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ORIGINAL RESEARCH

# Triple Therapy with Budesonide/Glycopyrronium/Formoterol Fumarate Dihydrate versus Dual Therapies for Patients with COPD and Phenotypic Features of Asthma: A Pooled Post Hoc Analysis of KRONOS and ETHOS

Shigeo Muro[1], Munehiro Seki[2], John R Hurst[3], David Petullo[4], Jonathan Marshall[5], Karin Bowen[4], Patrick F Darken[4], Elizabeth A Duncan[6], Ayman Megally[4], Mehul Patel[5]

[1]Department of Respiratory Medicine, Nara Medical University, Nara, Japan; [2]AstraZeneca K.K., Osaka, Japan; [3]UCL Respiratory, University College London, London, UK; [4]AstraZeneca, Gaithersburg, MD, USA; [5]AstraZeneca, Cambridge, UK; [6]AstraZeneca, Durham, NC, USA

Correspondence: Mehul Patel, AstraZeneca, Academy House, 136 hills Road, Cambridge, CB2 8PA, UK, Email mehul.patel1@astrazeneca.com

**Background:** We evaluated the inhaled corticosteroid/long-acting muscarinic antagonist/long-acting $\beta_2$-agonist (ICS/LAMA/LABA) triple therapy with budesonide/glycopyrronium/formoterol fumarate dihydrate (BGF) versus dual LAMA/LABA and ICS/LABA therapies in patients with chronic obstructive pulmonary disease (COPD) and phenotypic features of asthma (bronchodilator reversibility and elevated blood eosinophils), but no asthma diagnosis, for whom treatment guidelines are limited.

**Patients and methods:** KRONOS (NCT02497001) and ETHOS (NCT02465567) enrolled patients with moderate-to-very-severe COPD, no current asthma diagnosis, and either ≥0 (KRONOS) or ≥1 (ETHOS) moderate/severe exacerbations in the prior year. This pooled post hoc analysis evaluated trough forced expiratory volume in 1 second ($FEV_1$) and $FEV_1$ area under the curve from hours 0 to 4 ($AUC_{0–4}$) change from baseline over 12–24 weeks, moderate/severe exacerbation rates, and St George's Respiratory Questionnaire (SGRQ) total score over 24 weeks with ICS/LAMA/LABA (BGF 320/14.4/10 µg), LAMA/LABA (glycopyrronium/formoterol fumarate dihydrate [GFF] 14.4/10 µg), and ICS/LABA (budesonide/formoterol fumarate dihydrate [BFF] 320/10 µg) in patients with phenotypic features of asthma defined as reversibility to salbutamol and blood eosinophils ≥300 cells/$mm^3$. Analyses were not adjusted for multiplicity.

**Results:** BGF improved trough $FEV_1$ and $FEV_1$ $AUC_{0–4}$ versus GFF (least squares mean [LSM] difference [95% confidence interval (CI)] 125 [39–211] and 153 [59–247] mL) and BFF (LSM difference [95% CI] 118 [30–207] and 146 [49–243] mL). Exacerbation rates were estimated to be lower with BGF versus GFF and BFF (respective rate ratios [95% CI] 0.28 [0.19–0.43] and 0.69 [0.45–1.05]) and SGRQ total score was estimated to be improved with BGF versus GFF and BFF (respective LSM differences [95% CI] –5.18 [–8.11 to –2.24] and –1.09 [–4.08 to 1.91]).

**Conclusion:** BGF was estimated to have benefits on lung function, exacerbations, and health-related quality of life versus dual therapies in patients with COPD and phenotypic features of asthma.

**Trial Registration:** ClinicalTrials.gov NCT02497001 and NCT02465567.

**Keywords:** asthma, budesonide/glycopyrronium/formoterol fumarate dihydrate, COPD, exacerbation, health-related quality of life, lung function

## Introduction

Elevated blood eosinophils and bronchodilator reversibility—phenotypic features of asthma—are present in a considerable proportion of patients with chronic obstructive pulmonary disease (COPD).[1–6] In patients with COPD, increased blood eosinophils have been associated with higher sputum eosinophils and type 2 inflammation markers in the

