CASE AUTH/3699/10/22

ASTRAZENECA/DIRECTOR v GSK

Allegations about GSK's use of a Network Meta-analysis (NMA)

CASE SUMMARY

This case was in relation to GSK's presentation of a Network Meta-analysis (NMA) on the efficacy of Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) versus other triple therapies for the treatment of Chronic Obstructive Pulmonary Disease (COPD).

The allegations related to the methodology used to produce the NMA and comparative claims for GSK's medicine Trelegy (FF/UMEC/VI) versus single-inhaler triple therapies (SITTs), including Trixeo. In addition, AstraZeneca alleged that GSK was in breach of an undertaking provided in relation to a previous case.

The outcome under the 2021 Code was:

Breach of Clause 5.1	**Failing to maintain high standards**
Breach of Clause 6.1	**Making a misleading claim**
Breach of Clause 14.1	**Making a misleading comparison**

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 3.3	**Requirement to comply with an undertaking**
No Breach of Clause 6.1	**Requirement that comparisons must not be 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

AstraZeneca submitted a complaint in relation to unresolved inter-company dialogue with GSK regarding GSK's use of a Network Meta-analysis (NMA) of the efficacy of Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) versus other triple therapies for the treatment of Chronic Obstructive Pulmonary Disease (COPD) to make claims of superiority versus single-inhaler triple (SIT) therapies, including Trixeo, in promotional activities.

Trelegy (FF/UMEC/VI) was GSK's medicine indicated as a maintenance treatment in adult patients with moderate to severe COPD who were not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (for effects on symptom control and prevention of exacerbations see section 5.1).

Trixeo (formoterol fumarate dihydrate, budesonide, glycopyrronium) was AstraZeneca's medicine indicated as a maintenance treatment in adult patients with moderate to severe COPD who were not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist or combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1).

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

COMPLAINT

AstraZeneca stated that this complaint followed unsuccessful inter-company dialogue with GSK.

Background

AstraZeneca explained that the NMA was originally presented as two posters at the American Thoracic Society (ATS) conference in May: one focused on pre-dose trough FEV_1 and the other on moderate or severe exacerbations (Ismaila AS *et al*. Poster presented at: American Thoracic Society; May 2022; Am J Respir Crit Care Med. 2022) (Ismaila AS *et al*. Poster presented at: American Thoracic Society; May 2022; Am J Respir Crit Care Med. 2022). The analysis was subsequently published in a manuscript, along with additional analyses looking at St George's Respiratory Questionnaire (SGRQ) total score and SGRQ responders, transition dyspnoea index focal score, and rescue medication use (Ismaila AS *et al*. Adv Ther. 2022).

AstraZeneca's complaint

AstraZeneca had significant concerns about use of the GSK NMA on the efficacy of FF/UMEC/VI versus other SIT therapies for the treatment of COPD, to make claims of superiority vs other SIT therapies, including Trixeo, in UK promotional materials.

These were materials hosted on the 'Clinical Data' tab of the Trelegy GSKpro website, including the page itself and the video 'Comparative efficacy of Trelegy Ellipta (FF/UMEC/VI) versus other COPD: A systematic literature review and network meta-analysis'.

The key claims of concern to AstraZeneca were:

'• Greater annualised moderate/severe exacerbation reduction vs, other COPD single-inhaler Triple Therapies (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).

- 38% fewer exacerbations (vs. Trixeo Aerosphere); IRR: 0.62 (95% CI: 0.45, 0.86); p=0.0044.'

AstraZeneca noted that correct reporting of the results of an analysis did not, of itself, absolve GSK of responsibility to be accurate, balanced, fair, and objective. The supplementary information to Clause 6.1 of the Code noted that there had been prior instances where issues

had arisen because of claims that were based on published papers in which the methodology was incorrect.

AstraZeneca maintained the GSK NMA contained significant methodological flaws which invalidated the results of the analyses and, as a consequence, the conclusions drawn from them were neither sustainable nor aligned to, or supported by, the wider body of evidence. In addition, GSK had decided to report the analyses in a selective way which further compromised any reader's ability to objectively interpret the results of the NMA.

In this context, use of the GSK NMA to make claims of superiority vs other SIT therapies, including Trixeo was misleading, unbalanced, lacked objectivity, distorted and exaggerated both in terms of the information and claims that had been included and the information and claims that had been deliberately excluded and which could have provided context. As a result, these materials did not enable the health professional to form their own opinion of the therapeutic value of the medicinal products concerned, and so they were disparaging to other SIT therapies including Trixeo. By using these claims in promotional activity, GSK breached Clauses 5.1, 6.1, 6.6 and 14.1 of the Code.

Below AstraZeneca summarised key information about the GSK NMA in support of its complaint.

Key information on GSK NMA to support AstraZeneca's complaint

1 The GSK NMA in question had significant methodology flaws, therefore its use to make claims of superiority versus other SIT therapies, including Trixeo in promotion, was inappropriate

NMAs were useful and important statistical tools, but it was well known that meta-analyses could yield misleading results and therefore Cochrane and ISPOR (and others) provided guidance on conducting NMAs (Deeks JJ *et al*. Chapter 10: Analysing data and undertaking meta-analyses. 2022; Chaimani A *et al*. Chapter 11: Undertaking network meta-analyses. 2022; Jansen JP *et al*. Value Health. 2014). AstraZeneca submitted that there were two major methodological flaws with the GSK NMA which meant that the resulting data was inappropriate for use to make claims of superiority versus other SIT therapies in the promotion of Trelegy.

a) Major methodology flaw: Substantial differences and clinical heterogeneity of core linking studies for Trelegy and Trixeo in the GSK NMA

An NMA was based on assumptions of similarity, exchangeability, and transitivity of the studies (Ismaila AS *et al*. Adv Ther. 2022; Tonin FS, *et al*. Network meta-analysis: a technique to gather evidence from direct and indirect comparisons. Pharm Pract (Granada). 2017).

Cochrane (Deeks JJ *et al.* Chapter 10: Analysing data and undertaking meta-analyses. 2022; Chaimani A *et al*. Chapter 11: Undertaking network meta-analyses. 2022) acknowledged that clinical and methodological differences between studies included in an NMA were inevitable but highlighted that a valid NMA relied on the assumption that the different studies included in the analysis had similar effect modifiers, ie, factors that could effect treatment response. If these clinical or methodological differences were sufficiently large, this might introduce intransitivity(Chaimani A *et al.* Chapter 11: Undertaking network meta-analyses. 2022). Cochrane, therefore, noted that an important step was the thoughtful consideration of whether it

was appropriate to combine the numerical results of all, or perhaps some, of the studies and that a meta-analysis should only be considered when a group of studies was sufficiently homogeneous in terms of participants, interventions, and outcomes to provide a meaningful summary. If studies were not sufficiently homogenous, Cochrane recommended possibly excluding studies if their results might introduce bias, or even question whether a meta-analysis should be done at all (Deeks JJ *et al*. Chapter 10: Analysing data and undertaking meta-analyses. 2022).

