferred, easy to use Ellipta device'

Chiesi complained about this claim on two pages of the GSKPro website. During inter-company dialogue, Chiesi asserted the words 'the' and 'preferred' were misleading but conceded that 'preferred' might be able to be substantiated. In an effort at resolution, GSK believed this had been settled during inter-company dialogue by offering to change the wording to 'Don't settle for an MDI when you can give the Ellipta device – patient preferred and easy to use' and Chiesi agreed in this formal complaint that the new wording removed the superlative element but, again, Chiesi were bringing this to the Panel which seemed to ignore the purpose of inter-company dialogue.

Chiesi now asserted that the claim 'preferred' did not reflect the weight of evidence and breached Clause 6.1.

GSK used one reference on the material (Van de Palen *et al* 2016), and the Code did not mandate that all references must be cited on materials, but that claims and information must be capable of substantiation. Van der Palen found most patients preferred the Ellipta DPI compared with placebo MDI. An additional patient preference study by Svedsater *et al*. 2013, demonstrated that 85% of COPD patients expressed preference for Ellipta DPI when compared to MDI.

There were also other studies supporting the preference for Ellipta over other DPIs; Van der Palen 2018: In two sub-studies, significantly more patients showed a preference for Ellipta for taking their COPD medication (81% and 84% for Ellipta compared with 9% and 4% for Diskus + Handihaler and Turbuhaler + HandiHaler, respectively, $P<0.001$; Kerwin 2020: Patient

Preference was evaluated via questionnaire in 215 patients; more patients preferred ELLIPTA to DISKUS plus HandiHaler in terms of number of steps required to take medications (72% versus 22%, respectively); Van der Palen 2022 : Overall, 85 (75%) patients preferred the ELLIPTA inhaler, 19 (17%) preferred BREEZHALER and 10 (9%) had no preference ($p < 0.001$).

Thus, it would seem clear that COPD patients did prefer Ellipta over many other devices, including MDIs. In support of its position, Chiesi introduced two studies using patients who were not within the licensed indication for Trelegy (Ohbayashi *et al*. 2021, 44 Japanese asthma patients and Ciciliani *et al*. 2019, 62 participants from 5 years old with a variety of conditions, none of which were COPD) and, as such, GSK believed they should be discounted in this case as patient preference was a complex area with many elements coming into play, and to make a claim using data in an unlicensed population would be inappropriate, and similarly refuting a claim on the same basis would not be correct.

<u>'Don't settle for a MDI'</u>

Chiesi believed this could be disparaging to MDIs although it did not elucidate how or in what way, and that '*such a recommendation cannot be substantiated by clinical guidance efficacy and/or safety data*'. GSK pointed to NHS, NICE, BTS [British Thoracic Society] who all recommended moving away from MDIs where clinically appropriate to reduce the carbon footprint, eg From BTS recommendations '*That during all respiratory reviews, prescribers recommend low carbon alternatives to patients currently using Pressured Metered Dose Inhalers (pMDIs), where patients are able to use these safely*'.

From NHS '*Supporting patients over the age of 12 to consider using lower carbon inhalers, where clinically appropriate, creates an opportunity to improve patient outcomes while reducing harmful carbon emissions.*' (copy provided)

Or PrescQuipp resources that made clear '*The NHS supports the change to environmentally friendly inhalers if this is the right choice for you.*' .

Health professionals were well aware that no one device would suit everybody and that individual patient needs and preferences must be taken into consideration for all prescriptions. Chiesi referred to Usmani 2019 to support the claim that not all patients could generate adequate inspiratory flow to activate a DPI, but it was a review article and cited a 2007 paper (Al-Showair RA, *et al*, 'Can all patients with COPD use the correct inhalation flow with all inhalers and does training help?' *Respir Med*. 2007) as the source of this information and the study did not include Ellipta which was not authorised until 2013. It was therefore inappropriate to use this data to raise potential safety concerns about discouraging MDI use as DPIs had numerous different mechanisms, inspiratory flow rate requirements and ease of use. GSK submitted that it would like to reassure the Panel that it took patient safety extremely seriously and that two studies supported the fact that **>99%** of patients were able to generate the inspiratory flow required to use Ellipta (Anderson M, *et al*. 2021 and Prime D, *et al*. 2019), ensuring that patients were able to get their required medication and were not put at risk. The prescribing decision was, of course, for the health professional to make on an individual basis and would always take patient preference and suitability into account.

As such, GSK believed it was reasonable to advocate for moving away from MDIs where clinically appropriate in line with independent guidance and denied breaching Clauses 6.1 or 14.4.

PANEL RULING

The Panel noted that inter-company dialogue had been unsuccessful on certain matters with four being escalated to PMCPA. The Panel noted that it was not for the Panel to revisit matters which had been resolved during the inter-company dialogue in accordance with Paragraph 5.3 of the Constitution and Procedure.

The Panel noted that triple therapy for COPD comprised an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA) and a long-acting beta agonist (LABA) and could be delivered via a single or multiple inhaler devices. At the time of the complaint and when the material in question was used single inhaler triple therapy products were available as combinations of either FF/UMEC/VI (Trelegy), BUD/GLY/FOR (Trixeo) or BDP/FOR/GLY (Trimbow). The Panel noted that Chiesi's submission that UK-based prescribing data demonstrated market shares within the single inhaler triple therapy market were 57.4% for Trimbow compared with 41% for Trelegy.

Trelegy Ellipta was indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who were not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta agonist and a long-acting muscarinic antagonist.

The complaint concerned a banner advertisement that appeared on the Trelegy website homepage, superiority claims for Trelegy on the website and in other materials, the use of data from a GSK NMA and a claim for the Ellipta device.

Matter 1: Banner Advertisement

The Panel noted the layout of the webiste homepage; at the top was a blue banner containing the claim 'Time for Change' 'Don't settle for anything less than the worlds no1 prescribed COPD triple therapy inhaler' and an image of the Trelegy Ellipta device. This was followed by the indication statement and another blue banner containing three white boxes. The first box stated 'The only choice with 21st century molecules & evidence of in-class superior components' followed by the name of a GSK product in each of the ICS/LABA, LABA/LAMA, and LAMA classes and a link to 'Learn about the molecules'. The second box stated 'A carbon neutral choice. Tackle climate change together.' followed by a link to 'Learn more about sustainability'. The third box stated 'A simple choice. One inhaler, easy to use, quick to teach.' and a link to 'Learn more about the Ellipta device.'. The banner advertisement appeared immediately below these three boxes.

The Panel noted that the banner advertisement had been amended during inter-company dialogue. As agreement had not been reached during inter-company dialogue the Panel determined that it would make its ruling in respect of the original banner advertisement.

The Panel noted that the banner advertisement was an integral part of the Trelegy website homepage and thus had to be considered within the overall context of the homepage.

The first frame of the five-frame advertisement depicted a man sitting at a table, with his elbows resting on the table, holding a bright orange cup of tea. Upon the table, to the left of the man, was a pile of unopened post and a bright blue 7-day pill organiser. To his right on the table was

a black and off-white newspaper with the capitalised headline 'Climate Emergency' above, in much smaller font, the caption 'We're losing but we can win'. In front of the man were three inhalers coloured pink, blue and red and a spacer device. To the forefront of the table to the left was a brightly coloured bowl of fruit and to the right what appeared to be a white clock with a yellow post-it note on its side. The Panel noted GSK's submission that the image represented a COPD patient on a mixture of device types including highlighting the well-known position that there was a need for us all to reduce our environmental impact.

The Panel noted that each of the five frames was superimposed with a different caption. The first frame was in colour as described above and the caption read 'Meet John. Click through to find out more about his life'. The remaining frames were largely in black and white although different items on the table were in colour in frames 2, 3, 4 and 5. In Frame 2 the caption read '58% of COPD patients in UK are juggling multiple devices. Would a simpler routine make their lives easier?', and the inhalers and spacer were in colour. In Frame 3 the oral medication dosing box and the pile of unopened post were in colour and the caption read 'Comorbidities. COPD is often associated with other conditions. About 40% have heart disease and 10% have diabetes, and significant numbers have high blood pressure and osteoporosis. A UK COPD patient is managing (on average) 2.6 co-morbidities in addition to their COPD'. In frame 4 the newspaper was in colour and the caption read 'The BTS recommend use of low carbon inhalers where clinically safe and appropriate to do so. The NHS Long Term plan aims for a shift to low carbon inhalers to deliver a 4% reduction in overall NHS carbon footprint.'. The fifth frame showed the post it note in colour and the caption stated '83% of COPD Triple Therapy patients on multiple inhalers in UK are managing once and twice daily dosing concurrently. Make their lives easier with Trelegy Ellipta – UK's only once-daily, single device COPD triple therapy'.

The Panel noted that Chiesi alleged that the use of the images of the inhalers alongside the newspaper headline was likely to result in health professionals associating these inhalers with the newspaper headline and as such was misleading and disparaging. The Panel noted that Chiesi also alleged that the inclusion of the pink Fostair inhaler and the absence of a GSK inhaler was disparaging to Fostair. The Panel noted GSK's submission that the choice of inhalers was indicative of an average COPD patient. The Panel noted that during the inter-company dialogue GSK had confirmed that the images of the inhalers shown in the advertisement were Fostair (Chiesi), Braltus (Teva) and Salamol (Teva). The Panel noted GSK's submission that the advertisement depicted a typical patient sitting at their table with several different inhalers representing the various medications a patient might be using to control their COPD. The purpose was to show a patient who could potentially be prescribed Trelegy (COPD inadequately controlled on dual therapy), and therefore simplify their treatment regimen by reducing the number of inhalers required to be taken as maintenance therapy and, at the same time, reduce the carbon footprint. The Panel further noted GSK's submission that the most prescribed combination was Fostair (ICS/LABA MDI) with Spiriva (LAMA soft mist inhaler), the second most common was Fostair with Braltus (LAMA DPI) which was the combination depicted and that it was not unreasonable to have the patient on the market-leading ICS/LABA with a commonly prescribed LAMA, and a SABA, as was the case for many individual patients. The Panel noted that the blue reliever MDI was chosen to represent a salbutamol MDI, which could be Ventolin (GSK's product) or one of the numerous branded or unbranded generic alternatives, many of which looked like the originator. GSK submitted that Fostair had been chosen as it was the UK market leader for the ICS/LABA class and is commonly prescribed with a LAMA such as Braltus and a SABA such as Salbutamol.

