CASE AUTH/3795/7/23

EMPLOYEE v ASTRAZENECA

Alleged misleading promotion of Trixeo on the product website and within the Trixeo IDA (sales aid)

CASE SUMMARY

This case was in relation to the use of a mortality graph and a claim of 46% risk reduction between Trixeo and its dual comparators on the product website and in an interactive detail aid. The complainant alleged this was misleading and did not represent an accurate reflection of the merits of Trixeo because the study investigators had concluded there was no significant difference between Trixeo and its dual therapy comparators.

The outcome under the 2021 Code was:

Breach of Clause 6.1 (x2)	**Making a misleading claim**
Breach of Clause 6.2	**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	**Making misleading comparisons**
Breach of Clause 14.4	**Not encouraging the rational use of the medicine**

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 at all times**
No Breach of Clause 6.1 (x2)	**Requirement that claims/information/comparisons must not be misleading**
No Breach of Clause 6.2	**Requirement that claims/information/comparisons must be capable of substantiation**
No Breach of Clause 6.3	**Requirement that all artwork must conform to the letter and spirt of the Code**
No Breach of Clause 14.1	**Requirement that misleading comparisons must not be made**
No Breach of Clause 14.4	**Requirement that claims should not imply that a medicine or an active ingredient has some special merit, quality or property unless this can be substantiated**

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 about AstraZeneca was received from an anonymous, contactable complainant (who later became non-contactable) who described themselves as an employee of AstraZeneca.

COMPLAINT

The complaint wording is reproduced below:

> "I am an AZ employee and have tried internally to solve a concern about an item that appears on an AZ Trixeo product website & within the IDA (the sales aid) used by the AZ field based field force.
>
> My concerns relate to a secondary endpoint in the ETHOS study where the peer reviewed publication by the investigators conclude that no difference in mortality was observed between Trixeo (BGF) and the dual comparators in the study.
>
> However AZ have decided to keep a mortality graph in which a claim of 46% risk reduction between Trixeo (the AZ triple combination) & its dual comparators.
>
> The graph is also titled "difference observed in all cause mortality in all treatment arms".
>
> These are highly misleading claims & I believe that when the investigators of Ethos have concluded that there is no significant difference, to be making risk reduction claims of 46% do not represent an accurate reflection of Trixeo's merits.
>
> I believe that the PMCPA should be considering clauses:
>
> Clause 2 - as this has been flagged and the current signatories are being that this piece has been signed off by previous signatories, so they need to follow suite [*sic*].
>
> Additional clauses to be included are;
>
> High Standards & Suitability – (5.1)
> Information, Claims, Comparisons –
> (6.1) – as not accurate fair or balanced (risk reduction without comparison with absolute risk)
> (6.2) – lacks substantiation
> (6.3) – graph is misleading (mortality graph on website)
> (14.1) – misleading mortality claim
> (14.4) exaggerated claim on mortality despite Ethos investigators concluding no significant mortality difference."

When writing to AstraZeneca, the PMCPA asked it to consider the requirements of Clauses 5.1, 6.1, 6.2, 6.3, 14.1, 14.4 and 2 of the 2021 Code.

FURTHER INFORMATION FROM THE COMPLAINANT

The complainant later provided additional information, reproduced below:

> "I made a recent complaint about Breztri & an all cause mortality claim I was being forced to sign off.
>
> I have submitted this to you at the PMCPA but it looks like the FDA have or are dealing with the exact same complaint in the US too.
>
> FDA Issues Warning Letter to AstraZeneca Regarding Breztri Aerosphere [link to online article provided]."