The network connection between Trelegy and Trixeo hinged on two studies, FULFIL(Lipson D *et al*. Am J Respir Crit Care Med. 2017) and KRONOS (Ferguson GT *et al Lancet Respir Med*. 2018), with a common comparator of Symbicort Turbohaler. GSK had suggested that these two studies were broadly similar (as in patient age, % female, % current smokers, post-bronchodilator FEV_1 % predicted, and % patients with inhaled corticosteroids ((ICS) use at study entry) and the only aspect in which KRONOS might be considered different to FULFIL was the number of prior exacerbations. Prior exacerbation history was widely recognised as the strongest predictor of the future risk of exacerbations, and therefore, a key differentiator and treatment effect modifier in the studies (Hurst *et al*. N Engl J Med 2010). There were also a number of other important differences in study designs which should be considered to have significant treatment effect modifying potential and were not accounted for, or acknowledged by, GSK, including: the run-in treatment; blinding of Symbicort (open-label in KRONOS and blinded in FULFIL); inclusion/exclusion criteria; definitions of exacerbation events; and patient characteristics.

The impact of these effect modifiers was seen in the performance of Symbicort in KRONOS and FULFIL where differences in the rate of moderate or severe exacerbations (a ~50% greater exacerbation rate in KRONOS) and change from baseline in pre-dose FEV_1 (increase from baseline in KRONOS and a decrease in FULFIL) were observed. The fact that the exacerbation rate with the common comparator Symbicort was lower in FULFIL than in KRONOS, despite patients in FULFIL having more severe COPD and a higher baseline rate of prior exacerbations, highlighted the clinical heterogeneity of the two studies. These differences introduced a considerable amount of bias into the analyses, particularly with respect to the indirect comparisons of Trelegy vs Trixeo, and produced misleading results. ISPOR noted ‘if there is an imbalance in study and patient characteristic–related effect modifiers across the different types of direct comparisons in a network meta-analysis, the corresponding indirect comparisons are biased’ (Jansen JP *et al*. Value Health. 2014).

A tangible example of the misleading results of the GSK NMA could be seen in Figure 3b of the Ismaila *et al*. paper (Ismaila AS *et al*. Adv Ther. 2022.). The figure implied that there would be an estimated ~40% reduction in exacerbation rate with Umeclidinium/Vilanterol (UMEC/VI) versus Glycopyrronium/Formoterol (GLY/FOR), however, in a direct head-to-head (H2H), randomised controlled trial (RCT) comparing these two treatments (AERISTO (Maltais *et al*. Adv Ther. 2019), there was no difference in the number of exacerbations between treatments (GLY/FOR 16.7% vs UMEC/VI 17.6%; time to first moderate or severe exacerbation HR=0.97, CI: 0.73,1.29, p=0.42) (Maltais *et al*. Adv Ther. 2019). The lack of difference on exacerbations rate between UMEC/VI vs GLY/FOR was also demonstrated in a separate NMA using a different network of studies (without KRONOS and FULFIL) by the same GSK authors, published at the same time, in the same journal (Ismaila AS *et al*. *Adv Ther*. 2022). This example clearly demonstrated that using KRONOS and FULFIL to form a network connection between Trelegy and Trixeo was methodologically unsound, biased comparisons and produced misleading results.

GSK defended the inclusion of KRONOS and FULFIL by stating that the studies were also included in two NMAs performed and published by AstraZeneca which showed no difference between the various SIT therapies (Ferguson GT *et al*. Adv Ther. 2020; Bourdin A *et al.* Adv Ther. 2021). It was, however, important to note that the two NMAs took a different methodological approach. In these NMAs, ICS/long-acting beta agonists (LABAs) and LABA/long-acting muscarinic antagonists (LAMAs) were grouped together as classes to strengthen the network connections between the triple therapies: that was, the analyses did not solely hinge on KRONOS and FULFIL to form a network for analyses, reducing the risk of bias.

Furthermore, these NMAs, along with two others conducted by independent investigators (Lee HW *et al*. Respiration. 2021; Rogliani *et al.* J Clin Med. 2022) recognised the need to accommodate heterogeneity of the included studies and primarily used and reported the Random Effects (RE) model (as discussed in the next section).

AstraZeneca considered that GSK had failed to address the legitimate concerns raised by AstraZeneca concerning the NMA methodology.

AstraZeneca maintained that using KRONOS and FULFIL to establish a network between Trelegy and Trixeo was inappropriate and invalidated the results of the GSK NMA.

b) Additional methodology flaw: Use of the Fixed-effects (FE) model as the primary analysis and reporting method

The FE model assumed that there was only one true effect and there were no differences in effect modifiers between studies (Deeks JJ *et al*. Chapter 10: Analysing data and undertaking meta-analyses. 2022; Jansen JP *et al*. Value Health. 2014). Cochrane (Deeks JJ *et al*. Chapter 10: Analysing data and undertaking meta-analyses. 2022) highlighted that 'Fixed-effect meta-analyses ignore heterogeneity', and that when heterogeneity was identified '…the summary fixed-effect estimate may be an intervention effect that does not actually exist in any population, and therefore have a confidence interval that is meaningless as well as being too narrow'. One option for dealing with heterogeneity was to perform a RE model (Deeks JJ *et al*. Chapter 10: Analysing data and undertaking meta-analyses. 2022) which incorporated some degree of heterogeneity, although 'this is not a substitute for a thorough investigation of heterogeneity' (Deeks JJ *et al*. Chapter 10: Analysing data and undertaking meta-analyses. 2022). ISPOR also advocated the use of a RE model where there was between study heterogeneity (Jansen JP *et al*. Value Health. 2014).

One test to assess the statistical heterogeneity of the results of studies in meta-analyses was the I^2 test (Higgins JPT *et al*. Measuring inconsistency in meta-analyses. BMJ. 2003). Cochrane had outlined a guide to interpretation of this test as follows: 0% to 40%, might not be important; 30% to 60%, might represent moderate heterogeneity; 50% to 90%, might represent substantial heterogeneity; and 75% to 100%, considerable heterogeneity.

In the GSK NMA, the I^2 for moderate or severe exacerbations ranged from 85% to 95%, which were in highest category of heterogeneity outlined by Cochrane above, suggesting that a RE model would be more suitable. As mentioned earlier, the RE model was deemed most appropriate by authors of 4 other NMAs comparing SIT therapies.

The selected model for primary analysis and reporting in the GSK NMA (FE model) was not consistent with recommendations by Cochrane and ISPOR and not consistent with previous NMAs conducted.

Taken together, these two major methodological flaws rendered the GSK NMA results at risk of significant bias. When used to substantiate claims of superiority versus other SIT therapies, those claims were unbalanced, misleading, and disparaging to Trixeo.

2 Reporting of the GSK NMA was not transparent, further complicating the ability to interpret results

The authors of the GSK NMA recognised the importance of the RE model and conducted the model in addition to the FE model, but they decided to only report and present the full results from the FE model. They simply stated that the results of the RE model were similar (Ismaila AS *et al*. Adv Ther. 2022).

AstraZeneca performed a RE model analyses using similar methodology, with the same studies and software. These analyses confirmed the presence of substantial heterogeneity and inconsistency across the network, and importantly, showed that there was no significant difference in moderate or severe exacerbations between Trelegy and Trixeo. The confidence intervals (CIs) were wide, ranging from 0.33 to 1.66, straddling the 1.0 line. Even if the point estimate was directionally in favour of Trelegy, this was likely resultant from the bias caused by the methodological flaws in forming a network through KRONOS and FULFIL as outlined previously.

During the video conference, AstraZeneca asked GSK whether the results for moderate or severe exacerbations of the RE model were statistically significant, but GSK did not provide AstraZeneca with an answer.