The Panel noted that whilst the banner advertisement must be capable of standing alone context was relevant in the particular circumstances of this case as the banner advertisement was an integral part of a Trelegy webpage. The Panel noted that visitors to the webpage would see the claim 'Time for change' at the top of the webpage, followed further down the webpage, immediately above the banner advertisement in question by 'A carbon neutral choice. Tackle climate change together.'

In the Panel's view, the environmental impact of propellants used in aerosols including metered dose inhalers was well established and it was common knowledge that the NHS had committed to reducing emissions by increasing the use of low carbon alternatives where it was clinically safe and appropriate to do so. The Panel noted that the BTS recommendation and information about the ambition, in the NHS Long Term Plan, for a 4% reduction in overall NHS carbon footprint by moving patients onto low carbon inhalers did not appear until Frame 4. It also noted the Wilkinson paper showed that SABAs account for 70% of the total UK inhaler market and contribute disproportionately to emissions compared to other classes of medicines delivered by metered dose inhalers, and Chiesi's submission that GSK had intentionally depicted competitor inhalers in the advertisement to avoid the association between their products and the climate emergency.

The Panel noted that the banner advertisement required the viewer to click through to each frame. The Panel had no information about how many readers clicked through each frame but noted that each frame should be capable of standing alone in relation to the requirements of the Code. The Panel noted the bold use of colour in the first frame and queried whether the newspaper and its headline were as prominent in the first frame as asserted by Chiesi. In the Panel's view, at frame 1, some readers might be drawn to other features of the colourful content rich advertisement. The Panel also accepted that some readers might indeed note the newspaper headline having noted the claim 'A carbon neutral choice. Tackle climate change together.' on the webpage immediately above.

In the Panel's view, within the context of the webpage, the advertisement was referring both to the general commitment to emission reduction by the NHS and others in both the caption at frame 4 and the newspaper headline and also to patients who could be prescribed Trelegy and thereby simplify their treatment regimen by reducing the number of inhalers required and, at the same time, reduce their carbon footprint. The inhalers appeared in this general context of the need for inhaler reduction. In this context, whilst the Panel considered that some readers might identify Fostair, on balance, the Panel did not consider that any frame of the banner advertisement implied that any one specific medicine was particularly associated with the climate emergency of the newspaper heading as alleged. The Panel considered that the banner advertisement was not misleading on this point as alleged and therefore ruled **no breach of Clause 6.1**.

In relation to the selection of inhalers and disparagement the Panel noted its comments above and GSK's explanation about the selection of inhalers above. The Panel queried whether on balance GSK's explanation was satisfactory. However, the Panel noted the purpose of the advertisement was amongst other things to depict a patient who might transfer to Trelegy from the inhalers depicted. The inhalers also appeared in the general context of the need for inhaler reduction. Given the Panel's decision above that the advertisement did not imply that any one specific medicine was particularly associated with the climate emergency, the Panel did not consider that the advertisement disparaged Fostair as alleged. **No breach of Clause 6.6** was ruled.

Noting its rulings above of no breaches of the Code the Panel considered that Chiesi had not established that GSK had failed to maintain high standards and ruled **no breach of Clause 5.1**.

The Panel noted Chiesi alleged the use of the claim 'Worlds no1 prescribed (COPD) Triple Therapy inhaler' on a website for UK health professionals was misleading but noted that Chiesi had not cited the clauses alleged to have been breached. The Panel noted that this omission was contrary to Paragraph 5.3 of the Constitution and Procedure which required complainant pharmaceutical companies to state the relevant clauses. The Panel noted that this aspect of the complaint was inconsistent with the Constitution and Procedure and the Panel therefore made no ruling on this matter.

Matter 2: Claim: 'The only choice with 21st century molecules and evidence of in-class superior components'.

The Panel noted that the allegation related to claims that appeared on two pages of the Trelegy product website, the homepage and the molecules webpage which could be accessed via a link on the homepage. The Panel noted GSK's submission that Chiesi had incorrectly cited the claims at issue that read 'Only choice with 21st century molecules and evidence of in-class superior components', and 'The only choice with 21st century molecules & evidence of in-class superior components'. The Panel noted that Chiesi also initially referred to a second webpage but neither party provided a copy of that page or subsequently referred to it and the Panel made no ruling specifically on that webpage. The Panel noted that Chiesi's concerns related to the phrase 'evidence of in-class superior components', other aspects having being resolved during inter-company dialogue.

The Panel noted that on the homepage the claim 'Only choice with 21st century molecules and evidence of in-class superior components' appeared immediately below a reference to Trelegy's licensed indication. The claim in question appeared within the first of three white boxes which sat within a blue band. The following text appeared immediately beneath the claim:

> 'ICS/LABA: Relvar Ellipta (fluticasone furoate/vilanterol) vs twice daily ICS/LABA
> LABA/LAMA: Anoro▼Ellipta (umeclidinium bromide/vilanterol) vs Spiolto & improvement vs Bevespi
> LAMA: Incruse▼Ellipta (umeclidinium bromide) vs Spiriva'

Text at the bottom of the white box, a hyperlink, stated 'Learn about the molecules'.

The molecules webpage included the claim 'The only choice with 21st century* molecules & evidence of in-class superior components' and the same explanatory text immediately beneath the claim with the addition of two qualifying statements; the first related to LABA/LAMA: Anoro▼Ellipta (umeclidinium bromide/vilanterol) vs Spiolto & improvement vs Bevespi and stated 'Anoro demonstrated improvement on the co-primary endpoint of trough FEV_1 while peak FEV_1 was similar'. The second related to the asterisk adjacent to '21st century' and stated that this was 'based on global date of first use'.

The Panel noted that the product related website was likely to be of interest to a wide audience not all of whom would be experts in the classes of medicines used in the treatment of COPD and therefore it was important that sufficient context was provided to ensure the claim was unambiguous.

The Panel noted that Chiesi had alleged that the claim appeared immediately adjacent to a prominent image of Trelegy, which was next to an image of Trixeo and Trimbow, however this was not the case in the webpages provided to the Panel by either party. The Panel also noted GSK's position that the comparisons of in-class superior components related to the licensed use of GSK medicines, ie, the GSK ICS/LABA (marketed as Relvar) had shown superiority over another ICS/LABA, the GSK LAMA/LABA (marketed as Anoro) had shown superiority versus another LAMA/LABA, and the GSK LAMA (marketed as Incruse) had shown superiority over another LAMA.
Thus, GSK submitted that each of the components of Trelegy that were authorised for COPD had evidence of in-class superiority as outlined immediately below the claim in question where the three component classes (ICS/LABA, LABA/LAMA and LAMA) were listed.

The Panel considered that in isolation readers might interpret the claim differently. The word 'choice' might imply a comparison with other triple therapy inhalers. In this regard the Panel considered that the layout of the relevant part of the webpages was important.

In relation to the homepage the Panel noted that the qualifying text appeared to be in the same font size and the same colour as the main claim, although the qualifying text was not emboldened. Further the qualifying text appeared immediately beneath the main claim and both the claim and qualifying text appeared within a white box and within a blue band such that the claim and qualifying text were likely to be read together. The Panel considered, on balance, that in this context the phrase '....evidence of in-class superior components' in the claim, 'Only choice with 21st century molecules and evidence of in-class superior components' did not create a misleading impression and was capable of substantiation and ruled **no breach of Clauses 6.1 and 6.2**. These rulings were the subject of an appeal.

In relation to the Molecules webpage the Panel noted that the layout of the relevant part of the scrolling webpage was different. Both the claim and qualifying text appeared in a white box at the top of the webpage but, in the Panel's view, the reader's eye would be equally drawn to the main claim and the prominent adjacent colour image of a Trelegy inhaler with superimposed bright imagery of ICS, LAMA, and LABA components in green, pink and blue. These colours were visually linked to and mirrored in the prominent illustration immediately beneath which showed the duration of action of each component. The Panel noted that unlike the claim in question on the home webpage the font size of the main claim was notably larger than the qualifying text beneath and thus eye catching in its own right such that it would not necessarily be read in conjunction with the qualifying text below but in conjunction with the adjacent imagery. In this context the Panel considered some viewers might consider that the claim in question at the start of the Molecules webpage related to the individual components rather than combinations of components. Further, the Panel did not accept GSK's submission that the claim did not state or imply that individual Trelegy components were superior to individual Trixeo or Trimbow components. The Panel noted that additional qualifying text was available if viewers scrolled further down the continuously scrolling webpage beyond two intervening sections but this was not within the visual field of the claim in question. In the Panel's view, the presentation of the main claim in question at the top of the Molecules webpage, was such that the claim was ambiguous. On balance, the Panel considered that the phrase '...evidence of in-class superior components' in the claim 'The only choice with 21st century* molecules & evidence of in-class superior components' was ambiguous as the comparator was not sufficiently clear and ruled a **breach of Clause 6.1**. In the Panel's view, an ambiguous comparison was incapable of substantiation and a **breach of Clause 6.2** was ruled.

Matter 3: Misleading use of data from a network meta-analysis (NMA) publication

General comments

The Panel noted a network meta-analysis (NMA) was a useful technique of combining both direct and indirect treatment comparisons across a network of studies to provide a comparison of interventions within a single analysis. Whilst NMAs were an established and valid methodology, particularly in the absence of head-to-head trials, the Panel noted their validity relied, amongst other things, upon several assumptions being met including that studies in the network were sufficiently homogenous and thus care should be taken when interpreting the results and drawing conclusions from an NMA. The Panel noted that NMAs were more statistically complex than meta-analyses with which health professionals might be more familiar and thus it was particularly important that the nature of the analysis was made clear and that readers were given sufficient information to enable them to form their own opinion of the therapeutic value of the comparison.