ASTRAZENECA'S RESPONSE

The response from AstraZeneca (updated and resubmitted following receipt of the additional information from the complainant) is reproduced below:

> "Thank you for your letter dated 11th July 2023, concerning a complaint from an AstraZeneca employee with respect to the promotion on the Trixeo product website (Trixeo Website – Efficacy page) and Trixeo IDA. We note the FDA Warning Letter dated 4th August 2023 which was sent to PMCPA after the original complaint. We confirm that AstraZeneca US has received and responded to the FDA on the matters raised by the Agency and are pleased to provide information to assist the Panel in its consideration of the UK complaint.
>
> You have asked AstraZeneca to consider the requirements of the following Code clauses when responding to this complaint, **5.1, 6.1, 6.2, 6.3, 14.1, 14.4 and 2**. We will therefore address each of the complainant's allegations according to the relevant clauses of the ABPI Code of Practice.
>
> The website page in question is specifically aimed at UK healthcare professionals. The Efficacy page of the website can be found by UK HCPs by clicking on the Efficacy tab located in the header of the Trixeo Website Wireframe when visiting [URL provided], through call-to-action links from promotional emails, or through a Google search. However, before the content of this website page or any other page on the Trixeo website at [URL provided] is displayed, the HCP will have to self-certify they are a UK HCP no matter which route of access into the site.
>
> The IDA (Interactive Detail Aid), sales aid, in question is used specifically in both virtual and in-person interactions between a sales representative and a healthcare professional. The IDA is made available for commercial sales representatives to use via their iPads. The IDA was NOT sent by email to the representatives and was only available via Veeva Vault. The IDA is intended to be used exactly as is detailed in the briefing document. The target Healthcare Professionals this asset is to be used with and how the IDA should be used are explained in the briefing material/training provided to representatives.
>
> **The original complaint alleges;** "My concerns relate to a secondary endpoint in the ETHOS study where the peer reviewed publication by the investigators conclude that

no difference in mortality was observed between Trixeo (BGF) and the dual comparators in the study. However AZ have decided to keep a mortality graph in which a claim of 46% risk reduction between Trixeo (the AZ triple combination) & its dual comparators."

Alleged breach 5.1, 6.1, 6.2, 6.3, 14.1 & 14.4

AstraZeneca Response:

The ETHOS study (Rabe et al, N Engl J Med 2020) was a randomised, double-blind parallel group study over 52 weeks conducted in 26 countries. The study had two different comparators which were dual therapies as follows: GFF (glycopyrronium/formoterol fumarate) as LAMA/LABA comparator and BFF budesonide/formoterol fumarate) as ICS/LABA comparator. The primary endpoint of the study was the annual rate of moderate/severe COPD exacerbations, and secondary endpoints included time for first COPD exacerbation (moderate/severe and severe only), SGRQ total score, EXACT total score, TDI score and time to death.

The order of the content in the sales materials reflects the design of the study by leading with the primary outcome of rate of exacerbations before discussing the secondary endpoints of the study which include the mortality claim. **In both the IDA and on the website, the mortality claim does not say Trixeo demonstrated a 46% risk reduction versus both dual comparators as complainant states.** The 46% risk reduction claim clearly specifies that this difference is observed only between Trixeo and LAMA/LABA comparator. The claim excludes the comparison between Trixeo and ICS/LABA comparator. The claim does not therefore state that Trixeo demonstrated a 46% risk reduction versus dual comparators as the complainant implies, as such a claim would include both LAMA/LABA and ICS/LABA comparators.

The original publication of the ETHOS study shows a hazard ratio of 0.54 (95% CI, 0.34 – 0.87) with a nominal p value of 0.0111 when comparing time to death from any cause over 52 weeks between BGF320 (Trixeo; budesonide/glycopyrronium/formoterol fumarate) and GFF (LAMA/LABA comparator glycopyrronium/formoterol fumarate) (Table 2 in the Rabe paper), which leads the authors to conclude that "*the risk of death from any cause in the 320 µg budesonide triple therapy group was 46% lower than that in the glycopyrrolate–formoterol group (28 vs. 49 deaths; hazard ratio, 0.54; 95% CI, 0.34 to 0.87)*" [Rabe KF, *et al*. N Engl J Med 2020]

Additionally, the Martinez *et al*. paper that specifically focuses on the mortality outcomes in the ETHOS study supports the difference already observed in the Rabe et al. paper, showing a mortality reduction of 49% in the final dataset compared with 46% from the original dataset. [Rabe KF, *et al*. N Engl J Med 2020, Trixeo, Summary of Product Characteristics, Martinez FJ, *et al*. Am J Respir Crit Care Med. 2021] The abstract of the Martinez et al. publication that the complainant has provided a screenshot of also clearly states that ***"risk of death with BGF320 was significantly lower than GFF"***. [Martinez FJ, *et al*. Am J Respir Crit Care Med. 2021]