Furthermore, GSK defended its focus on the FE model by saying that heterogeneity was investigated through sensitivity analysis, including the exclusion of open-label studies, and the overall findings remained unchanged. Following this logic, then the Symbicort arm in KRONOS should be excluded as it was administered open-label in the KRONOS study, and the network connection between Trelegy and Trixeo would be dissolved.

AstraZeneca noted that in the accompanying NMA by the same authors (mentioned in Concern 1), which assessed dual bronchodilator therapies (Ismaila AS *et al*. Adv Ther. 2022.), the results of the RE model were published and presented in the supplement.

AstraZeneca maintained that the reporting of the GSK NMA had not been transparent and appeared to be selective, which further compromised the ability to objectively interpret the results and for the results to be used to make promotional claims of superiority versus other SIT therapies.

3 The results of the GSK NMA were not supported by the wider body of evidence

There were four other peer-reviewed, published NMAs (Ferguson GT *et al*. Adv Ther. 2020; Bourdin A *et al*. Adv Ther. 2021; Lee HW *et al*. Respiration. 2021; Rogliani *et al*. J Clin Med. 2022) comparing single inhaler triple (SIT) therapies for the treatment of COPD, and none found evidence suggesting one triple therapy was better than another at reducing moderate or severe

exacerbations. The results of the GSK NMA were therefore in marked contrast to other published data in this area.

GSK had suggested that the results of the GSK NMA were supported by other studies. GSK claimed that a 38% reduction in rate of moderate or severe exacerbations with Trelegy versus Trixeo was supported by H2H clinical trial data with the respective licenced dual components, citing superior efficacy of UMEC/VI vs GLY/FOR in AERISTO (Maltais et al. Adv Ther. 2019), and superiority on moderate or severe exacerbations of Fluticasone Furoate/Vilanterol (FF/VI) versus twice daily ICS/LABAs in the Salford Lung Study (Vestbo J *et al*. N Engl J Med 2016). However, the exacerbation rates were observed to be similar between treatments in the AERISTO trial, numerically favouring GLY/FOR (GLY/FOR 16.7% vs UMEC/VI 17.6%; time to first moderate or severe exacerbation HR=0.97, CI: 0.73,1.29, p=0.42), and GLY/FOR was nominally non-inferior to UMEC/VI for all symptom endpoints. The only difference observed in the study was on one lung function endpoint, trough pre-dose FEV1, and not the other, post-dose peak FEV1. Hence, it was unclear how these data, with the respective dual bronchodilator components of Trelegy and Trixeo, supported a 38% difference in moderate or severe exacerbations.

Furthermore, there were no data comparing FF/VI with BUD/FOR (the ICS/LABA components of Trelegy and Trixeo respectively) in COPD to support GSK's claims between Trelegy and Trixeo. The Salford Lung Study in COPD (Vestbo J *et al*. N Engl J Med 2016) cited by GSK, was an open-label pragmatic real-world trial, and the data referred to was a post hoc analysis from this study in which FF/VI showed a modest 8% reduction in moderate or severe exacerbations vs other ICS/LABAs. As was noted by the authors in the primary publication, the results could be influenced by the open-label nature of the trial which might have introduced bias and potentially impacted by patients' knowledge of receiving the trial medication. Notwithstanding whether this would be seen in a blinded randomised clinical trial, it was hard to see how a marginal 8% difference between these products would support 38% difference between Trelegy and Trixeo reported in the GSK NMA.

The results of the GSK NMA were inconsistent with existing data, which was expected given the methodological and reporting flaws of the GSK NMA outlined above. This was an additional reason for AstraZeneca to maintain that use of the NMA to make claims of superiority was inappropriate.

Summary of AstraZeneca's position

The GSK NMA had significant methodological flaws which invalidated the results of the analyses; the selective reporting of the results further compromised objective interpretation; and the results did not align with the wider body of evidence.

GSK had developed claims of superior efficacy from the NMA despite, and without fully disclosing, the clear limitations highlighted to ensure the maximum impact of the claims in promotional activity.

The use of the GSK NMA to claim superiority or greater efficacy of Trelegy over other SIT therapies, including Trixeo, was deliberately misleading, unbalanced, lacked objectivity, distorted, and exaggerated, both in terms of the information that had been included and the information that had been excluded, did not enable the health professional to form their own

opinion of the therapeutic value of the medicinal products concerned, and was disparaging to other SIT therapies including Trixeo.

Support of inaccurate and misleading claims in promotional materials jeopardised patient safety and compromised the high standard of patient care AstraZeneca committed to uphold. GSK had not maintained the high standards expected from companies in this instance.

AstraZeneca alleged that GSK was in breach of Clauses 5.1, 6.1, 6.6 and 14.1 of the Code.

Additionally, AstraZeneca drew parallels to a previous case brought against GSK (Case AUTH/3229/7/19). In promotional material for Relvar, the claim 'Relvar Ellipta was superior to other ICS/LABAs (usual care) in helping more patients improve asthma control in everyday clinical practice in the Salford Lung Study' was ruled as misleading as the results were not put in the context of the study's limitations nor other study data about Relvar. In this case it was deemed that not enough information was provided to enable readers to form their own opinion of the therapeutic value of the medicine. Due to the similarities between this case and the concerns outlined in this letter, AstraZeneca believed that GSK was likely to have breached the undertakings made and AstraZeneca therefore asked the Panel to consider whether GSK was also in breach of Clause 3.3 of the Code and whether the repetitive deployment of misleading claims warranted a breach of Clause 2 of the Code.

Given the seriousness of these concerns and the potential consequences of continuing GSK promotional activity using the GSK NMA, AstraZeneca requested that the complaint was reviewed by the Panel at the earliest possible opportunity.

AstraZeneca subscribed fully to the high ethical and moral spirit of the Code and did not believe that GSK was upholding these values in this instance.

RESPONSE

GSK stated that it was disappointed to receive a complaint from AstraZeneca via the PMCPA. As set out in the letter of complaint from AstraZeneca, GSK attempted to resolve the issue through inter-company dialogue, but this was unsuccessful in resolving the difference of opinions. GSK stated that it was committed to following both the letter and the spirit of the Code and all other relevant regulations and took this complaint very seriously.

GSK noted that in its complaint, AstraZeneca had highlighted significant concerns about use of the GSK NMA on the efficacy of Trelegy (fluticasone furoate/umeclidinium/vilanterol or FF/UMEC/VI) versus other single-inhaler triple therapies (SITTs) for the treatment of COPD, to make claims of superiority versus other SITT, including Trixeo, in UK promotional materials.

GSK stated that it would first defend the materials against which the specific allegations had been made. GSK would then address the three specific points raised by AstraZeneca with regard to the NMA itself.

AstraZeneca had specifically complained about two promotional items: A webpage on the GSK health professional promotional website and a video embedded on the same page. It should be noted that following inter-company dialogue the webpage had been updated to version 7 and the video updated to version 2.0, highlighting GSK's desire to find solutions which satisfied both parties. The key changes between the two versions were:

- The text '(no head-to-head randomised clinical trials exist for single inhaler triple therapies)' had been added to bullet point 1 above in the video, to further emphasise this point outside of the video itself. In addition, equivalent text had also been added to the slides in the video to accompany the clear voiceover (with subtitles) of this point.
- The text 'Other NMAs exist which differ in their methodology and study inclusion which *do* not show any statistical differences between different SITTs.' had been added onto the slides shown in the video where the results of the NMA were shown pictorially.
- The bold text 'Other NMAs exist which differ in their methodology and study inclusion which *do* not show any statistical differences between different SITTs.' had been moved from sitting below the pictorial representation of the NMA results to sitting above.