The Panel noted the limitations of the Ismaila *et al*. network meta-analysis; differences in study design, definitions of moderate and severe exacerbations and the patient inclusion/exclusion criteria of the trials included in the analysis, and clinical heterogeneity between the participants included in each study. The limited number of studies on SITTs available for inclusion was another limitation, while the lack of a common comparator in the network meant that some comparisons were not possible and, modelled estimates were used as input if available in the publications, and if they were not available estimates were modelled from the raw data. In relation to the limitations and the definitions of moderate and severe exacerbations the Panel noted that there was substantial heterogeneity in the definition of severe exacerbations ie with respect to hospitalisation across multiple studies and that the analysis of severe exacerbations alone was not deemed robust and therefore was not published. Consequently, the results of moderate and severe exacerbations were pooled to reduce the impact of the observed heterogeneity in definitions between trials. Noting that the authors of the network meta-analysis had concluded that while the findings of this network meta-analysis suggested favourable efficacy with single inhaler therapy comprising FF/UMEC/VI further analysis was required as additional evidence became available.

The Panel noted that the Code did not prohibit the use of network meta analyses (NMAs) in promotional material as long as the requirements of the Code were met. It also noted that whether the methodology and limitations of the NMA were highlighted in material might be relevant and that the supplementary information to Clause 6.1 stated that emerging clinical or scientific opinions which have not been resolved in favour of one generally accepted viewpoint must be referred to in a balanced manner.

The Panel noted Chiesi's allegations that two claims (and variations of them) made by GSK were misleading and could not be substantiated as they exaggerated the evidence base in a network meta-analysis, Ismailia *et al*. The claims at issue concerned the primary endpoint, the mean change from baseline in trough FEV_1 at 24 weeks (lung function) and a secondary endpoint, the annualised exacerbation rate. The claims appeared on the Trelegy product website in the clinical data section and in an embedded video titled 'Comparative efficacy of TRELEGY Ellipta (fluticasone furoate/umeclidinium/vilanterol) vs. other COPD SITTs' and were also used in a leavepiece.

Claim 1: Exacerbation reduction claim:

The Panel noted that Chiesi raised two matters in relation to exacerbation reduction. Firstly the implication of statistical significance versus Trimbow and the claim' Greater annualised moderate/severe exacerbation reduction vs. other COPD single-inhaler triple therapies' (and variations of it) in relation to the product webpage and the leavepiece. Secondly the imagery including the use of prominent percentages in bold colours to mimic the results, in combination with the claim in question, increased the likelihood that the wrong conclusions would be drawn. These concerns related to the leavepiece, a bar chart on the webpage headed 'Difference in annualised exacerbation incidence of Trelegy versus other COPD single inhaler triple therapies and a slide which was part of the video.

The Panel noted that Chiesi provided what appeared to be an earlier version of the webpage in support of its complaint although it referred to this as version 7 its layout slightly differed from Version 7 provided and responded to by GSK. The Panel made its rulings on the version provided by Chiesi.

The Panel noted that the exacerbation reduction section within the clinical data webpage of the Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) product website for health professionals started with a prominent box which included in large bold font:

> **'Greater annualised moderate/severe exacerbation reduction vs. other COPD single-inhaler triple therapies'**

Below this, text in smaller font stated:

> **'**In a network meta-analysis (NMA) of 23 randomised control trials (RTCs) involving adult COPD patients eligible for triple therapy, 17 of which reported moderate/severe exacerbation endpoint. Analysis is based on a Frequentist Fixed Effect (FE) model.'

This was followed by what appeared to be, an expandable box titled 'New data-Single Inhaler Triple Therapies compared in a NMA', which when expanded, encouraged readers of the website to watch a short video below, that provided an overview of:

- 'What a network meta-analysis is and how they sit in the evidence hierarchy;
- How this particular network meta-analysis was structured and its limitations; and
- An overview of the key conclusions from this network meta-analysis.'

The video explained the role of single inhaler triple therapies in treatment of COPD patients who remain at risk of exacerbations despite maintenance treatment with ICS/LABA or LABA/LAMA. The speaker identified the available COPD single inhaler triple therapies and their active ingredients and stated that their efficacy had been demonstrated in randomised clinical trials versus dual and monotherapies, but that there were no head-to-head trials comparing them directly. The speaker then discussed the role of a network meta-analysis in allowing the comparison to be made by using the data from direct head-to-head studies as well as indirect comparisons across trials based on a common comparator. The video concluded with a discussion about how the particular network meta-analysis had been undertaken and its findings.

The Panel noted that the slide at issue in the video at approximately 5.15 minutes was headed 'Comparative effectiveness of Trelegy Ellipta vs other COPD therapies on annualised moderate and severe exacerbations from a frequentist fixed effect model: all studies' and showed a forest plot with the results for the comparators including p values, although non-significant p values were not highlighted on the slide. A downward arrow was superimposed on the slide adjacent to 27% reduction, there was no indication near the prominent arrow indicating that this was a numerical difference and not statistically significant. The presentation was accompanied by a voiceover which stated that the analysis showed results favouring Trelegy over comparator treatments. The speaker focused on the comparison with the other single inhaler triple therapies, stating that Trelegy demonstrated statistically significant improvements in the annualised rate of combined moderate and severe exacerbations versus both doses of Trixeo, and in both cases there was a reduction in the incidence rate ratio of around 38%. The presenter then stated that versus the other single inhaler triple therapy Trimbow, Trelegy showed a favourable 27% reduction in the incident rate ratio but this was not statistically significant. A contemporaneous pop up text box also referred to the non-significance of the 27% reduction rate ratio. The Panel noted that a footnote to the bottom left of the forest plot stated that 'Other NMAs exist which differ in their methodology and study inclusion which do not show any statistical differences between different SITTs' however, attention was not drawn to this footnote either on screen for example by the use of bold text or by the speaker when describing the slide.

Returning to the webpage in question the Panel noted that in the version of the webpage provided by GSK beneath the section containing the video was a statement in bold that 'Other NMAs exist which differ in their methodology and study inclusion which do not show any statistical differences between different SITTs.' and a bar chart showing the difference in annualised exacerbation incidence of Trelegy vs. other COPD single inhaler triple therapies. However in the version of the webpage provided by Chiesi, which was the subject of complaint, the statement about other NMAs appeared below the bar chart in small but bold font. This bar chart showed the difference in exacerbation incidence of Trelegy was 38% fewer vs Trixeo Aerosphere (IRR 0.62 (95% CI: 0.45, 0.86); p=0.0044) and 27% numerically fewer exacerbations vs Trimbow pMDI (IRR 0.73 (95% CI: 0.51, 1.04); p=0.0774 (not significant)). The two arrows denoting the reductions were given equal visual prominence. Below the bar chart was the statement 'In a network meta-analysis (NMA) of 23 randomised controlled trials (RCTs) involving adult COPD patients eligible for triple therapy, 17 of which reported moderate/severe exacerbation endpoint. Analysis based on a Frequentist Fixed Effect (FE) model.'. The Panel noted that the webpage did not provide any information on the limitations of the NMA.

With regard to use of the headline claim 'Greater annualised moderate/severe exacerbation reduction vs other COPD single inhaler triple therapies' on the webpage and in the video the Panel noted GSK's submission that it regretted not resolving Chiesi's concerns during inter-company dialogue and its acceptance that the claim should have been worded more carefully as improvement was significant for comparison to Trixeo (BUD/GLY/FOR) but the improvement versus Trimbow (BDP/FOR/GLY) although numerically in favour of Trelegy was not significant. The Panel noted that Chiesi referred to the claim at issue, and variations on it but raised particular concerns in relation to the webpage and the leavepiece.

The Panel noted that the relevant section of the leave piece was headed 'Comparative efficacy of COPD triple therapies in a network meta-analysis' and included the claim – Exacerbation reduction vs other single inhaler triple therapies. Below this were two boxes positioned next to

each other; the box on the left stated 38% in large orange text followed by in much smaller orange text fewer exacerbations vs BUD/GLY/FOR 320/18/9.6 mcg and in white IRR 0.92 (95% CI: 0.45,0.86) p=0.0044. The box on the right stated 27% in large orange text followed by in much smaller orange text fewer exacerbations vs BDP/FOR/GLY 100/6/12.5 mcg and in white IRR 0.73 (95% CI: 0.51,1.04) p=0.0774 (not significant). A summary of the NMA limitations was provided in a box below the results together with a statement that adverse events (AEs) across the respective SITT studies were similar in incidence and type across treatment arms, no formal evaluation through statistical analysis was undertaken and a note that AEs from the NMA were tabulated and available in the full publication.

The Panel noted that GSK submitted that the leavepiece was approved for use solely at the ERS conference in 2022 and that it had assured Chiesi during intercompany dialogue that it had no intention of reissuing the leavepiece. However, the Panel noted that withdrawal of the leavepiece was not the same as stating that it would not make the claims etc at issue in other materials and therefore considered that this matter had not been resolved during inter-company dialogue and, in this regard, considered that allegations about the leavepiece fell within the scope of the Code, noting that the case had been transferred to the Panel in accordance with the Constitution and Procedure.

The Panel noted that Clause 6.1 required, among other things, that comparative information must be sufficiently complete and unambiguous and the supplementary information to Clause 6.1 concerned the need for particular care when presenting comparisons based on statistical information to ensure that differences which did not reach statistical significance were not presented in such a way as to mislead. It was an established principle under the Code that recipients were provided with sufficient information to enable them to form their own opinion of the therapeutic value of medicines. When making comparative claims it was, in the Panel's view, important to be clear about the nature of the comparative evidence and that this was especially important in a small market such as SITTs where only three products were currently available.

Chiesi alleged that the claim 'greater annualised moderate/severe exacerbation reduction vs. other COPD single inhaler triple therapies' was very broad and implied there was evidence to support an improvement in exacerbation rates with Trelegy compared to all triple combinations which was not the case from Ismailia *et al* or any other published evidence. This was particularly pertinent as Trimbow was the current UK market leader for single inhaler triple therapies.