Furthermore, the results from the ETHOS study have been considered by the committee of the GOLD (Global Initiative for Obstructive Lung Disease) management strategy (2023 GOLD report, available from [URL provided]), a group composed of

leading clinicians in the field of COPD management from around the world (with strong representation from the UK), and have been included as the following statement that further supports the recognition of the importance of the mortality results:

"*Recently, evidence has emerged from two large randomized clinical trials, IMPACT and ETHOS, that fixed-dose inhaled triple combinations (LABA+LAMA+ICS), reduce all-cause mortality compared to dual inhaled long-acting bronchodilation therapy. These trials were enriched for symptomatic patients (CAT ≥ 10) with a history of frequent (≥ 2 moderate exacerbations) and/or severe exacerbations (≥ 1 exacerbation requiring a hospital admission)*." [2023 GOLD Report, 2023 Global Initiative for Chronic Obstructive Lung Disease]

In addition, the table 3.6 *Evidence Supporting a Reduction in Mortality with Pharmacotherapy and Non- pharmacotherapy in COPD Patients* of the GOLD 2023 Report lists relative risk reduction observed in ETHOS and IMPACT studies as shown on the screenshot below. [2023 GOLD Report, 2023 Global Initiative for Chronic Obstructive Lung Disease]

[screenshot provided]

AstraZeneca maintains that both papers [Rabe KF, *et al*. N Engl J Med 2020, Martinez FJ, *et al*. Am J Respir Crit Care Med. 2021; 203] clearly support the mortality reduction claim of BGF320 vs GFF therefore refute a breach of clauses *5.1, 6.1, 6.2, 6.3, 14.1 & 14.4.*

The complaint further alleges; "The graph is also titled 'difference observed in all-cause mortality in all treatment arms'. These are highly misleading claims & I believe that when the investigators of Ethos have concluded that there is no significant difference, to be making risk reduction claims of 46% do not represent an accurate reflection of Trixeo's merits."

Alleged breach of 5.1, 6.1, 6.2, 6.3, 14.1 & 14.4

AstraZeneca Response:

The claim in the IDA of "Difference observed in all-cause mortality across all treatment arms" is based on the observed differences. On the page we clearly state the results of the comparisons between BGF320 vs GFF ("*Over 52 weeks, Trixeo demonstrated a 46% reduction vs a LAMA/LABA, HR 0.54; 95% CI 0.34 to 0.87, unadjusted p=0.0111*") and BGF320 vs BFF (*"28% reduction vs an ICS/LABA, HR 0.72; 95% CI 0.44–1.16; p=0.1721 (NS*)") so that the reader is provided with the information required to accurately interpret each treatment comparison. The point estimates for both comparisons are numerically in favour of Trixeo and reach nominal significance for BGF320 vs GFF. On the website, the same claim is also clearly accompanied by comparison between BGF320 vs GFF ("*Over 52 weeks, Trixeo (ICS/LAMA/LABA) demonstrated a 46% reduction vs a LAMA/LABA, HR 0.54; 95% CI 0.34 to 0.87, unadjusted p=0.0111*").

It is not accurate to assert that the investigators of ETHOS have concluded that there is no significant difference. Within the secondary endpoints section of the results, it is stated:

"*In time-to-first-event analyses performed with the use of the treatment policy estimand in the intention- to-treat population, the risk of death from any cause in the 320-µg–budesonide triple therapy group was 46% lower than that in the glycopyrrolate–formoterol group (28 vs. 49 deaths; hazard ratio, 0.54; 95% CI, 0.34 to 0.87) and 22% lower than that in the budesonide–formoterol group (28 vs. 34 deaths; hazard ratio, 0.78; 95% CI, 0.47 to 1.30). The risk of death from any cause in the 160-µg–budesonide triple- therapy group was lower than that in the glycopyrrolate-formoterol group (39 vs. 49 deaths; hazard ratio, 0.79; 95% CI, 0.52 to 1.20) but higher than that in the budesonide–formoterol group (39 vs. 34 deaths; hazard ratio, 1.13; 95% CI, 0.72 to 1.80)*" [Rabe KF, *et al*. N Engl J Med 2020]