The key claims of concern highlighted by AstraZeneca were:

- Greater annualised moderate/severe exacerbation reduction versus, other COPD SITTs (In an NMA of 23 RCTs involving adult COPD patients eligible for triple therapy, 17 of which reported moderate/severe exacerbation endpoint. Analysis based on a Frequentist FE model).
- 38% fewer exacerbations (vs. Trixeo Aerosphere); IRR: 0.62 (95% CI: 0.45, 0.86); p=0.0044.

AstraZeneca alleged in its letter that 'In this context, use of the GSK NMA to make claims of superiority vs other SIT therapies including Trixeo is misleading, unbalanced, lacks objectivity, distorts, and exaggerates both in terms of the information and claims that have been included and the information and claims that have been deliberately excluded and which could have provided context. As a result, these materials do not enable the HCP to form their own opinion of the therapeutic value of the medicinal products concerned, and so they are disparaging to other SIT therapies including Trixeo'.

AstraZeneca had also alleged that due to significant methodological flaws, the results of the NMA were invalid, specifically highlighting three arguments why they believed this to be the case.

As a result, AstraZeneca alleged breaches of Clauses 5.1, 6.1, 6.6 and 14.1 of the Code.

Finally, AstraZeneca claimed that GSK had breached an undertaking from a previous ruling by the Panel (Case AUTH/3229/7/19) and, as such, alleged breaches of Clauses 3.3 and 2.

Background

GSK submitted that the NMA in question was originally presented at the 2022 Annual meeting of the American Thoracic Society (ATS). The posters presented the results from an NMA conducted by GSK and were entitled:

- 'Network meta-analysis of the efficacy of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus other triple therapies for the treatment of chronic obstructive

pulmonary disease (COPD): A comparison of annual moderate and severe exacerbations.

- Comparative efficacy of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus other triple therapies for the treatment of chronic obstructive pulmonary disease (COPD): A systematic literature review and network meta-analysis.'

The NMA was subsequently published containing additional detail in the high index scientific journal: *Advances in Therapy.*

GSK stated that AstraZeneca had referred to the two posters mentioned above in its letter. The two posters were presented at the 2022 annual meeting of the ATS. ATS was one of the foremost international respiratory meetings in the world and, as such, was respected by respiratory physicians worldwide. Posters presented at the ATS were accepted based on their quality of scientific research and were peer-reviewed. The results of the NMA had also been published in full in 'Advances in Therapy', a high index medical journal, following a similarly robust process of peer-review further highlighting its credibility and relevance from a scientific standpoint.

GSK strongly refuted all aspects of the complaint and therefore denied all breaches of the clauses of the Code quoted. GSK's response to each aspect of the complaint to support GSK's position was given below.

General Points:

1 GSK was confident in the robustness of the results of the NMA presented at the ATS 2022 and also published in full [Ismaila AS *et al*, Adv Ther; 2022]. GSK had been rigorous and transparent about the number of studies identified, the criteria for studies included, the statistical methodology and the heterogeneity associated with the NMA. The assumptions informing the NMA had been clearly stated in the ATS posters and in the full publication. GSK strongly believed that it had taken a fair and robust approach with full transparency.

These data were consistent with the existing body of evidence which showed intra-class superiority of the respective COPD-licensed components of Trelegy. Additionally, Trelegy's clinical programme had shown that Trelegy consistently met significance at key primary, secondary and other relevant endpoints (lung function, moderate/severe exacerbations, severe exacerbations, all-cause mortality, and HRQoL outcomes) versus comparators. Therefore, where there were no H2H data, the NMA was important and should be communicated to health professionals to enable them to make a fully informed, optimal treatment decision for their COPD patients.

2 As part of the study selection for this SITT NMA, GSK had included those studies conducted in populations that were consistent with the licensed indication for COPD triple therapy: 'indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist'. The comprehensive systematic literature review identified randomised control trials (RCTs) conducted in adults aged ≥40 years with a COPD diagnosis including the relevant SITT studies that were presented specifically within the respective summary of product characteristics (SPCs) of

the licensed SITTs. It should be noted that both pivotal registration trials ETHOS and KRONOS were included within the Trixeo SPC and were presented as supportive of the efficacy with respect to lung function and moderate/severe exacerbations. It would, therefore, have been remiss to exclude either of these key registration studies from the GSK SITT NMA.

3 This SITT NMA was based on a systematic literature review (SLR) of COPD Triple therapies studies. All the studies that met the following inclusion criteria had been included in the SLR:

- **Study designs**: RCTs with a minimum duration of 8 weeks.
- **Population**: adults aged ≥40 years with a moderate to severe COPD diagnosis as defined by GOLD guidelines or any other major guideline.
- **Interventions**: Triple therapy combinations, these being the combination of three molecules' classes: ICS, LABA bronchodilators and LAMA in SITT or multiple inhalers triple therapy (MITT).
- **Comparators**: Studies that compared treatments of interest (above) to any therapy (including combination therapies) licensed for the treatment of COPD in any country.
- **Outcomes**: The outcomes of interest included Lung Function (trough FEV1), Annual or annualised exacerbation rates, Health-Related Quality of Life (SGRQ score), Transition Dyspnoea Index, rescue medication use and Adverse Events.
- **Database search date limits**: March 2017 - October 2020.

Clauses 6.1, 6.6, 14.1 and 5.1

GSK submitted the two jobs referred to in the complaint were part of the same webpage on the website which was a UK health professional promotional website. The entire website, including the Trelegy section, was only accessible to UK health professionals who had self-validated that they were a UK health professional; it provided a wide range of information about GSK products. Different tabs in the header of the Trelegy section allowed the reader to access different information, including, but not limited to, clinical data, safety, the different molecules which make up Trelegy, dosing, the device and cost, to provide accurate, fair, and balanced information about Trelegy Ellipta.

The claim at the top of the page in question stated 'Greater annualised moderate/severe exacerbation reduction vs other COPD single-inhaler triple therapies'. It then immediately made it clear that this claim related to a NMA of 23 randomised trials, involving adult COPD patients eligible for triple therapy, 17 of which reported a moderate/severe exacerbation endpoint. It also stated that the analysis was based on a Frequentist FE model.

Given that network-meta-analyses were less widely encountered by the audience compared to RCTs, this was then immediately followed by text actively encouraging the health professional to watch a video from one of the study authors. This video gave an overview of what an NMA was and where it sat in the hierarchy of evidence, how this NMA was structured, its limitations, and an overview of key conclusions that could be drawn. Throughout the video, many of the points made above were reiterated, as well as additional clarity such as stressing that no H2H clinical trials for SITTs existed. The updated versions of the webpage and the video had

evolved to what GSK believed to be a fair, balanced, and accurate representation of the data into one that was of an even higher standard.

Following the video, a graphical representation of the NMA results was shown, with a prominent statement in bold in the immediate proximity, stating 'Other NMAs exist which differ in their methodology and study inclusion which do not show any statistical differences between different SITTs', further reflecting GSK's commitment to transparency in the use of the NMA data. This visual included the relevant p-values and CIs. Finally, RCT data for Trelegy relating to exacerbations was then presented to support the contextualisation of the NMA data.

GSK strongly believed the promotional items about which AstraZeneca had complained, as described above, were fully compliant with Clauses 5.1, 6.1, 6.6 and 14.1. The claims were both accurate and up-to-date, with each being substantiated by the NMA as presented at the ATS conference 2022 and which was also now published in full post peer-review.