The Panel noted it was an established principle of the Code that material must be capable of standing alone in relation to the requirements of the Code and that any qualification necessary for Code compliance should be apparent within the same field of vision as the claim. In the Panel's view, when presenting comparative data it was important to distinguish clearly between outcomes which were statistically significant and therefore clinically meaningful and those which were numerically favourable but did not achieve statistical significance.

The Panel noted that GSK accepted a breach of the Code in relation to the narrow matter of the claim 'greater annualised moderate/severe exacerbation reduction vs. other COPD single inhaler triple therapies' as it should have been clearer that the difference between Trelegy and Trimbow was not statistically significant. The Panel noted that Chiesi had raised general concerns about how the results of the NMA were presented but raised specific concerns in relation to the webpage and the leavepiece. Noting its comments above the Panel considered

that overall, and on balance, that the claim 'Greater annualised moderate/severe exacerbation reduction vs. other COPD single-inhaler Triple Therapies' on the exacerbation reduction webpage, and the claim 'Exacerbation reduction vs other single inhaler triple therapies' within the context of the ERS leavepiece misled as to the statistical significance and clinical relevance of certain results presented. In neither item was it sufficiently clear that the reduction in exacerbation rate for Trelegy versus Trimbow (BDP/FOR/GLY) although numerically in favour of Trelegy was not significant in Ismalia *et al*. The Panel considered that these claims each created a misleading impression that was not capable of substantiation and therefore ruled **breaches of Clauses 6.1 and 6.2** for the webpage and the leavepiece. Furthermore on the basis that comparisons are only permitted in promotional material if they are not misleading the Panel ruled **a breach of Clause 14.1** in relation to both the webpage and the leavepiece.

The Panel noted that the supplementary information to Clause 6.3 advised that particular care was required in relation to graphs and tables to ensure that they do not mislead particularly when presenting differences which do not reach statistical significance. The Panel noted Chiesi's concerns appeared to be that the imagery was such that the use of bold percentages was likely to mislead as to the significance of the exacerbation reduction. The Panel noted that Chiesi raised these concerns in relation to leavepiece, webpage and video slide. The Panel noted its descriptions of, and comments about the materials above. The Panel considered that the visual prominence given to the 27% reduction in exacerbations of Trelegy versus Trimbow in each of the materials implied statistical significance and was thereby misleading and on balance ruled a **breach of Clause 6.3** in relation to this imagery on each of the webpage, leavepiece and video.

Claim 2: Lung function improvements and exacerbation reductions assessed in a network meta-analysis vs other single inhaler triple therapies

Chiesi alleged that this claim implied that there was evidence to support an improvement in exacerbation rate and lung function with Trelegy compared to all triple combinations. This combined claim appeared in the ERS leavepiece as one of four key messages for Trelegy. The claim in question appeared in bold text with the exception of the words 'assessed in a' effectively drawing the eye to the bold text. The Panel noted it was not immediately apparent that the exacerbation rate related to the annualised rate of combined moderate and severe exacerbations. In its view, this was particularly important as the two previous 'key messages' related to significant reductions in the annual rate of moderate/severe COPD exacerbations vs a different comparator (BUD/FOR 400/12mcg) and the annual rate of hospitalised exacerbations and risk of all-cause mortality vs a LAMA/LABA (UMEC/VI).

The Panel noted that the relevant leavepiece had been withdrawn and was no longer in use and that GSK believed that this element of the complaint had been resolved during inter-company dialogue. However, this was not Chiesi's impression as no assurance had been received that the claim would not be used again in other materials. The Panel considered that inter-company dialogue had not been resolved and noted that the matter had been referred to the Panel for consideration.

The Panel noted there was no clear separation between the two phrases, which formed part of the same sentence. In the Panel's view, the reader would likely have been led to believe that there were statistically significant improvements in both lung function **and** exacerbation reduction for Trelegy over all other single inhaler triple therapies and that was not so. The Panel considered that the claim created a misleading impression which was not capable of

substantiation and therefore ruled **a breach of Clauses 6.1 and 6.2**. **A breach of Clause 14.1 was also ruled** on the basis that GSK had used a misleading comparison. These rulings related to the leavepiece.

Exaggeration of available evidence

The Panel noted Chiesi's general concern regarding the material overall and GSK's use of broad statements throughout without adequate qualification which Chiesi believed exaggerated the data and was not a fair representation of the wider evidence base including the other available NMAs.

In particular the Panel noted Chiesi's specific allegation that the speaker in the video titled 'Comparative efficacy of TRELEGY Ellipta (fluticasone furoate/umeclidinium/vilanterol) vs. other COPD SITTs' made strong and broad statements which overemphasised the evidence available in Ismaila *et al.* NMA including:

- 'Meta-analysis is now widely recognised as a useful tool by national and international policy making bodies and by guideline developers……such a comparison would be important to us as clinicians as this provides insights that could inform our treatment decisions within the single inhaler triple therapy class for COPD patients';
- 'This analysis shows that Trelegy could offer favourable benefits versus other single inhaler triple therapies with regards to exacerbation reduction and lung function improvement. These are important results to take into consideration when selecting triple therapy for your patients with COPD' and
- 'This NMA will help clinicians in their choice of triple therapy for the optimal management of their patients with COPD'.

The Panel noted that NMAs can be used to support claims but that in the hierarchy of evidence they have a lower weighting than other study methodologies especially randomised controlled trials which are considered the gold standard. In the Panel's view, it was of particular importance that care was taken to ensure that materials relying on a NMA provided a clear and balanced picture of the totality of evidence to afford health professionals with sufficient information to determine the weight to give it.

The Panel acknowledged that early in the video the speaker pointed out that there were no head to head trials to compare the relative benefits of the treatments but nonetheless considered that overall the voiceover to the video did not give sufficient information about the status of the results discussed, the limitations of the study and the availability of other NMAs with differing results. Consequently viewers might be misled about how much weight to attach to the data. The Panel considered that the voiceover as highlighted by Chiesi in the absence of appropriate qualification was misleading in this regard and **ruled a breach of Clause 6.1**.

With regard to the broad issue of whether or not the materials provided a fair and accurate representation of the wider body of existing evidence, the Panel noted Chiesi questioned the reliability and robustness of the NMA analysis given that four other NMAs had not demonstrated statistical differences between SITTs, GSK's choice of a frequentist fixed effect model and why it had not reported the results of the random effects model undertaken. The Panel noted GSK's submissions regarding the absence of head to head comparisons of single inhaler triple therapies for COPD and that while other NMAs had been undertaken there were differences in how these NMAs were conducted, the number of studies included and those omitted, and the

assumptions made in each. GSK stated that the Ismaili *et al.* NMA was the largest, most robust NMA to date and included all relevant studies that fitted the inclusion criteria and reflected the licensed indication for Trelegy. The Panel noted there appeared to be differing views on the methodology used for NMAs within the scientific community.

The Panel noted Chiesi's submission that GSK had also undertaken a random effects model analyses and alleged that GSK had been selective by deciding to only report and present the full results from the Frequentist Fixed Effects model. In this regard, the Panel considered that GSK had to present sufficient information to allow readers to form their own opinion of the medicines presented. In its view it was not for the Panel to adjudicate on the suitability of the methodology used in the NMA or whether a fixed effects or random effects model was more suitable; in this regard, the Panel noted the Ismaila *et al.* NMA had been peer reviewed and published in a recognised scientific journal.

Chiesi acknowledged that reference to the other NMAs was made by way of footnotes in some materials but alleged that this did not negate the misleading impression created.

The Panel noted its comments above regarding the presentation of comparative data based on the NMA data in the materials, in its view the omission of important information including the limitations of the study, the statistical status and clinical relevance of the results created an overall impression of superiority for Trelegy which was not a balanced reflection of the totality of the evidence. Accordingly the Panel ruled a **breach of Clause 6.1**. The Panel noted that this did not apply to the speaker's comments in the video which was covered by the discrete ruling above.

Noting its rulings of breaches above the Panel considered that GSK had demonstrated poor decision making in relation to how it had portrayed the results from the NMA in promotional material included on the Trelegy product website on GSKPro, and in a leavepiece for the 2022 ERS Congress. In this respect, the Panel considered that GSK had failed to maintain high standards and it **ruled a breach of Clause 5.1.** However, the Panel did not consider that GSK's conduct in this respect was such that it had brought discredit upon, or reduced confidence in, the pharmaceutical industry. The Panel **ruled no breach of Clause 2**.

Breach of undertaking

The Panel noted that the previous case, Case AUTH/3260/10/19, concerned promotional material comparing quality of life improvements for Trelegy and ICS/LABA and the claim 'Improvements in QoL vs ICS/LABA', implying evidence compared to all ICS/LABA combinations for COPD when the evidence base was very specific (Trelegy vs Symbicort), it was not clear that a comparison with Fostair was based on extrapolated data and a breach was ruled. In the Panel's view, the current case differed from the previous case, it did not concern quality of life data, extrapolated data or a comparison vs ICS/LABA. Whilst there was a similarity the cases were not sufficiently similar such that the Panel considered that GSK had breached the undertaking provided in the previous case and ruled **no breach of Clause 3.3**. Consequently, the Panel **ruled no breach of Clause 5.1 and Clause 2**. These rulings were each the subject of an appeal by Chiesi.

Matter 4: Ellipta Claim – Don't settle for an MDI, when you can give the preferred, easy-to-use Ellipta device

The Panel noted Chiesi's submission that the claim appeared on landing page and the dosing page of the Trelegy product website. Its complaint related to three elements within the claim. Firstly, it alleged that use of the definitive article 'the' breached Clause 14.4 which stated that exaggerated or all-embracing claims must not be made and superlatives not used except for those limited circumstances where they relate to a clear fact about a medicine. Secondly, it alleged that the weight of evidence did not support the broad claim of 'preferred' in relation to a comparison between the Ellipta device and pressurised metered dose inhalers and thus that the claim was contrary to Clause 6.1. Thirdly, Chiesi alleged that the phrase 'Don't settle for an MDI' was disparaging to pressurised metered dose inhalers and that such a recommendation could not be substantiated. Chiesi alleged a breach of Clause 6.1.