Subsequently in the discussion section, it is stated:

"*Furthermore, despite a mortality of 1.8% overall, when the triple-therapy regimens were compared with glycopyrrolate–formoterol, a lower risk of death from any cause was observed only in the 320 µg budesonide triple-therapy group, as shown by the 95% confidence interval. The hazard ratio for death from any cause in the 320 µg budesonide triple-therapy group, as compared with the 160-µg– budesonide triple-therapy group, was 0.69, but the 95% confidence interval was 0.42 to 1.13, which precluded any definitive conclusions regarding a dose–response relationship. This is the second trial to show a benefit of triple therapy over dual therapy with LAMA-LABA with respect to mortality among patients with COPD. In analyses including both on-treatment and off-treatment data, the risk of death from any cause was 46% lower in the ETHOS trial (for 320 µg budesonide triple therapy vs. glycopyrrolate-formoterol) and 29% lower in the Informing the Pathway of COPD Treatment (IMPACT) trial (for triple therapy with fluticasone furoate-umeclidinium-vilanterol vs. umeclidinium-vilanterol). The difference observed between the 320-µg– budesonide and the 160 µg budesonide triple therapy groups with respect to mortality but not the other end points is unexplained but may reflect a beneficial effect on cardiovascular outcomes in this high-risk population*." [Rabe KF, *et al*. N Engl J Med 2020]

It is clear that the investigators of the ETHOS study not only demonstrate the differences in mortality in the results from the study, but also wish to highlight for discussion the fact that the positive mortality results from this study are consistent with another study that compared triple therapy with another LABA/LAMA treatment.

AstraZeneca maintains that all relevant information to help HCPs to understand the data and provide further context for the claim were included in the material and therefore refute a breach of clauses *5.1, 6.1, 6.2, 6.3, 14.1 & 14.4.*

The complaint further alleges; "this has been flagged and the current signatories are being that this piece has been signed off by previous signatories, so they need to follow suite." (sic)

Alleged breach of 2 & 5.1

AstraZeneca Response:

AstraZeneca promotes an internal culture of speaking up in all functions across our business and has multiple channels for any employee to flag any issue or concern they might have.

With respect to the approval process for promotional materials, there are specific Nominated Signatory and Medical Ethics forums, Compliance Governance Group meetings, and regular meetings with an external ABPI Code expert consultant. All three channels are suitable gatherings where examples of current concern can be shared and discussed between nominated signatories, reviewers, material owners and compliance leads in a safe environment without fear of repercussion. The examples of concerns that the complainant has listed in their complaint could have been raised using any, or all, of these channels. There is an additional 'fail-safe' mechanism for any employee to report a concern anonymously via AZEthics if required.

After AstraZeneca became aware of this complaint, in which the complainant alleged that the issue was previously flagged up internally and ignored, AstraZeneca has undertaken an investigation of whether the issue was flagged through the above-mentioned channels. As such the records of relevant meetings, forums and discussions, emails as well as signatory comments were reviewed. The investigation has confirmed that there is neither a record from meetings or discussion forums nor any awareness within the team of these issues being raised in any meeting, forum or discussion. The investigation has confirmed that through the approval process of the material, the mortality data included in the material was discussed resulting in a consensus and the material was updated following the signatory instructions. There were no ignored comments requesting any changes to the mortality information beyond those agreed with and signed off by the signatories. In addition, any amendments requested were aligned and confirmed with the signatory.

The complainant asserts that the job bag was described by senior team members as a 're-approval', by implication suggesting that fresh perspectives are not welcome and cannot be re-discussed. This is simply incorrect. In AstraZeneca, every piece of promotional material is reviewed and certified on its own merits by the reviewers and the nominated final signatory, no matter if the material has been previously reviewed or not. In this specific case the nominated final signatory reviewed the material and made a fresh judgement before certification.