Additionally, GSK had been fully transparent that there was no H2H RCT data to help inform decision making, and thus why NMA studies were of value here. Furthermore, GSK had also made it very clear that there were other NMAs whose results and conclusions differed to those reported here. Finally, a detailed overview of the design of the NMA, including its limitations, was provided in the video (an integral part of the webpage). This information was placed at the top of the exacerbations clinical data section, as many health professionals were now familiar with the triple therapy class and thus would be looking for information related to intra-class data.

GSK stated that given the claims versus other medicines, as described above, were based on peer-reviewed and published analyses, it was not clear why highlighting the nature of the difference in exacerbation rates was disparaging. Medicines for the same condition with the same indications were compared. A major role of these medicines was to reduce exacerbations and thus a material and relevant characteristic was being compared. As described, the data was transparently placed with accompanying detail on the nature of the data source, its limitations, the lack of H2H data, and that other NMAs had produced different conclusions.

AstraZeneca referenced supplementary information from Clause 6.1 which stated how instances had occurred where claims had been based on published papers in which the arithmetic and/or statistical methodology was incorrect. However, they had not provided any evidence that there was anything inaccurate in how any of the results had been calculated, rather they had provided alternate viewpoints on areas of methodology which were a matter of debate within the scientific community; indeed, this had been the very reason why GSK had provided the relevant additional information required to give health professionals context and to be fully transparent. It was noteworthy that GSK was unaware of AstraZeneca having provided any discourse on this matter with the journal, authors, or editors in question.

Taken together, GSK believed that the totality of the information provided was accurate, up-to-date, balanced and was sufficiently complete to allow individual health professionals to form their own opinion of the therapeutic value of the medicines discussed. Appropriate clinical and scientific comparisons were made, in a non-disparaging manner, between medicines belonging to the same class and with the same indication. Therefore, GSK strongly refuted the alleged breaches of Clauses 6.1, 6.6 and 14.1.

Accordingly, GSK believed that high standards had been maintained and denied a breach of Clause 5.1.

Scientific dialogue regarding the NMA methodology

GSK noted that the points of critique raised by AstraZeneca, and responded to by GSK below, related to areas of scientific debate and discussion concerning alternative viewpoints around methodological and statistical analysis approaches when undertaking an NMA. Notwithstanding the above, for completeness and transparency, GSK provided below a detailed response to the three specific areas of critique that had been raised by AstraZeneca about the published, peer-reviewed NMA.

1 The GSK NMA in question had significant methodology flaws, therefore use to make claims of superiority versus other SIT therapies including Trixeo in promotion was inappropriate

a) 'Major methodology flaw: Substantial differences and clinical heterogeneity of core linking studies for Trelegy and Trixeo in the GSK NMA'

- Both FULFIL and KRONOS were among the 23 trials that met the inclusion criteria specified above. Both studies had also been included in previous AstraZeneca sponsored NMA studies which compared SITTs. To date no scientific rationale had been presented for excluding these two high quality studies from a triple therapy NMA, given that the methodology of such an analysis acknowledged, and accounted for, heterogeneity between studies.

- Some heterogeneity existed and was, in fact, a known and accepted characteristic of all NMAs. As part of the feasibility assessment for this NMA, covariates had been compared over the studies, finding that the similarity assumption held, and differences between covariates were acceptable to allow pooling. Important covariates assessed were sex, age, smoking status, disease severity, number of exacerbations in the previous year, %ICS at baseline, COPD duration in years. In this NMA, GSK had, additionally, performed and reported statistical tests to quantify heterogeneity within GSK's selected studies, namely a chi-squared test and Higgins I^2 test both of which were common and well-established tests. For most analyses, I^2 showed a mild to moderate amount of heterogeneity. For the exacerbation analyses, I^2 was higher than the other analyses; the source of heterogeneity was investigated through sensitivity analysis, such as excluding open-label studies and excluding studies with duration of follow-up of less than 24 weeks. The overall findings remained unchanged.

- The patient population included in the 2 studies specifically mentioned above (KRONOS and FULFIL) was broadly similar in relation to many parameters including the patient age, % female, % current smokers, post-bronchodilator FEV_1 % predicted, % patients with ICS use at study entry. In addition, these two studies had the same duration and measured similar outcomes in a similar statistical hierarchy.

- The only aspect in which KRONOS might be considered different to FULFIL, based on their inclusion criteria, was the number of prior exacerbations of the patients at baseline (65% of patients with ≥1 exacerbation in FULFIL versus 26% in KRONOS). However, this fact did not seem to differentially affect the exacerbation rate experienced during the study duration. In fact, there was an opposite trend observed in the exacerbation rates recorded with the common comparator namely BUD/FOR DPI; with 0.34 and 0.36 exacerbations occurring by 24 and 52 weeks, respectively, in FULFIL, versus 0.55 in KRONOS (annual rate of moderate/severe exacerbations based on 24-week core phase). Thus, GSK could not assume, as AstraZeneca seemed to have, that this difference had any significant effect on GSK NMA findings. This was likely the reason why these two studies had been also included in other NMAs AstraZeneca referred to.

- GSK maintained that the studies were sufficiently similar to be included within the NMA.

- GSK disagreed with the 'tangible example of misleading results' provided by AstraZeneca. The figure, referred to by AstraZeneca in the example, was specifically looking at triple therapy (FF/UMEC/VI) vs comparators therefore the statistical analysis applied could not be used to compare LAMA/LABAs to each other (UMEC/VI versus GLY/FOR). It would be misleading and inappropriate to compare a dual therapy RCT – with a study population not suitable for triple therapy – within a triple therapy NMA.

b) 'Additional methodology flaw: Use of the Fixed-effects (FE) model as the primary analysis and reporting method'

- The statistical method used in the GSK NMA analysis was not incorrect as alleged but rather was well-established and could be readily and independently reproduced in the statistical software. GSK had described this method fully in the company's publication.

- GSK explained that its model selection was based on how the analyses [fixed effect (FE) or random effect (RE)] was best able to reproduce the known direct H2H results from the individual clinical trials included in the NMA. It was very important to note that the RE meta-analyses were not always conservative. The Cochrane Handbook for Systematic Reviews of Interventions (Section 10.4.4.1) recommended '**performing both fixed and random effect models and selection of the model that best fits the available data**'. This validation of most closely reproducing the results of randomised clinical trials was a critical step in the choice of the FE model for publication. GSK therefore strongly contended that the NMA was not inconsistent with Cochrane as suggested by AstraZeneca in its selective reference of it.

- It was also important to note that Cochrane stated: '**The decision between fixed- and random-effects meta-analyses has been the subject of much debate, and we do not provide a universal recommendation**' and '**The choice between a fixed-effect and a random-effects meta-analysis should never be made on the basis of a statistical test for heterogeneity**'.

- A FE model was driven by the sample size of studies as well as the precisions of the estimates from the individual RCTs included in the NMA. Consequently, this allowed studies that were powered for the endpoint of interest (eg, exacerbations) to be weighted higher than studies that were not powered for that endpoint. Since several large studies informed the network, the FE model was an appropriate choice. In the RE model, there was inverse variance weighting and smaller studies had a larger impact on the result whereas a FE model assumed that for each comparison all studies in the network were estimating the same comparison specific true effect; a RE model assumed that the underlying effects of each comparison followed a distribution and was particularly useful in networks of evidence including a large number of studies that drove the results. However, the network of evidence was relatively sparse making a FE model more suitable.