The Panel considered that the first two elements of the complaint were inextricably connected and therefore considered them together. It noted that during inter-company dialogue GSK had offered to change the wording to 'Don't settle for an MDI when you can give the Ellipta device – patient preferred and easy to use' which Chiesi agreed removed the superlative element, however it disagreed that the amendment sufficiently addressed its concerns. As it appeared that inter-company dialogue had been unsuccessful the Panel ruled on the original version of the claim. In addition, the Panel noted that whilst, according to Chiesi, the claim in question had been removed from the homepage, it remained on the dosing page.

In the Panel's view, little context was provided for the claim on the landing webpage or the dosing webpage; what was provided referred to a study showing that fewer COPD patients made critical errors with the Ellipta device compared with other commonly used COPD inhalers after reading the patient information leaflet. In the Panel's view, the reader was likely to associate the claims in question with the critical error data.

In addition the Panel considered that the phrase 'don't settle for an MDI' created an unfair impression about competitor products and went beyond advocating a move away from MDIs where clinically appropriate in line with independent guidance as stated by GSK. In the Panel's view, 'don't settle for an MDI' implied that an MDI would invariably be a lesser choice and that was not necessarily so, many factors affected the selection of the right inhaler for a patient. The same concerns applied to the landing page which although it did not feature a bar chart did refer to critical errors and defined critical errors as errors likely to result in no or minimal medication being delivered to the lung.

The Panel noted the parties' submissions about the preference studies and noted GSK's submission that the preference studies cited by Chiesi were for an unlicensed population and Chiesi's comments about the age of the patient populations.

In the Panel's view, the basis for the claim should be unambiguous and it considered that the claim was unclear; it was not clear in what way the Ellipta device was preferred; whether it was in relation to prescription volumes or a patient preference claim relating to ease of use or safety in relation to fewer critical errors. The Panel considered that the use of the term 'preferred' in this context was misleading and **a breach of Clause 6.1 was ruled**. The Panel considered that the use of a definitive article in this context was inappropriate and ruled **a breach of Clause 14.4**.

The Panel considered that the phrase 'don't settle for an MDI' created an unfair impression about competitor products and went beyond advocating a move away from MDIs where clinically appropriate in line with independent guidance as stated by GSK. In the Panel's view,

'don't settle for an MDI' implied that an MDI would invariably be a lesser choice and that was not necessarily so, many factors affected the selection of the right inhaler for a patient. The implication was compounded by the references to critical errors on each webpage. The Panel noted that Chiesi referred to disparagement and substantiation but referred to Clause 6.1. The Panel considered that the phrase 'don't settle for an MDI' created an unfair implication and **ruled a breach of Clause 6.1**.

APPEAL BY CHIESI

Chiesi appealed five Panel rulings related to two out of four matters previously escalated to the Panel as follows:

1. **Use of data from a network meta-analysis (NMA) publication**
    - Chiesi appealed the Panel's ruling of no breach of Clauses 3.3, 5.1 and 2 related to a breach of undertaking.

2. **Claim: 'The only choice with 21st century molecules & evidence of in-class superior components'**
    - Chiesi appealed the Panel's ruling of no breach of Clauses 6.1 and 6.2 on the Trelegy homepage.

Matter 1: Breach of undertaking - use of data from a network meta-analysis (NMA) publication

Chiesi specifically highlighted the two Trelegy claims, and the associated comments from the Panel which considered both claims to be broader than the specific evidence base (i.e. share the same key case learning) and thereby misleading:

- AUTH/3260/10/19: claim '**Improvements in QoL vs. ICS/LABA'**
- AUTH/3719/12/22: claim '**Greater annualised moderate/severe exacerbation reduction vs other COPD single-inhaler triple therapies'**

Chiesi alleged that as the key case learning was the same in both cases there had been a breach of undertaking and Chiesi had set out below the specific grounds of appeal of the ruling of no breach of Clause 3.3.

Definition of Similarity and Key Case Learnings

Chiesi highlighted Section 7.1 of the PMCPA Complaints Procedure which stated, when signing an undertaking, '**that all possible steps will be taken to avoid a similar breach of the Code in the future**.'

Chiesi alleged that given the above, the claims met the definition of 'similar' as described in The Oxford Dictionary: '**like somebody / something but not exactly the same**' and Chiesi summarised the points that strongly confirmed similarity as follows:

- There was similarity in terms of the **same promoted product** used in materials; both claims being relevant to **a study clinical endpoint** and both claims being relevant to **a competitor drug class**.

- The key learning was identical from each case report: **Trelegy claims were broader than the specific evidence base used to support them**, leading to the intended audience being misled.

- GSK was found in breach of the **same clauses** in both cases: Clauses 7.2, 7.3 and 7.4 of 2019 Code (equivalent to Clauses 6.1, 6.2 and 14.1 of 2021 Code).

A table comparing aspects of the previous cases to the current case was provided.

Chiesi noted that complying with undertakings underpinned self-regulation. Following a signed undertaking, Guidelines on Company Procedures Relating to the Code of Practice for the Pharmaceutical Industry (2021) advised that companies should ensure relevant information was communicated internally to all appropriate members of staff as part of a compliance programme covering prevention, detection and correction as a minimum. It was, therefore, reasonable to expect the GSK Trelegy team responsible for development and approval of both claims/materials to have been sufficiently trained to avoid a similar error in approving Trelegy **product claims that were broader than the specific evidence base**. This was an important step as part of the expectation outlined in the ABPI Complaints Procedure (Section 7) of ensuring **all possible steps would be taken to avoid a similar breach of the Code in the future**. Furthermore, Chiesi was concerned that the current ruling of insufficient similarity would curtail the ability of the PMCPA, and Appeal Board, to effectively administer breaches of undertakings.

Misleading GSK response

Chiesi noted that GSK asserted in their response that '**Chiesi state the evidence was specific only to Symbicort which was inaccurate as there was also data vs Relvar and indirect data vs Fostair**'. This referred to claims used in AUTH/3260/10/19 which reference the FULFIL Study:

FULFIL (Lipson et al, 2017): Randomized, double-blind, double-dummy study comparing 24 weeks of once-daily triple therapy (Trelegy) with twice-daily ICS/LABA therapy (Symbicort).

When the above study data was referred to by the Panel in Case AUTH/3260/10/19 and in Case AUTH/3719/12/22, they clearly state the data related to a '**very specific evidence base (Trelegy vs. Symbicort)**' which was consistent with the interpretation Chiesi submitted and not that of GSK.

Chiesi alleged that should the Appeal Board accept the Panel's and Chiesi's interpretation of the evidence base in Case AUTH/3260/10/19, and subsequent breaches in both cases, then it would seem reasonable to rely on the aspects of similarity between the two claims as described in the table above when making a ruling on breach of undertaking.

Consistency

Chiesi alleged that the current Panel ruling was inconsistent with the previous approach and ruling as described below:

- **Case AUTH/3480/3/21:** The Panel assessed whether a case arising as a result of the difference in legibility of generic name between a staging and live site was 'similar' to the difference between HTML vs PDF formats of digital material. Despite differences in the materials/claims themselves, the Panel considered that both arose due to insufficient signatory checks on digital material (ie. share the same key case learning), and thereby ruled a breach of undertaking.

Chiesi alleged that the current case similarly highlighted that key learnings had not been implemented leading to subsequent breaches. In the event that Chiesi's appeal against the Panel's ruling of Clause 3.3 was successful, and taking into account the 10 breaches of the Code the Panel had ruled in relation to the use of the NMA data, it would seem reasonable and proportionate for the Appeal Board to decide that GSK had not '**maintained high standards'** and was therefore in breach of Clause 5.1.

Clause 2 supplementary information provided examples of activities likely to be in breach of Clause 2, including '**multiple breaches of a similar nature in the same therapeutic area within a short period of time**' and '**inadequate action leading to a breach'** and therefore it would also seem reasonable for the Appeal Board to also rule a breach of Clause 2.

Given the details summarised above, Chiesi alleged that there was sufficient similarity between case reports Case AUTH/3260/10/19 & Case AUTH/3719/12/22 to respectfully invite the Appeal Board to reconsider the Panel's ruling of no breach of Clause 2, 3.3 and 5.1 on the basis of the following points:

- Identical key case learnings, i.e. Trelegy team using product claims broader than the specific evidence base used to substantiate them
- GSK's misleading response to the alleged breach of undertaking
- The Panel's approach to previous complaints on this issue involving breach of undertaking.

Matter 2: Claim – 'The only choice with 21st century molecules & evidence of in-class superior components'

Chiesi stated that the Panel assessed the homepage and molecules page separately.
The Panel considered whether the word '**choice' might imply a comparison with other triple therapy inhalers**' and that '**the layout of the webpage was important**'. The Panel concluded that the '**claim and qualifying text were likely to be read together'** on the homepage but not on the molecules page, and therefore ruled GSK in breach of Clauses 6.1 and 6.2 on the molecules page but not on the homepage.

Chiesi appealed the 'no breach' ruling of Clauses 6.1 and 6.2 on the homepage for the following reasons:

The word 'choice' implied a comparison with other single inhaler triple therapies

Clause 6.1 stated that '**Information, claims and comparisons… must not mislead either directly or by implication'**. Within the context of the Trelegy homepage, Chiesi alleged that the use of the word 'choice' implied a comparison with other single inhaler triple therapies.

Despite the Panel considering that '**the layout of the webpage was important**', in the ruling they only considered the information included within one text box; there was no evidence that the Panel considered the homepage as a whole. Chiesi alleged that consideration of the content and layout of the whole homepage was crucial, given the prominent call to action for Trelegy of '**Time to change**', the subtext of '**Don't settle for anything less than the world's no 1 prescribed COPD triple inhaler therapy'**, both next to a large image of Trelegy at the top of the homepage. Chiesi believed that this content would give the perception to any user that any other claims on the page relate to Trelegy.