AstraZeneca maintains no breach of clauses 5.1 and 2 based on the robust internal processes in place for material approval, the absence of evidence to support the assertions made by the complainant and the high standards to which we are fully committed at all levels of the Company.

FDA Warning Letter

The FDA raised two points regarding the presentation of all-cause mortality data from the ETHOS study in a US sales aid. Though we have responded to the specifics of the UK complaint in the sections above, AstraZeneca is pleased to provide the Panel with our position on these additional points as follows.

1) ETHOS was designed with all-cause mortality as one of multiple secondary endpoints. AstraZeneca acknowledges that the study failed to show statistically significant results on endpoints higher in the analysis hierarchy. The UK promotional materials cited in this complaint prominently state 'Significant p-values in the original dataset are unadjusted due to an endpoint in the Type I error control testing hierarchy not reaching significance'. We consider that the all-cause mortality data is therefore presented in an accurate and objective manner.

2) FDA describes the withdrawal of inhaled corticosteroids (ICS) in the ETHOS study as a potential confounding factor for interpretation of the all-cause mortality data. We note that this point was not included in the UK complaint but take this opportunity to provide our position to the Panel. AstraZeneca has conducted several post-hoc analyses to specifically assess the impact of ICS withdrawal by excluding mortality events occurring early in the treatment period both in the overall population and in the population who entered the trial on an ICS. These analyses have been published and demonstrate that the risk reduction in all-cause mortality between BREZTRI vs. LAMA/LABA was not predominantly driven by an early period of ICS withdrawal in the study. [Martinez FJ, *et al*. Am J Respir Crit Care Med. 2021] Though this was not part of the substance of the UK complaint, AstraZeneca would be pleased to provide the Panel with further information about these analyses if that would assist.

AstraZeneca does not consider that the FDA correspondence changes the substance of our response to the complaint but hopes the Panel finds the additional information helpful.

In conclusion, AstraZeneca takes compliance with the Code and responsibility to uphold confidence in the industry extremely seriously and is committed to maintaining high standards in relation to all information provided about our products and in complying with the Code. We consider these promotional materials to be within the Code and are also confident in our approach to their internal approval."

PANEL RULING

The complaint related to the use of a mortality graph and a claim of 46% risk reduction between Trixeo and its dual comparators on the efficacy webpage of the Trixeo product website and in an interactive detail aid used in virtual and in-person interactions between a sales representative and a healthcare professional. The complainant alleged this was misleading and did not represent an accurate reflection of the merits of Trixeo because the study investigators had concluded there was no significant difference between Trixeo and its dual therapy comparators.

The Panel noted the mortality graph and claim related to a pre-specified secondary endpoint in the ETHOS study.

The Panel considered the clinical study provided by the complainant and AstraZeneca; it noted the ETHOS study was a 52-week, phase 3, randomised, double-blind parallel group study to evaluate the efficacy and safety of triple therapy at two dose levels of inhaled glucocorticoid (320 mcg or 160 mcg of budesonide) vs one of two dual therapies as comparators, GFF (glycopyrronium/formoterol fumarate) a LAMA/LABA and BFF (budesonide/formoterol fumarate) an ICS/LABA. The primary endpoint was the annual rate of

moderate/severe COPD exacerbations, and secondary endpoints were time to first moderate or severe COPD exacerbation, annual rate of severe COPD exacerbation, and time to death from any cause.

The Panel noted the original publication of the ETHOS study (Rabe et al.) showed a hazard ratio of 0.54 (95% CI, 0.34–0.87) with a nominal p value of 0.0111 when comparing time to death from any cause over 52 weeks between Trixeo and the LAMA/LABA comparator and AstraZeneca's submission that the positive mortality results from the ETHOS study were consistent with another study that compared triple therapy with another LABA/LAMA treatment.

The Panel noted the Martinez paper was a subsequent analysis of the all-cause mortality data after additional data retrieval for 384 of 8,509 patients who were missing week 52 vital status in the original analysis in the ETHOS study. This analysis of the final retrieved dataset stated the risk of all-cause mortality was significantly lower with Trixeo relative to the LAMA/LABA comparator (HR 0.51; 95% CI 0.33–0.80 49% reduction; unadjusted p value of 0.0035). The Panel noted this information was included in a table titled "Evidence supporting a reduction in mortality with pharmacotherapy and non-pharmacotherapy in COPD patients" in the 2023 GOLD Report (Global Initiative for Chronic Obstructive Lung Disease).