- Under the FE model, all studies were estimating the same effect size, and the weights assigned were based entirely on the amount of information captured by that study. It was therefore important to note that FULFIL and KRONOS, highlighted in AstraZeneca's letter, had very similar study population sizes and thus would weigh similarly in the true effect.

RE and FE models were both accepted methodologies for conducting NMAs and GSK strongly disagreed that an assertion could be made about one being better than the other or that the FE modelling used was incorrect.

GSK stated that, as highlighted above, it had explained why the FE model was used and strongly contended that it was not for AstraZeneca to decide which methodology was most appropriate for the NMA subject to discussion.

The GSK NMA had been peer-reviewed and accepted on two separate occasions by the robust scientific peer-review process of the ATS as well as '*Advances in Therapy*'.

2 'Reporting of the GSK NMA is not transparent, further complicating the ability to interpret results'

GSK noted that in point 2 of its letter, AstraZeneca had failed to refer to the promotional materials noted at the beginning of its letter, but rather its claim of a lack of transparency appeared to be with respect to the journal publication. GSK, as outlined above, believed the reporting within the NMA publication was clear and transparent. GSK stated that it believed the reporting to be comprehensive and no further information was requested by the editors of the journal as part of their appraisal of the submitted paper. Furthermore, as highlighted already,

GSK had been fully transparent in providing the relevant context for readers within its promotional materials. GSK's rationale for the use, and subsequent publication of the FE model, was covered in the company's response to point 1 above.

3 *'The results of the GSK NMA are not supported by the wider body of evidence'*

GSK strongly disagreed with the comment about the results of this NMA being in 'marked contrast' to other published data. Whilst there were no available H2H studies between single inhaler triple treatments in COPD (thus the need for this NMA), there were H2H data for the respective COPD-licensed components of SITTs:

- Umeclidinium was the only LAMA to have shown interclass class superiority versus tiotropium. In contrast, in the PINNACLE-1 study, the mean change from baseline in trough FEV_1 at Week 24 for the AstraZeneca formulation of glycopyrronium was 39ml less than that of tiotropium. In fact, glycopyrronium, had failed to show superiority and shown non-inferiority to tiotropium in multiple studies.
- UMEC/VI had shown superior efficacy in improving lung function in four H2H studies versus other LABA/LAMA's, including in AERISTO, an AstraZeneca-sponsored clinical trial.
- Fluticasone Furoate/Vilanterol had shown superiority in reducing moderate to severe COPD exacerbations versus twice daily ICS/LABAs.

In addition, in Trelegy's clinical program, it had been shown that Trelegy consistently met significance at key primary, secondary and other relevant endpoints (lung function, moderate/severe exacerbations, severe exacerbations, all-cause mortality and HRQoL outcomes) versus comparators.

In relation to AstraZeneca's statement that GSK's NMA was in 'marked contrast' to the conclusions of other NMAs, GSK believed that this was driven by fundamental differences in assumptions and inclusion criteria of the other NMAs which were in marked contrast to the body of scientific evidence. For example:

- Regarding the assumptions made, Bourdin *et al* was the only NMA that had a large body of evidence but as stated in their manuscript, one of their limitations was that they assumed all LABA/LAMAs and ICS/LABAs had the same efficacy based on previous NMAs. Based on H2H RCTs, it was clear that this was not the case and there were efficacy differences between LABA/LAMAs and ICS/LABAs (as detailed above). This was further reinforced by the Ismaila dual therapy NMA.

- Regarding the inclusion criteria, Ferguson *et al* and Woo lee *et al* did not reflect the current body of evidence due to the omission of ETHOS (a 52-week, 8000+ patient AstraZeneca-sponsored RCT). Rogliani had very narrow inclusion criteria and therefore only included 4 studies forming a very small network and omitting the data from FULFIL (a 26 week with a 52-week extension, 1800+ patients GSK-sponsored RCT).

It should be noted that despite ignoring the evidenced differences within the respective LABA/LAMA and ICS/LABA classes, in Ferguson *et al* and Bourdin *et al*, FF/UMEC/VI showed numerical improvements versus BUD/GLY/FOR for key endpoints.

Taken together, GSK was confident that the results published in Ismaila AS *et al*, Adv Ther; 2022 were not only accurate but also aligned with the body of existing evidence in the patient population aligned to the Trelegy indications in the SPC.

4 Alleged breach of undertaking from the previous, Case AUTH/3229/7/19

GSK stated that AstraZeneca had alleged a breach of undertaking from the previous case, Case AUTH/3229/7/19, against GSK. The case in question was related to a completely different situation. The therapeutic disease area in question was asthma. Additionally, the findings in the case related to not setting the study results (of the Salford Lung study) in the context of other study data for Relvar, which was clearly not the case in this instance.

There were no H2H trials between the licensed SITT, something which was made clear within the material in question. Furthermore, the fact that other NMAs also existed, and that these had drawn different conclusions, was also made very clear.

As made clear in the webpage on the GSK health professional promotional website, additional data from Trelegy registration studies were included; these related to studies versus dual therapies. The inclusion criteria of the studies for the GSK NMA were clearly laid out above and were within the licence for Trelegy. The website also made abundantly clear what patient population Trelegy was licensed for. The NMA data was presented with the statistical significance for results clearly displayed.

For these reasons, GSK strongly refuted a breach of undertaking and thus a breach of Clause 3.3. Consequently, there was no repetitive deployment of misleading claims and GSK strongly refuted the alleged breach of Clause 2.

Summary:

- The presentation of the data from the NMA, within the promotional materials cited by AstraZeneca, had been carried out in an accurate, balanced, fair, objective and unambiguous way, without being disparaging to any other medicines. The information on the NMA in the material was the latest newly published evidence available. Furthermore, GSK strongly contended that it had been presented in a way to allow health professionals to form their own opinion of the therapeutic value of Trelegy.

- GSK noted that a significant proportion of AstraZeneca's complaint related to issues surrounding the methodology and statistical analysis of the network meta-analysis. GSK strongly contended that the NMA had been carried out in a scientifically robust way, consistent with recognised best practice (eg, Cochrane). Furthermore, the NMA had been peer-reviewed prior to publication in the high index scientific journal 'Advances in Therapy'.

- GSK strongly refuted the allegation that high standards had not been maintained in the way it had conducted itself.

- GSK stated that it took its obligation to comply with the Code extremely seriously. GSK strongly contended that, for the reasons quoted above, GSK had not breached

any of the clauses mentioned in AstraZeneca's letter of complaint (Clauses 2, 3.3, 5.1, 6.1, 6.6 and 14.1).

PANEL RULING

The Panel noted that AstraZeneca and GSK appeared to have had unsuccessful intercompany dialogue with reference to two promotional items: a webpage on the GSK health professional promotional website and a video embedded on the same page. The Panel noted GSK's submission that the webpage and video had been updated following inter-company dialogue; as such, the Panel made its rulings in relation to the updated versions.

The Panel noted that the Trelegy Ellipta (FF/UMEC/VI) webpage of the GSKpro promotional website for health professionals at issue 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 (RCTs) 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 remained 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 an NMA 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 NMA had been undertaken and what it had found.