Chiesi also highlighted the section of the webpage where the claim in question appeared was immediately adjacent to two other calls to action, all referencing 'choice' of triple therapy, and thereby placing additional emphasis on the perception that the claim referred to a comparison to other single inhaler triple therapies.

Chiesi stated that should the Appeal Board agree that, within the overall context of the homepage, the reader would be in no doubt that the claim in question refers to Trelegy versus other single inhaler triple therapies, then it would seem reasonable and proportionate for the Appeal Board to rule that the '**claim is ambiguous'** and '**misleading'** and thereby in breach of Clause 6.1 in accordance with the Panel ruling on the molecules page.

Chiesi provided screenshots of the text box, the webpage and the relevant section of it.

References cited by GSK did not substantiate the claim

Clause 6.2 stated that '**Any information, claim or comparison must be capable of substantiation**'. Chiesi alleged that even if (which Chiesi firmly did not accept) the claim was a comparison between Trelegy and ICS/LABA, LABA/LAMA and LAMA classes as submitted by GSK, there was no evidence that the Panel considered whether the references cited by GSK were capable of substantiating the claim.

Chiesi highlighted to the Appeal Board the areas of its concern regarding the data GSK used to substantiate its ICS/LABA, LABA/LAMA and LAMA claims, as set out in its complaint to the PMCPA. It provided a table summarising its concerns.

Given the above, Chiesi alleged that there was no substantive body of evidence to support the claim that Trelegy had '**evidence of in-class superior components'** compared to either Trimbow or Trixeo, and therefore that this claim was not capable of substantiation and in breach of Clause 6.2.

Chiesi invited the Appeal Board to reconsider the Panel's ruling of a no breach of Clause 6.1 and 6.2 for the claim on the homepage in the following contexts:

- The claim should be considered in the context of whole Trelegy homepage and therefore be considered as implying comparison with other triple inhaler therapies
- If assessed to imply comparison with other single inhaler triple therapies, then this would be misleading, given the stated intention by GSK of comparison against individual components
- Even within the context of a comparison with the individual components, the references cited by GSK did not substantiate the claim that superiority was shown against each component

In summary, for the reasons stated above, Chiesi appealed the Panel rulings in breach of Clauses 2, 3.3, 5.1, 6.1 and 6.2 of the 2021 Code.

APPEAL RESPONSE BY GSK

GSK was keen to re-iterate that the rulings of the Panel concerning the misleading nature of the claim at issue had been fully accepted by GSK and this was not at issue in this appeal. GSK was confident that the findings would provide important guidance for companies, including GSK, when using data from Network Meta Analyses to substantiate claims in the future.

Matter 1: No breach of Clauses 3.3, 5.1 and 2 with respect to breaches ruled on use of claim 'Greater annualised moderate/severe exacerbation reduction vs other COPD single-inhaler triple therapies'

GSK recognised that a number of factors must be considered when deciding whether or not a new breach of the Code was also a breach of a previous undertaking. GSK also accepted that the answer to this question was not always clear cut and that an element of judgement would be required when making such a decision, whether that was by the Panel or the Appeal Board. However, GSK disagreed with Chiesi's assertion that a breach of undertaking was automatically triggered if a breach in a subsequent complaint related to the same clause and same medicine and was again related to a claim where a comparison was made with another medicine through the use of a clinical trial endpoint. Given that such content was the mainstay of promotional material, such a broad and simplistic definition would result in multiple breaches of undertaking for completely unrelated matters. Indeed, the clauses in question for any complaint which related to claims, whether or not they related to a comparison with another medicine, were Clauses 6.1 and 6.2. Furthermore, if the claim related to a comparison with another medicine, then Clause 14.1 was also in scope. Accordingly, these were some of the most cited clauses within complaints. What was covered by these clauses was also very broad and thus a wide range of disparate issues raised within complaints fall within scope of these clauses. Therefore, each case must be assessed individually, taking into consideration all the relevant background detail and context for each individual breach; it was this that determined whether or not there had been a breach of undertaking.

GSK submitted that in this current case, the fact that there were breaches of Clauses 6.1, 6.2 and 14.1 and that they related to Trelegy and claims made versus another medicine did not automatically mean, with no consideration of the actual details, that there must be a breach of undertaking. Nonetheless, GSK accepted the breaches that were ruled in both cases and understood that in both circumstances health professionals were provided with information which was misleading about how Trelegy compared with competitor medicines.

Notwithstanding the above, GSK submitted that there were important differences between Case AUTH/3260/10/19 and Case AUTH/3719/12/22. Chiesi asserted that GSK had not taken reasonable steps to prevent a breach of undertaking from occurring. That was not the case; learnings from the earlier case had been put into effect, as evidenced below.

GSK submitted that in Case AUTH/3260/10/19, the item in question was a Trelegy advertisement placed by GSK on a third party website. The claim that was found in breach was 'Improvement in quality of life vs. ICS/LABA'. Although the reference for this claim was cited, no further qualifying information was provided; of note there were no details provided of the study which was referenced, no data was presented, nor was the comparator/s identified. In its ruling

on that case, the Panel had noted that the supporting data was very specific, relating to one named ICS/LABA, Symbicort, whereas the claim was very broad and implied there was head-to-head data in relation to every ICS/LABA combination available. Importantly, there were several ICS/LABAs commercially available in the UK at the time, and thus such a broad claim with no qualifying information implied that there was data to substantiate an improvement in quality of life versus all of these ICS/LABAs, which was not the case. The Panel also noted that material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. Hence, GSK accepted the Panel's ruling that the comparison was misleading, as it implied the existence of data versus other medicines where none existed. Additionally, GSK accepted that this impression was compounded by the lack of any qualifying information for the claim on the advertisement itself.

GSK submitted that the issues within this Case AUTH/3719/12/22 were different, irrespective of the fact that there were breaches of the same clauses, and that the medicine in question was the same - Trelegy. Firstly, the materials in scope contained far more information and detail about the nature of the data, with it being clear that it all came from a single network meta-analysis (NMA). Further caveats associated with NMAs e.g. limitations, existence of other NMAs with differing results, were also communicated. It was also made very clear that comparisons were being made against only two other medicines and what these were - Trimbow and Trixeo. On this occasion, the actual data for both of these comparisons was provided. It was also highlighted, albeit not at the outset, that for the exacerbation reduction endpoint the comparison versus Trixeo was statistically significant, whilst the comparison versus Trimbow was not statistically significant, even though there was a numerical difference in favour of Trelegy. Therefore, in this case there was no misleading impression that comparison data existed versus other medicines where in fact there was no data. All the necessary data existed and was included. As highlighted in Chiesi's complaint, GSK made three accommodations within materials to highlight the differences in statistical significance between the Trixeo and Trimbow data. This was done to ensure that the claims made were not misleading, and to ensure that material was sufficiently complete to enable the audience to form their own opinions. These actions also demonstrate GSK's commitment to ensuring that lessons learnt from the breaches in Case AUTH/3260/10/19 were being implemented, and that the exact same mistakes were not repeated. These three accommodations were:

- 'numerically' fewer is stated with the font used being bold
- the p value being clearly stated
- the words 'not significant' stated in a bold font.

However, GSK now accepted that the way in which the aforementioned information was presented relative to the overarching claim under discussion was not optimal, and that taken in isolation certain claims were indeed misleading with respect to the exact nature of the data which existed for the comparison between Trelegy and Trimbow. GSK agreed that the established principle of claims needing to be able to stand alone - and not rely on qualification which was not immediately visible in the same field of vision - was not clearly met. This was particularly important here given the complex nature of NMAs, methodology that many health professionals would not be immediately familiar with. Taken together this might have resulted in health professionals believing that the reduction in exacerbation rate seen for Trelegy, when compared to Trimbow, was statistically significant, when this was not the case. Therefore, the issue in this current case was not that a claim gave the impression of comparison data existing

where none existed, nor that the relevant information required to help reasonably contextualise a claim was not provided, but rather that where comparison data was presented, it should have been much clearer to the audience, from the outset, that the values in question were not statistically significant.

Furthermore, GSK noted that the Panel ruled no breach of undertaking, with its view being that the current case also differed by not being related to quality of life data, by not using extrapolated data, nor being a comparison versus an ICS/LABA. GSK accepted that the end result was the same, namely health professionals were misled to believe that Trelegy was superior, where it was not, however, GSK submitted that this alone did not mean that there was also a breach of undertaking. As demonstrated, there were many differences between the two cases in question, thus demonstrating GSK's commitment to complying with undertakings. GSK took such breaches very seriously, and, contrary to Chiesi's assumptions, did have a number of steps in place to ensure that the lessons learned from such case rulings were carried forward by the work of signatories, both at the time of the undertaking and subsequently. Firstly, the cross-functional Trelegy brand team responsible for the relevant material presented the case (copy provided) to the whole UK organisation involved with the creation, review and approval of promotional materials. This ensured that everyone was familiar with the case so that similar mistakes would not be made for any of GSK's medicines, not just Trelegy. Secondly, recognising that signatories for products change over time, all new signatories were required to familiarise themselves, as a minimum, with past PMCPA cases relevant to the therapy area that they would be working in. This was evidenced by GSK's Medical Signatory Assessment Checklist and Fast-track ABPI and GSK Code Signatory Assessment Checklist , both of which stipulate the need to familiarise oneself with relevant GSK PMCPA cases. All signatories at GSK must complete these checklists, whether brand new signatories or already experienced signatories respectively, before they could be assessed and registered with the PMCPA and MHRA.

In summary, GSK refuted breaches of Clauses 3.3. and 5.1. Additionally, GSK did not agree with Chiesi's assertion that multiple breaches of a similar nature in the same therapeutic area within a short period of time had occurred, nor that, as demonstrated above, inadequate action led to the breach in question. GSK therefore also refuted a breach of Clause 2.

GSK submitted that it was important to highlight that the ruling made in this appeal would set a significant and binding precedent on how narrow, or broad, the similarities must be for a medicine's claim versus a competitor medicine to be found in breach of a previous undertaking. This would have clear implications moving forwards given how commonplace claims of such a nature were and GSK was keen to understand the final ruling of the Appeal Board on this matter.