The Panel acknowledged the data had shown a reduction in all-cause mortality however it also noted that endpoints higher in the analysis hierarchy had failed to reach significance and therefore great care had to be taken in presenting the mortality data to avoid creating a misleading impression as to the statistical significance of the results.

1. <u>Webpage</u>

The efficacy webpage headed "Our evidence" provided an overview of the results of the ETHOS and KRONOS studies. Buttons linking to the study designs and definitions of exacerbations and hospitalisations were provided directly below the heading. The ETHOS study primary endpoint, the rate of moderate or severe COPD exacerbations, was presented first followed by a secondary endpoint, the annual rate of severe exacerbations (hospitalisations). This was followed by results from the KRONOS study; the Panel noted no complaint had been made about the presentation of this data.

The complaint concerned the presentation of the ETHOS secondary endpoint data on time to death from any cause over 52 weeks which appeared below the information described above.

This section was headed "ETHOS secondary endpoint" and broadly consisted of a Kaplan-Meier curve and the claims at issue.

The claim "Difference observed in all-cause mortality across all treatment arms" appeared in large black bold font above a statement "Significant p-values in the original dataset are unadjusted due to an endpoint in the Type I error control testing hierarchy not reaching significance" in smaller font. Underneath, the Kaplan-Meier curve showing the time to all-cause mortality was presented in a pale blue box. The box also contained a table showing the number of patients at risk for each treatment and time point and the following claim:

"Over 52 weeks
TRIXEO
(ICS/LAMA/LABA)

demonstrated a:
46%
Risk reduction
versus LAMA/LABA
HR 0.54; 95% CI 0.34 to 0.87;
unadjusted p=0.0111”

Below the blue box, there was a statement “Results shown include additional data from 354 patients who had incomplete 1-year vital status at the time of trial completion (NNT=80). The percentage of patient deaths included in the time-to-death analysis in each arm were as follows: BUD 320/GLY/FORM, 1.4%; BUD 160/GLY/FORM, 2.1%; GLY/FORM, 2.6%; BUD/FORM, 1.9%.”

The mortality graph was annotated as being adapted from the Martinez paper which was itself adapted from one in the original publication of the ETHOS study (Rabe et al.). The Panel noted the relevant artwork in the original publication comprised two graphs. In the main graph, the y-axis was labelled “Cumulative incidence (%)” and was shown from 0 to 100. As all data related to points between 0 and 3%, a second graph with the y-axis amended to show only this range was also included to clearly demonstrate the differences between treatment arms. The Panel noted that this context was not included in the Martinez paper or the webpage at issue (which included only the second graph).

The 46% risk reduction claim was referenced to the original publication (Rabe et al.) and the subsequent Martinez paper which had considered the full retrieved dataset and resulted in finding a higher numerical value of the hazard ratio (HR 0.51; 95% CI 0.33-0.80; unadjusted p value of 0.0035).

The Panel noted the risk reduction claim was presented to draw attention to specific elements through the use of different fonts and graphical elements. The 46% figure was prominently presented in large, bold font, in a black circle superimposed on a yellow downward arrow. “TRIXEO (ICS/LAMA/LABA)” was in purple emboldened text, while “Over 52 weeks” and “demonstrated a:” were in the normal black body font. “Risk reduction versus LAMA/LABA” was in bold in a smaller font and the remainder of the claim was in a smaller non-bold (Roman) black font.

The Panel noted COPD was a leading cause of death globally and, as such, claims that a medicine could reduce the risk of death compared with other treatment options would likely be of interest to a wide range of health professionals. It was critical that information provided was unambiguous and sufficiently complete to ensure health professionals viewing the webpage could form their own opinion of the therapeutic value of the medicine. In the Panel’s view this was particularly important given that in this instance an endpoint higher in the analysis hierarchy had failed to reach significance.