In summary, a systematic literature review had identified 23 trials to be included in the NMA including the IMPACT, ETHOS and KRONOS studies. Of these, 17 studies informed the network for exacerbation while 15 and 5 studies informed the FEV_1 analysis at 12 weeks and 24 weeks respectively. The results in terms of annualised exacerbation reductions and the mean difference in trough FEV_1, were presented. This was followed by a discussion about the limitations of the NMA, specifically heterogeneity due to study inclusion/exclusion criteria, design or duration, transitive comparators and the selection of studies. It went on to say that, in

this instance, these factors had been mitigated by selecting studies with similar treatments and indications, similar inclusion/exclusion criteria and similar design and patient populations. Thus the speaker concluded that this NMA provided useful insights to help clinicians in their choice of triple therapy for the optimal treatment of their patients with COPD.

Beneath the embedded video was the statement 'Other NMAs exist which differ in their methodology and study inclusion which do not show any statistical differences between different SITTs' in bold font of the same size as the heading for the bar chart which followed 'Difference in annualised exacerbation incidence of Trelegy vs. other COPD single inhaler triple therapies'. The bar chart that illustrated Trelegy Ellipta benefit being superior in terms of annualised exacerbation incidence compared with Trixeo Aerosphere at 12 and 24 weeks and compared with Trimbow pMDI at 12 weeks. The claim '38% fewer exacerbations [IRR:0.62 (95% CI: 0.45, 0.86); p=0.0044' was cited in relation to Trelegy compared with Trixeo Aerosphere and '27% numerically fewer exacerbations [IRR:0.73 (95% CI: 0.51, 0.1.04); p=0.0774 (not significant)' was cited in relation to Trelegy compared with Trimbow pMDI.

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 AstraZeneca's submission that the GSK NMA contained significant methodological flaws which invalidated the results of the analyses and, as a consequence, the conclusions drawn from them were neither sustainable nor aligned to, or supported by, the wider body of evidence; AstraZeneca further submitted that the analyses had been reported in a selective way which further compromised any reader's ability to objectively interpret the results of the NMA.

The Panel noted AstraZeneca's submission, therefore, that use of the GSK NMA to make claims of superiority versus other SIT therapies, including Trixeo was misleading, unbalanced, lacked objectivity, distorted and exaggerated both in terms of the information and claims that had been included and the information and claims that had been deliberately excluded and which could have provided context; further that the materials did not enable health professionals to form their own opinion of the therapeutic value of the medicinal products concerned, and were disparaging to other SIT therapies, including Trixeo.

The Panel noted that AstraZeneca alleged a breach of Clauses 5.1, 6.1, 6.6 and 14.1 of the 2021 Code in relation to the following key claims of concern:

1 'Greater annualised moderate/severe exacerbation reduction vs, other COPD single-inhaler Triple Therapies. 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'.
2 '38% fewer exacerbations (vs. Trixeo Aerosphere); IRR: 0.62 (95% CI: 0.45, 0.86); p=0.0044'.

The Panel noted AstraZeneca's submission that the NMA in question was flawed and not supported by the wider body of evidence:

- Four other peer-reviewed, published NMAs comparing single inhaler triple therapies for the treatment of COPD did not find evidence suggesting one triple therapy was better than another at reducing moderate or severe exacerbations.
- GSK's submission that the 38% reduction in the rate of moderate or severe exacerbations with Trelegy versus Trixeo was supported by H2H clinical trial data in the AERISTO trial was incorrect as, according to AstraZeneca, this study found similar exacerbation rates between treatments and numerically favoured Trixeo (GLY/FOR 16.7% versus UMEC/VI 17.6%; time to first moderate or severe exacerbation HR=0.97, CI: 0.73,1.29, p=0.42), hence it was unclear to AstraZeneca how these data supported a 38% difference in moderate or severe exacerbations.
- There were no data comparing FF/VI with BUD/FOR (the ICS/LABA components of Trelegy and Trixeo respectively) in COPD to support GSK's claims between Trelegy and Trixeo. The Salford Lung Study in COPD cited by GSK, was an open-label pragmatic real-world trial, and the data referred to was a *post hoc* analysis from this study in which FF/VI showed an 8% reduction in moderate or severe exacerbations versus other ICS/LABAs. As noted by the authors in the primary publication, the results could be influenced by the open-label nature of the trial which might have introduced bias and was potentially impacted by patients' knowledge of receiving the trial medication. Notwithstanding whether this would be seen in a blinded-randomised clinical trial, AstraZeneca maintained that it was hard to see how a marginal 8% difference between the products would support the 38% difference between Trelegy and Trixeo reported in the GSK NMA.

GSK submitted, in its defence, that differences in the conclusions of the four other published NMAs were driven by fundamental differences in assumptions and inclusion criteria of the other NMAs, which were in marked contrast to the body of scientific evidence. GSK submitted that:

- Regarding the assumptions made, Bourdin *et al* was the only NMA that had a large body of evidence but one of their limitations was that they assumed all LABA/LAMAs and ICS/LABAs had the same efficacy based on previous NMAs. Based on head-to-head RCTs, it was clear that this was not the case and there were efficacy differences between LABA/LAMAs and ICS/LABAs which was further reinforced by the Ismaila dual therapy NMA.
- Regarding the inclusion criteria, Ferguson *et al* and Woo lee *et al* did not reflect the current body of evidence due to the omission of ETHOS (a 52-week, 8000+ patient AstraZeneca sponsored RCT). Rogliani had very narrow inclusion criteria and therefore only included 4 studies forming a very small network and omitting the data from FULFIL (a 26 week with a 52-week extension, 1800+ patients GSK sponsored RCT).
- Despite ignoring the evidenced differences within the respective LABA/LAMA and ICS/LABA classes, in Ferguson *et al* and Bourdin *et al*, FF/UMEC/VI showed numerical improvements versus BUD/GLY/FOR for key endpoints.
- Although there were no available H2H studies between single inhaler triple treatments in COPD, there were H2H data for the respective COPD-licensed components of SITTs.
- Fluticasone Furoate/Vilanterol had shown superiority in reducing moderate to severe COPD exacerbations versus twice-daily ICS/LABAs in the Salford Lung Study.

Taken together, the Panel noted GSK's submission it was confident that the results published in Ismaila AS *et al*, Adv Ther; 2022 were accurate and aligned with the body of existing evidence in the patient population aligned to the Trelegy indications in the SPC.

The Panel noted an 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 there appeared to be differing views on the methodology used for NMAs within the scientific community. The Code did not prohibit the use of NMAs in promotional material as long as the requirements of the Code were met which included that the claims must be accurate, not misleading and the material sufficiently complete to enable the reader to form their own opinion of the therapeutic value of the medicine. Nor was it for the Panel to adjudicate on the suitability of the methodology used in the NMA; in this regard, the Panel noted the Ismaila *et al* NMA had been peer-reviewed and approved for a high index scientific journal. 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 had not been resolved in favour of one generally accepted viewpoint, must be referred to in a balanced manner.

The Panel noted the limitations of the NMA; 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. Other limitations were the limited number of studies on SITTs available for inclusion, and that some comparisons were not possible because of the lack of a common comparator in the network. Also modelled estimates were used as input if these were available in the publications and were modelled from raw data if estimates were not available. 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 NMA had concluded that, while the findings of this NMA suggested favourable efficacy with single inhaler therapy comprising FF/UMEC/VI, further analysis was required as additional evidence became available, the Panel questioned whether the webpage and presentation fairly reflected the caution expressed by the authors.

The Panel noted a claim of concern alleged to be misleading by AstraZeneca was 'Greater annualised moderate/severe exacerbation reduction vs, other COPD single-inhaler Triple Therapies (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)'. In this

regard, the Panel considered AstraZeneca appeared to allege the claim of superiority was misleading in relation to other therapies, including Trixeo and information had been deliberately excluded which did not enable health professionals to form their own opinion.