Matter 2 – No breach of Clauses 6.1 and 6.2 for use of the claim 'The only choice with 21st century molecules & evidence of in-class superior components' on Trelegy homepage.

GSK disagreed with Chiesi's assertion that the Panel did not fully review the whole of the homepage in question. A screenshot of the full content of the homepage was included in GSK's response to the complaint. In their ruling, the Panel stated, 'on the homepage the claim "Only choice with 21st century molecules and evidence of in-class superior components" appeared immediately below a reference to Trelegy's licensed indication.' Additionally, the Panel stated 'The claim in question appeared within the first of three white boxes which sat within a blue

band'. Furthermore, the Panel stated that 'the layout of the relevant part of the webpages was important'. Taken together, GSK was confident that the Panel did review the whole of this homepage. GSK was in agreement with the Panel's rulings. GSK accepted that the claim 'Only choice with 21st century molecules & evidence of in-class superior components' could only be reasonably stated if it was fully qualified by details of what the in-class superiority related to; this needed to be done in a transparent manner which ensured that the audience would not see the claim in isolation. As highlighted by the Panel, this requirement was met on the homepage through the use of qualifying text in the same font size and colour as the main claim, with this being positioned immediately beneath it. The Panel also noted that both the claim and qualifying text appeared within a white box and within a blue band such that the claim and qualifying text were likely to be read together. As a result, it would be clear to readers that the comparison referred to the following:

ICS/LABA: Relvar Ellipta (fluticasone furoate/vilanterol) vs twice daily ICS/LABA

LABA/LAMA: Anoro▼Ellipta (umeclidinium bromide/vilanterol) vs Spiolto & improvement vs Bevespi

LAMA: Incruse▼Ellipta (umeclidinium bromide) vs Spiriva

GSK submitted that, accordingly, it did not misleadingly imply that the superiority referred to was actually versus the components of Trimbow or Trixeo, as alleged by Chiesi. Additionally, nowhere on the page in question were these two competitor medicines referred to, either directly or indirectly.

Chiesi had also alleged that the use of the word 'choice' as well as the wording 'time to change' meant that some readers could be misled into believing that the Trelegy claim in question must be referring to the components within Trixeo and Trimbow. In response GSK submitted that in any promotional item for a medicine where other treatment options exist, part of the intended objective of that item would be to highlight the potential benefits and merits of the particular medicine being promoted, with the hope that prescribers would subsequently choose that option. It was not unreasonable to assume that those reading the item would either already be familiar with alternative treatment options or would also be reviewing other content related to such treatments. This supported them in making their own judgements on the differing merits of each available option. Ultimately, it would be their choice which medicine they chose to prescribe to any individual patient, based on their assessment of the perceived benefits of each available medicine. It was important to note that the options for COPD patients who required 'triple therapy' i.e. an inhaled corticosteroid (ICS), long-acting muscarinic antagonist (LAMA) and long-acting β2-agonist (LABA), were not limited to just single inhaler triple therapies (SITT), but also to multiple inhaler triple therapies, where both an ICS/LABA inhaler and a separate LAMA inhaler were prescribed. For this latter option, there were a multitude of treatment combination options available. As stated in GSK's initial response letter such multiple inhaler options represented 40% of the market share at the time. As a result, in this clinical scenario health professionals had numerous treatment options from which to choose.

It was also important to note that, as per the licensed indications of the SITT medicines, patients would step up to these medicines from other dual therapies, either an ICS/LABA or a combination of a LABA and a LAMA. Additionally, many health professionals would be considering using these SITT medicines where previously they would have prescribed a combination of two separate inhalers, an ICS/LABA and a LAMA. Therefore, it was clinically

sound to highlight superiority data related to GSK's available medicines across all of these aforementioned classes (Relvar, Anoro and Incruse), as the molecules within these were the same as those within Trelegy. GSK submitted that, in the context of the clear information provided on what data the superiority claim referred to, that such language alone did not create the misleading impression that the superiority referred to must be against the components of Trixeo and Trimbow.

In summary, GSK submitted that it was reasonable to present such data, if done transparently, to demonstrate the clinical merits of Trelegy. GSK therefore disagreed that the claim on the homepage was either ambiguous or misleading and agreed with the Panel's rulings of no breaches of Clauses 6.1 and 6.2.

Substantiation of claim

GSK referred to Chiesi's allegation that the Panel did not consider whether the references cited by GSK could substantiate the claims made within the qualifying text presented above. In response, GSK invited the Appeal Board to consider the position already presented on pages 5 and 6 of GSK's initial response letter dated January 2023. The studies referenced could substantiate the claim, and thus GSK denied a breach of Clause 6.2.

GSK submitted that Chiesi had raised one new point of complaint on this specific matter within its appeal **[see 'Decision of the Chair of the Appeal Board' below]**. Chiesi objected to the use of Maltais *et al* 2019 on the basis that UMEC/VIL was shown to be superior to GLY/FORM for one of the co-primary endpoints (morning pre-dose FEV1) but that the qualifying footnote did not specify for which endpoint UMEC/VIL was superior and therefore they believed that the claim and accompanying footnote was misleading. As stated in GSK's initial response letter, the Maltais (2019) publication was an AstraZeneca study to demonstrate non-inferiority of GLY/FORM over UMEC/VIL and non-inferiority of GLY/FORM was only met for one of the co-primary endpoints (peak change from baseline in FEV1 within 2h post-dosing) and not the other (change from baseline in morning pre-dose trough FEV1). Thus, via methods previously outlined in GSK's initial response UMEC/VIL was found to be superior to GLY/FORM on this endpoint and the two comparators were non-inferior for the other co-primary endpoint. This was not misleading as there was no restriction on the use of one co-primary endpoint which was superior when the other demonstrated non-inferiority. As a result GSK denied a breach of Clause 6.2 on this new point too.

In conclusion, GSK respectfully disagreed with the points of appeal put forward by Chiesi and agreed with the rulings made by the Panel on these two specific matters. GSK refuted the alleged breaches of Clauses 2, 3.3, 5.1, 6.1 and 6.2 of the 2021 Code.

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'Decision of the Chair of the Appeal Board'

The Chair decided, after consideration of Chiesi's final comments below, that:

'this is a new focus of argument, but is not a new allegation: the allegation remains that the claim (which must be read in the context of accompanying text) is misleading in breach of Clause 6.1 and unsubstantiated in breach of Clause 6.2, in part because it makes an assertion

which is not supported by the Maltais *et al* study. It follows that there is no bar on Chiesi raising this.'

GSK and Chiesi were so advised.

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FINAL COMMENTS FROM CHIESI

Matter 1: Breach of undertaking - use of data from a network meta-analysis (NMA) publication

Chiesi stated that GSK did not dispute the points of similarity set out in Chiesi's appeal, although, Chiesi acknowledged that GSK had highlighted perceived differences. These were specifically addressed in Point 3 below.

Chiesi stated that GSK now accepted Chiesi and the Panel's interpretation of both cases relating to misleading claims '**broader than the specific evidence base'**, despite disputing this in its initial response to the PMCPA. Notwithstanding the above, Chiesi responded to a number of GSK's comments on Chiesi's grounds of appeal as set out below:

1. GSK had asserted that a breach of undertaking should not be ruled in relation to the '**same clause'**, '**same medicine'** and a '**comparison with another medicine through use of a clinical trial endpoint'**, as otherwise this would result in '**multiple breaches of the Code'**.
    - In response Chiesi stated that it was an established principle that an undertaking required '**all possible steps to be taken to avoid a similar breach in the Code in the future**', and that similarity was defined by the Oxford Dictionary as '**like something but not exactly the same**'.
    - Chiesi alleged that this Case (AUTH/3719/12/22) was sufficiently similar to Case AUTH/3260/10/19 which culminated in GSK providing an undertaking as they both related to '**claims broader than the specific evidence base**'. Consequently, Chiesi invited the Appeal Board to rule a breach of undertaking.
    - On this point, Chiesi respectfully directed the Appeal Board to the points of similarity highlighted in Chiesi's appeal letter dated January 2024, and GSK's admission that both Cases (AUTH/3260/10/19 and AUTH/3719/12/22) related to '**how Trelegy compared with competitor medicines**' which were found to be '**misleading'**.

2. GSK had submitted that a breach of undertaking should not be ruled in relation to the points of similarity identified in the point above (referred to as '**broad and simplistic**'), as otherwise it would result in '**multiple breaches of the Code'** for **'completely unrelated matters**'.
    - In response Chiesi strongly denied that Case AUTH/3260/10/19 and Case AUTH/3719/12/22 were completely unrelated, for the reasons set out in Chiesi's appeal letter.
    - Chiesi re-emphasised that similarity could be established despite differences in materials/claims provided there was consistency in the key learning between cases (see Case AUTH/3480/3/21).

        - Chiesi noted that GSK had chosen not to comment on this point and therefore Chiesi assumed that it accepted the point.
    - Chiesi also noted that GSK had forecast multiple breaches of the Code related to the points of similarity identified in this case but had provided no explanation or evidence to validate this assertion. Chiesi had undertaken a comprehensive analysis of cases on the PMCPA database since 2016 (when the PMCPA added summaries to the database) to test this assertion. By applying to historical PMCPA cases the specific principles of similarity set out above by Chiesi between Case AUTH/3260/10/19 and Case AUTH/3719/12/22 to previous cases for GSK and Chiesi as respondent companies as well as one other company comparable to GSK:
        - This analysis was captured in a table with case report numbers available to the Appeal Board.

Chiesi stated that its analysis clearly demonstrated that GSK's assertion as to the consequence of the Appeal Board ruling a breach of undertaking in this instance was unfounded.

3. GSK had referred to three differences it perceived to exist between Case AUTH/3260/10/19 and Case AUTH/3719/12/22. In response Chiesi noted that these were not highlighted in GSK's initial response, and strongly denied that these 'new' differences were relevant to the determination of similarity for the following reasons:
    - Level of study detail included within the material.
        - Although Chiesi accepted there was more study detail included in Case AUTH/3719/12/22 than Case AUTH/3260/10/19, it still did not change the misleading impression of the material, the consequent breaches, and same key case learning.