The Panel considered the immediate overall impression created by the layout of the headline claim and the presentation of the all-cause mortality data. In the Panel’s view, the use of colour, graphical features and large bold font drew the reader’s eye to key elements – namely “Difference observed in all-cause mortality across all treatment arms”, “TRIXEO (ICS/LAMA/LABA)”, “46%” and the Kaplan-Meier curve showing three treatment groups (LAMA/LABA, ICS/LABA and TRIXEO).

The Panel noted the blue box contained statistical information in relation to the LAMA/LABA treatment arm, however in its view the nominal status of the unadjusted p value was not immediately clear to viewers. It further noted statistical information was not provided for the ICS/LABA treatment arm depicted in the Kaplan-Meier curve.

The Panel concluded that the combination of the prominent elements and the failure to draw attention to the nominal p value or state that conclusions could not be drawn from the data led to the creation of a misleading impression that Trixeo reduced the risk of death across all treatment arms. This could be mistakenly interpreted as having a positive clinical impact for patients which was not supported by the data and was therefore misleading. Accordingly, the Panel ruled **breaches of Clauses 6.1 and 14.1**.

Clause 6.2 required that any information, claim or comparison must be capable of substantiation. The Panel noted that its rulings above related to the context of the material as a whole and the misleading impression created for health professionals viewing the material which in the Panel's view could not be substantiated. The Panel ruled a **breach of Clause 6.2**.

Clause 6.3 required graphs and illustrations to be presented in such a way as to give a clear, fair and balanced view of the matters with which they deal and the supplementary information to Clause 6.3 counselled caution to ensure graphs and artwork did not create a misleading impression for example by using unusual scales that could distort or exaggerate results.

The Panel noted its comments above regarding the presentation of the Kaplan-Meier curve with the shortened y-axis; it acknowledged the Kaplan-Meier curve was adapted from the Martinez paper and was accurate in all relevant respects. Importantly, however, the context in which it appeared differed. Given the mortality graph and 46% risk reduction versus LAMA/LABA claim appeared directly alongside each other, together forming the content of the pale blue box, in the Panel's view, each element had a bearing on the interpretation of the other, and the blue box should be considered in its entirety as a single "artwork" element.

In relation to the 46% risk reduction claim the Panel, on balance, considered that the comparator for the risk reduction claim was sufficiently clear. However, the failure to draw attention to the nominal p value or to further explain the status of the data could result in health professionals imputing statistical significance to the finding which was not possible because of the statistical failure. In the Panel's view this impression was compounded by the proximity of the 46% risk reduction claim and the graph and the headline claim above the pale blue box. The Panel ruled a **breach of Clause 6.3** on the basis that the omission of important explanatory information within the artwork meant a fair and balanced view had not been presented.

The Panel noted Clause 14.4 required promotion to encourage the rational use of a medicine by presenting it objectively and without exaggerating its properties. Noting its comments above regarding the nominal status of the p value and that clarity was required as to the statistical status of the results being shown, the Panel ruled a **breach of Clause 14.4**.

The Panel noted that, at the end of their complaint, the complainant had made a specific allegation about the inclusion of a risk reduction claim without comparison with absolute risk. The supplementary information to Clause 6.1, Absolute risk and relative risk, stated "Referring only to relative risk, especially with regard to risk reduction, can make a medicine appear more effective than it actually is. In order to assess the clinical impact of an outcome, the reader also

needs to know the absolute risk involved. In that regard, relative risk should never be referred to without also referring to the absolute risk.

The Panel noted that the risk reduction claim appeared next to the Kaplan-Meier curve and associated table, which provided details of the numbers at risk for each treatment arm. Notwithstanding its comments above regarding the status of the data the Panel considered that if relative risk reduction was stated, the absolute risk reduction should be presented together with the relative risk reduction in such a way as to allow the reader to make an immediate assessment of the clinical impact of an outcome. The Panel therefore ruled a **breach of Clause 6.1** in this regard.