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lungs,[7,8] and this could, in part, explain the relationship between increased response to inhaled corticosteroid (ICS) treatment and elevated blood eosinophils.[9] The presence of asthma features in patients with COPD is associated with increased symptom burden, worse lung function, and increased likelihood of experiencing exacerbations compared with patients with COPD who do not have asthma features.[10] In a small prospective observational study of patients with COPD and no asthma diagnosis in Japan, approximately 50% of patients had at least one phenotypic feature of asthma.[11] The prevalence of individual phenotypic features of asthma among patients with COPD has been reported to range from 17% to 40% across several studies.[1–5]

Despite these observations, there is currently limited treatment guidance for patients who have COPD and features of asthma without a clinical diagnosis of asthma. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024[12] acknowledges that COPD and asthma can share common clinical features, such as a degree of bronchodilator reversibility and elevated blood eosinophils, and has proposed a "COPD & asthma" etiotype. In patients with concurrent asthma and COPD diagnoses, GOLD explicitly recommends that pharmacotherapy should primarily follow asthma guidelines.[12] For patients with features of asthma, but no formal asthma diagnosis, GOLD recommendations are less clear, although ICS/long-acting muscarinic antagonist (LAMA)/long-acting $\beta_2$-agonist (LABA) triple therapy is recommended as an initial pharmacological treatment for patients with a history of exacerbations and blood eosinophils ≥300 cells/mm$^3$.[12] The Japanese Respiratory Society (JRS) recommends dual ICS/LAMA therapy or dual ICS/LABA therapy as the initial pharmacological treatment for patients with a diagnosis of asthma–COPD overlap, with escalation to ICS/LAMA/LABA triple therapy when dual therapy is not sufficient.[13] For patients with COPD who do not have a concurrent asthma diagnosis, the recommended initial treatments are LAMA or LABA monotherapy or LAMA/LABA dual therapy, depending on symptom severity as determined by the physician,[13] as measured by tools such as the COPD Assessment Test or modified Medical Research Council scale. If patients experience exacerbations with dual therapy, escalation to triple therapy is a recommended option by the JRS, especially in those patients with blood eosinophils ≥300 cells/mm$^3$.[13] Other guidelines, such as those from the UK National Institute for Health and Care Excellence (NICE) and the European Respiratory Society/American Thoracic Society, are less current and do not consider asthma-like features with respect to escalation to triple therapy,[14,15] although NICE guidelines do note such features may be indicators to support the use of ICS.

The benefits of triple therapy with budesonide/glycopyrronium/formoterol fumarate dihydrate (BGF) metered-dose inhaler (MDI) versus dual therapies in patients with COPD have been demonstrated in two large, Phase III, global, randomized, controlled clinical trials. The 24-week KRONOS study (NCT02497001) evaluated BGF versus dual therapy with budesonide/formoterol fumarate dihydrate (BFF) MDI, glycopyrronium/formoterol fumarate dihydrate (GFF) MDI, or budesonide/formoterol fumarate dihydrate dry powder inhaler (BUD/FORM) in patients with moderate-to-very-severe COPD, without a requirement for a history of exacerbations in the prior year.[16] In KRONOS, BGF provided benefits on lung function versus BFF, GFF, and BUD/FORM dual therapies, and significant reductions in moderate/severe exacerbation rates for BGF versus GFF were also observed.[16] The 52-week ETHOS study (NCT02465567) evaluated BGF versus BFF or GFF in patients with moderate-to-very-severe COPD and ≥1 exacerbation in the previous year.[17] In ETHOS, BGF reduced moderate/severe exacerbation rates[17] and improved lung function[18] versus both GFF and BFF. Both the KRONOS and ETHOS studies excluded patients with a current diagnosis of asthma.[16,17] Ongoing clinical studies (NCT04609878 and NCT04609904) are evaluating the benefits of BGF in patients with inadequately controlled asthma, but data are not yet available at the time of this manuscript. However, there is evidence of treatment benefit with other multiple-inhaler and single-inhaler ICS/LAMA/LABA triple therapies in patients with asthma.[19] Accordingly, the Global Initiative for Asthma (GINA) includes ICS/LAMA/LABA triple therapy within the recommended treatment pathway for patients with uncontrolled asthma despite being prescribed ICS/LABA therapy.[6,20]

As available COPD guidelines lack clear consensus on the treatment of patients with COPD who have phenotypic features of asthma, but no current asthma diagnosis, this pooled post hoc analysis of the KRONOS and ETHOS studies aimed to assess the effects of ICS/LAMA/LABA triple therapy with BGF versus dual LAMA/LABA and ICS/LABA therapies on lung function, exacerbations, and health-related quality of life in patients with COPD who had phenotypic features of asthma.