    - Clarity of comparators within the data
        - Although Chiesi accepted that it was clear that Trixeo and Trimbow were the competitors in the NMA, the Panel still ruled that the exacerbation claim, '**Greater annualised moderate/severe exacerbation reduction vs. other COPD single-inhaler Triple Therapies**' and associated imagery was exaggerated, misleading and not capable of substantiation.
        - Chiesi noted GSK had accepted these rulings, and therefore Chiesi strongly believed that the clarity of comparators made no difference to the ruling and resulted in the same key case learning.

    - GSK had referred to three accommodations made to highlight the lack of significant difference in the data.
        - Although Chiesi accepted that these accommodations were implemented in some material, GSK accepted that they were not implemented across all materials as set out in Chiesi initial complaint.
        - Chiesi alleged that despite these inconsistent accommodations implemented by GSK, the Panel still ruled that the claim was misleading and not capable of substantiation, and GSK had accepted this ruling. Therefore, Chiesi strongly asserted that as these accommodations made no difference to the outcome, then these are irrelevant when determining whether the cases were similar.

4. GSK had referred to a number of steps put into place to learn from Case AUTH/3260/10/19, namely a training presentation and signatory checklist.
    - In response, while Chiesi had no reason to doubt that GSK implemented these steps, the fact that this did not stop a subsequent breach sharing the same key learning must mean those steps were not sufficient.
    - Chiesi also noted that the training presentation referred specifically to claims vs ICS/LABA and did not include reference to the key case learning of avoiding claims broader than the specific evidence base. Chiesi alleged that this further supported its assertion that this training presentation was insufficient to prevent a similar breach again, with the same key learning, as was in Case AUTH/3719/12/22.
    - Chiesi also observed that, although signatory checklists were provided by GSK to confirm that various training was adhered to, there was an absence of validation questions to ensure signatories understood the training provided. Chiesi alleged that this was another reason to conclude that the steps taken were insufficient to demonstrate that GSK took the previous undertaking seriously. Chiesi referred back to the requirement for companies who had provided an undertaking to take 'all possible steps', and respectfully alleged that GSK had not met this requirement.

In summary, Chiesi had not changed its position from that set out in its appeal.

Matter 2: Claim – 'The only choice with 21st century molecules & evidence of in-class superior components'

Chiesi responded to a number of GSK's comments on its appeal as set out below:

1. GSK had referred to the Panel's description of the Trelegy homepage as confirmation that the Panel took the whole page into consideration when arriving at its ruling.
    - In response Chiesi respectfully disagreed with GSK's interpretation. Although Chiesi accepted that the Panel described the whole page at the start, it only referred to the qualifying text when making its ruling. Chiesi, therefore, stood by its assertion in its appeal that there was no evidence that the Panel took the whole page into consideration when making its ruling.
    - Chiesi alleged that it was pertinent that the main difference between the Panel ruling on the home page and the molecules page was the size of the qualifying text, not the content on the remainder of the respective pages, and the same claim on the molecules page was ruled in breach – something which GSK accepted.

2. GSK had asserted that '**nowhere on the page in question**' were Trimbow and Trixeo '**referred to, either directly or indirectly**' and that it was clear that '**choice refers to multiple inhaler options available**'.
    - In response whilst Chiesi accepted that there was no direct mention of competitor medicines, Chiesi alleged that there was indirect reference given the prominent claim '**world's no1 prescribed COPD triple therapy inhaler**' and then three claims related to '**choice**' where it would not be unreasonable to assume the choice referred to alternatives within the same class as the product advertised on the page (i.e. single inhaler triple therapy). The term

used by GSK was, at best, confusing and misleading and its meaning was open to interpretation, including implied reference to single inhaler triple therapy. Following the established principle of 'contra proferentem', it was incumbent on GSK to make the meaning clear and it had failed to do that.

3. GSK had submitted that it was '**clinically sound to highlight superiority data related to GSK's available medicines across'** classes other than single inhaler triple therapies and that it did not believe that '**this alone creates the misleading impression that the superiority referred to must be against the components of Trixeo and Trimbow**'.
    - In response whilst Chiesi acknowledged that there was a footnote referring to three classes other than single inhaler triple therapies, Chiesi alleged that the claim implied a comparison against components contained in other triple therapy inhalers on the market (i.e. Trimbow and Trixeo) given the context at the top of the page as the '**world's no1 prescribed COPD triple therapy inhaler**'.
    - Chiesi also noted that competitors to Trelegy (namely Trimbow & Trixeo) could also show in-class superior components in terms of the LAMA component and therefore alleged that GSK could not claim that Trelegy was the only choice with evidence in-class superiority and therefore also rendered this claim misleading.

4. GSK had asserted that Chiesi raised a new complaint related to the use of Maltais 2019 [see 'Decision of the Chair of the Appeal Board' above]., namely that there was no qualifying footnote to communicate that only one co-primary endpoint of the study demonstrated superiority.
    - Chiesi did not accept this as it acknowledged in its appeal GSK's submission that CPMP guidance advises that a non-inferiority study could be interpreted as a superiority study under certain conditions, which appeared to be met in this study. Chiesi accepted in its appeal that superiority was shown in one co-primary endpoint, but went on to highlight that the footnote did not specify which endpoint was superior. Consequently, Chiesi's allegation remained that the footnote in question was misleading.

5. Chiesi stated that although GSK maintained its position that the claim was substantiable, they did not dispute its summary of the data included in Chiesi's appeal (with the exception of Maltais 2019 which Chiesi had addressed in Point 4 above).
    - Chiesi also question whether a superiority claim would be considered a hanging comparison when it was not clear the endpoint it referred to.
    - Should the Appeal Board agree with Chiesi's summary of the data, and alleged conclusion that the data could not be used to substantiate the claim, then it would be reasonable to consider the claim to be misleading and not capable of substantiation.

Chiesi refuted any suggestion that it had changed its position from that set out in its appeal, including that the Panel did not appear to consider whether the claim was capable of substantiation when arriving at its ruling on either the homepage or molecules page.

In conclusion, Chiesi respectfully disagreed with all points raised in GSK's response to Chiesi's appeal for the reasons stated above, and Chiesi respectfully invited the Appeal Board to allow Chiesi's appeal against the Panel rulings in respect of Clauses 2, 3.3, 5.1, 6.1 and 6.2 of the 2021 Code.

APPEAL BOARD RULING

Breach of undertaking allegation

The allegation in relation to breach of undertaking related to the Trelegy claim 'Greater annualised moderate/severe exacerbation reduction vs. other COPD single-inhaler triple therapies'. The Panel ruled breaches of the Code as it considered that the claim was a misleading comparison and created a misleading impression that was not capable of substantiation.

The Appeal Board understood that the previous case, Case AUTH/3260/10/19, concerned promotional material comparing quality of life improvements for Trelegy and ICS/LABA and the claim 'Improvements in QoL vs ICS/LABA'; a breach had been ruled by the Panel as it was not clear that the comparison with Fostair was based on extrapolated data. The Panel in that case considered that the claim did not reflect the evidence clearly and it was a misleading comparison, which was incapable of substantiation.

While both claims concerned the same medicine, Trelegy, the Appeal Board considered that the current case was sufficiently different to the previous case; it did not concern quality of life data, extrapolated data or a comparison vs ICS/LABA.

In the Appeal Board's view, the fact that similar clauses of the Code had been breached in each case did not necessarily mean there had been a breach of undertaking. Each case would be evaluated on its own particular merits bearing in mind the level of similarity.

The Appeal Board took account of the undertaking signed by GSK in Case AUTH/3260/10/19, which stated that GSK would 'take all possible steps to avoid similar breaches of the Code occurring in the future.' The company's actions following the provision of its undertaking was therefore also a relevant factor in determining whether there had been a breach of undertaking. The representatives from GSK at the appeal described the company's actions following the undertaking given in Case AUTH/3260/10/19, including training new and existing signatories on the case. The Appeal Board considered that the company's actions taken to avoid a similar breach of the Code occurring were reasonable.

The Appeal Board took account of the differences between the content and context of the claim in the current case (Case AUTH/3719/12/2) and the previous case (Case AUTH/3260/10/19), and the steps taken by GSK in relation to the undertaking given in the previous case. The Appeal Board determined that Chiesi had not established that GSK had breached its undertaking provided in Case AUTH/3260/10/19 and it upheld the Panel's ruling of **no breach of Clause 3.3**. Consequently, the Appeal Board upheld the Panel's **ruling of no breach of Clause 5.1 and Clause 2**. The appeal on this point was not successful.

Claim: 'The only choice with 21st century molecules & evidence of in-class superior components' on the homepage.

The Appeal Board examined the content and layout of the homepage. Above the claim at issue was the indication for Trelegy and above that was a picture of Trelegy with the claims 'Time for Change' and 'Don't settle for anything less than the worlds no 1 prescribed COPD triple therapy inhaler.'

Within the context of the homepage, the Appeal Board considered that the word 'choice' in the claim at issue 'The only choice with 21st century molecules & evidence of in-class superior components' might, to some readers, imply a comparison of Trelegy with other triple therapy inhalers including Trixeo and Trimbow. The Appeal Board considered that even with the data about component combinations below the claim at issue, some viewers might still consider that the phrase '....evidence of in-class superior components' might imply that individual Trelegy components were superior to individual Trixeo or Trimbow components.

The Appeal Board took account of the Panel's ruling of breaches of Clauses 6.1 and 6.2 in relation to the claim on the molecules page. The Appeal Board considered that the impression of the claim on the homepage was similar to that given on the molecules page.

In the Appeal Board's view, the phrase '...evidence of in-class superior components' in the claim 'The only choice with 21st century molecules & evidence of in-class superior components' on the homepage was ambiguous as the comparator was not sufficiently clear and it ruled a **breach of Clause 6.1**. The Appeal Board determined that the ambiguous comparison was incapable of substantiation and a **breach of Clause 6.2** was ruled. The appeal on this point was successful.

Complaint received **19 December 2022**

Case completed **14 March 2024**