2. Interactive detail aid

AstraZeneca's submission included the briefing material provided to representatives regarding the interactive detail aid. The interactive detail aid was intended to be presented to health professionals during face to face or virtual interactions by members of the sales team, who were trained to deliver Trixeo promotional calls. The Panel noted the briefing material stated that when presenting the clinical data for Trixeo:

- the primary endpoints of the ETHOS study must always be presented and discussed before the secondary endpoints,
- when discussing the differences observed in all-cause mortality as a secondary endpoint reference must be made to the absolute numbers in the respective trial arms and it must be made clear that the p value was unadjusted due to a type 1 error testing control hierarchy not reaching significance and
- should a health professional have further questions regarding this data, which the representative was unable to answer they should be referred to the medical education or medical science liaison team.

In the interactive detail aid, the slide at issue appeared after others showing the results for the primary endpoint and other secondary endpoints for the ETHOS study which were not the subject of the complaint. The Panel noted the layout of the slide. The title of the slide, "Difference observed in all-cause mortality across all treatment arms" appeared in white text on a turquoise background and was separated from the main body of the slide by a yellow line. The main body of the slide consisted of a white box containing the Kaplan-Meier curve showing time to all-cause mortality, the table showing the number of patients at risk for each treatment and time point, and a 46% reduction claim. The slide also included a yellow box with the statement "NNT 80 Prevent 1 death for every 80 patients treated with Trixeo for 1 year vs LAMA/LABA (95% CI 58–198)" and, below the white box, some footnotes and abbreviations.

The Panel noted a number of differences between the presentation of the information on the slide in the interactive detail aid and the webpage (described above). In the interactive detail aid, among other things:

- in the slide title, "Difference observed in all-cause mortality" was in bold text, while "across all treatment arms" was not
- the statement "Significant p-values in the original dataset are unadjusted due to an endpoint in the Type I error control testing hierarchy not reaching significance" appeared in large, bold, turquoise text directly within the white box, directly above the Kaplan-Meier curve
- the graph legend included the percentage of patient deaths (final retrieved dataset)

- the 46% reduction claim was presented as a large, turquoise “46% REDUCTION” superimposed on a pale turquoise downwards arrow, with the remainder of the text (which matched that used in the claim on the webpage) all in a single font with normal grey body text. The Panel noted the claim in the IDA was “46% reduction” rather than “46% risk reduction” as used on the webpage
- directly beneath the 46% reduction claim was the statement “Final retrieved dataset (post-hoc analyses) showed an improved signal. NNT = 80 vs a LAMA/LABA (95% CI 58–198). 28% reduction vs an ICS/LABA HR 0.72; 95% CI 0.44–1.16; p=0.1721 (NS)”.

The Panel noted the presentation of the data in the interactive detail aid included the statistical information relating to the ICS/LABA treatment arm including that the p value was “not significant”.

Having considered the differences to the format and presentation of this data compared to the webpage, and that the data would be presented to health professionals by a trained member from the sales team, the Panel concluded that recipients were not likely to be misled about the weight of the data and its statistical significance. Accordingly, the Panel ruled **no breaches of Clauses 6.1, 6.2, 6.3, 14.1 and 14.4**.

The Panel noted the complainant’s allegation about the inclusion of a risk reduction claim without comparison with absolute risk. Noting its rulings above, the Panel ruled **no breach of Clause 6.1**.

3. Approval of material

With regard to the allegation that the complainant had raised concerns about the presentation of the all-cause mortality data and associated claims but that these had been ignored, the Panel noted AstraZeneca’s submission that it had in place a number of channels and opportunities for raising issues in a safe environment and had undertaken an internal investigation into whether this matter had been raised in any of these. The Panel noted this investigation had failed to identify any issue or concern having been raised previously. The Panel noted that the complainant had provided no evidence to support their allegation that “the current signatories are being [told] that this piece has been signed off by previous signatories, so they need to follow suite [*sic*].” The Panel noted that the Constitution and Procedure stated that the complainant had the burden of proving their complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties.

Noting the complainant had not provided any evidence in support of these allegations, the Panel determined that they had not established their case on the balance of probabilities and ruled **no breach of Clause 5.1** and, accordingly, **no breach of Clause 2**.

Complaint received **7 July 2023**

Case completed **6 January 2025**