The Panel noted the claim above at issue was the key heading of the webpage, and this was followed by a video further down the webpage titled 'Comparative efficacy of Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) vs. other COPD'. The Panel noted the video provided an overview of NMAs generally as well as the structure of the GSK NMA along with its findings and limitations.

The Panel noted a slide in the aforementioned video which supported the claim 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-value. The Panel noted the speaker stated that 17 studies in the network showed results favouring Trelegy over the comparator treatments and stated that they would like to focus particularly on the comparisons of Trelegy with the other SITTs. In this regard, the speaker stated that Trelegy demonstrated statistically significant improvements in the annualised rate of combined moderate and severe exacerbations versus both doses of Trixeo, and that in both cases there was a reduction in the incidence rate ratio of around 38%. The 38% reduction was also highlighted on the screen. With regard to the other single inhaler triple therapy, Trimbow, Trelegy showed a favourable 27% reduction in the incident rate ratio but this was not statistically significant.

The Panel noted that a disclaimer, regarding the existence of other NMAs with different methodologies and study inclusion which did not show any statistical difference between different SITTs, was shown on screen when the comparison with other SITTs was discussed. However, the Panel considered attention was not drawn to this disclaimer either on screen for example by the use of bold text or by the speaker verbally.

In the Panel's view, it was important 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 noted that Clause 6.1 required, among other things, that comparative information must be sufficiently complete and unambiguous and the Code attached great importance to recipients being enabled to form their own opinion of the therapeutic value of medicines. The Panel noted it was an established principle that claims should stand alone.

The Panel noted a key claim of concern cited by AstraZeneca, which was the heading of the webpage at issue, was:

> 'Greater annualised moderate/severe exacerbation reduction vs, other COPD single-inhaler Triple Therapies (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 considered that the overall impression created by the claim was of statistical significance compared to other COPD therapies, in particular SITTs, including Trixeo and Trimbow, which was not so for Trimbow; additionally, the implication of clinical relevance was

unclear. It was an established principle of the Code that claims had to stand alone; in this regard, the Panel noted an expandable box contained a video which included qualifying information. In the Panel's view, the claim alone did not give sufficient information to enable viewers to know how much weight to attach to the data and assess its clinical significance for themselves. The Panel considered that overall, and on balance, that the exacerbation reduction claim did not fairly reflect the data and that health professionals might be misled as to the statistical and clinical significance of Trelegy compared to its comparators. The Panel considered that the comparative headline claim created a misleading impression and therefore ruled **a breach of Clauses 6.1 and 14.1**.

Clause 6.6 stated that another company's medicine must not be disparaged. The Panel considered there was a fine line between stating a positive outcome of one medicine and disparaging another. Whilst the Panel noted that the claim alluded to superiority of Trelegy for annualised moderate/severe exacerbation reduction over other SITTs and COPD therapies, the claim was presented within the same field of vision as information about the existence of other NMA with differing results. Nonetheless, noting its ruling of Clause 14.1 in relation to misleading comparison above, it did not consider, on balance, that the presentation of Trelegy, was such that it was disparaging to Trixeo or Trimbow. The Panel, on balance, made a **no breach ruling of Clause 6.6** accordingly.

The Panel noted AstraZeneca was also concerned with the claim '38% fewer exacerbations (vs. Trixeo Aerosphere); IRR: 0.62 (95% CI: 0.45, 0.86); p=0.0044' as there were other studies which showed similar results between the two medicines. The Panel noted the claim was presented on both the webpage and embedded video; for each, the results were presented in the same visual field as the disclaimer that other NMAs did not show statistical differences between SITTs. The Panel noted the claim closely reflected the wording of the authors in Ismaila et al which stated relative risk reduction of 38% (p = 0.0044) with Trelegy.

The Panel noted AstraZeneca's concerns that these results were in contrast to other studies and the results of the GSK NMA were inconsistent with existing data, due to methodological and reporting flaws. In this regard, the Panel noted AstraZeneca's allegations appeared to be underpinned by its belief that the methodology of the GSK NMA was flawed. The Panel also noted AstraZeneca challenged the methodology of the NMA in relation to GSK choosing to present random-effects model analyses. AstraZeneca submitted that it had performed random-effects model analyses using similar methodology which confirmed the presence of substantial heterogeneity and inconsistency across the network with no significant difference in moderate or severe exacerbations between Trelegy and Trixeo, contrary to the results presented to GSK. In this regard, AstraZeneca alleged GSK to have been selective by deciding to only report and present the full results from the Frequentist FE model.

The Panel noted that GSK had also appeared to have conducted the NMA using a RE model without presenting its results on the webpage at issue; reference to solely the frequentist FE model was made when substantiating claims. In this regard, the Panel considered that, regardless of whether the RE and FE model showed similar results, it would have been transparent for GSK to have also presented the results of the RE model to allow readers to form their own opinion of the medicines presented.

Whilst the Panel queried whether GSK had presented the emerging clinical and scientific opinion in a balanced manner, the Panel considered that AstraZeneca had not demonstrated that a RE model was more appropriate than the FE model. Neither AstraZeneca nor GSK had

provided the results for both the FE and RE analyses and therefore the Panel could not comment. It was not for the Panel to adjudicate on whether a fixed-effects or random-effects model was more suitable. In this regard, the Panel considered AstraZeneca bore the burden of proof. The Panel also did not consider, noting its comments above, that it had been established that the methodology was flawed such that the claim in relation to a 38% risk reduction claim for Trelegy compared to Trixeo, as cited in Ismaila et al and the webpage, was misleading. The Panel, therefore and, on balance, ruled **no breach of Clause 6.1**.

Nonetheless, considering its comments and ruling of a breach of Clauses 6.1 and 14.1 above in relation to the comparative claim, the Panel considered that GSK's portrayal of the NMA results of Trelegy, relative to its SIT comparators, was such that, on balance, high standards had not been maintained. **A breach of Clause 5.1 was therefore ruled**.

With regard to the alleged breach of Clauses 3.3 and 2 of the Code in relation to a breach of undertaking provided in Case AUTH/3229/7/19, the Panel noted GSK was found in breach of the Code for promotional material for Relvar in which the claim 'Relvar Ellipta was superior to other ICS/LABAs (usual care) in helping more patients improve asthma control in everyday clinical practice in the Salford Lung Study' was ruled as misleading as the results were not put in the context of the study's limitations nor other study data about Relvar; for example, the context of the study was not made clear, nor was the patient population nor information about the asthma control test.

In the current case (Case AUTH/3699/10/22), whilst the Panel considered the results of NMAs should be treated with caution, the comparative claim found in breach of the Code above was not on the basis of the limitations and design of the NMA not being made clear; the webpage included a video on the webpage which provided an overview of NMAs generally as well as the structure of the GSK NMA along with its findings and limitations. The Panel therefore considered the current case (Case AUTH/3699/10/22) differed in nature and was, on balance, sufficiently different to Case AUTH/3229/7/19; **no breach of Clause 3.3 was ruled**.

The Panel noted AstraZeneca cited a Clause 2 in relation to the 'repetitive deployment of misleading claims'. It followed that the Panel, noting its comments and ruling of no breach of Clause 3.3, consequently ruled **no breach of Clause 2**.

Complaint received **18 October 2022**

Case completed **18 December 2023**