# Methods

## Study Design and Population

Detailed descriptions of the KRONOS and ETHOS study designs have been previously published.[16,17,21] In brief, both were phase III, randomized, double-blind, multicenter studies that enrolled patients with moderate-to-very-severe COPD aged between 40 and 80 years who had an established clinical history of COPD, a smoking history of ≥10 pack-years, and a COPD Assessment Test score ≥10, despite receiving ≥2 inhaled maintenance therapies for ≥6 weeks before screening.[16,17] The eligibility criteria relating to COPD exacerbation history differed between KRONOS and ETHOS. In KRONOS, patients were not required to have had an exacerbation in the previous 12 months;[16] however, in ETHOS, patients were required to have a documented history of moderate or severe exacerbations in the 12 months before screening (≥1 moderate or severe if post-bronchodilator forced expiratory volume in 1 second [$FEV_1$] was <50% of predicted normal or ≥2 moderate or ≥1 severe if post-bronchodilator $FEV_1$ was ≥50% of predicted normal).[17] Both studies excluded patients with a current asthma diagnosis.[16,17] The present study included patients from KRONOS and ETHOS who had phenotypic features of asthma (blood eosinophils ≥300 cells/$mm^3$ and reversibility to salbutamol [≥12% and ≥200 mL increase in $FEV_1$ after administration of salbutamol]). These criteria are consistent with phenotypic features of asthma used for characterization of this type of population in the literature.[11,22,23]

Regarding treatment, patients in KRONOS were randomized 2:2:1:1 to receive BGF 320/14.4/10 µg, GFF 14.4/10 µg, BFF 320/10 µg, or BUD/FORM 400/12 µg (estimated delivered dose 320/9 µg) twice daily for 24 weeks. In ETHOS, patients were randomized 1:1:1:1 to receive BGF 320/14.4/10 µg, BGF 160/14.4/10 µg, GFF 14.4/10 µg, or BFF 320/10 µg twice daily for 52 weeks. A complete listing of Institutional Review Boards and Independent Ethics Committees for the ETHOS and KRONOS studies are included in Tables S1 and S2. The purpose of each study was disclosed to study participants in the informed consent documents.

## Outcomes

Primary and secondary endpoints for the KRONOS and ETHOS studies varied by regulatory registration requirements, and data from the overall KRONOS and ETHOS populations have been reported previously.[16,17] This post hoc analysis pooled data from KRONOS and ETHOS for various primary and secondary endpoints, including lung function over weeks 12–24 (both change from baseline in morning pre-dose trough $FEV_1$ and in post-dose $FEV_1$ area under the curve from hours 0 to 4 [$AUC_{0–4}$]), moderate/severe exacerbation rates over 24 weeks, and change in St George's Respiratory Questionnaire (SGRQ) total score over 24 weeks.

## Statistical Analysis

This post hoc analysis included patients in the KRONOS and ETHOS modified intention-to-treat (mITT) populations (including data from all randomized and treated patients obtained before treatment discontinuation) who had phenotypic features of asthma. In ETHOS, trough $FEV_1$ was assessed in the subset of patients from the mITT population who participated in the pulmonary function test substudy. Only patients within the treatment groups common to both KRONOS and ETHOS were included in this analysis (BGF 320/14.4/10 µg, GFF 14.4/10 µg, and BFF 320/10 µg),[16,17] and treatment comparisons were made for BGF versus GFF and BFF. Including only patients treated with BGF 320/14.4/10 µg from ETHOS (and not with BGF 160/14.4/10 µg) allowed for pooling of ETHOS data with data from the KRONOS study (which only included BGF 320/14.4/10 µg).[16,17] Furthermore, the BGF 320/14.4/10 µg dose is most relevant as it is the dose approved as maintenance treatment for COPD.[24]

For analysis of the lung function endpoints and change in SGRQ total score, least squares mean (LSM) change from baseline was estimated for each treatment group, and the LSM difference in the change from baseline was estimated for each treatment comparison. Lung function analyses were performed using a linear repeated measures model including the continuous covariates of baseline $FEV_1$, log baseline blood eosinophils, and percentage reversibility to bronchodilator and the categorical covariates of study, visit, treatment, treatment-by-visit interaction, and ICS use at screening (yes/no). Change in SGRQ total score was analyzed using a similar linear repeated measures model and included the continuous covariates of log baseline blood eosinophils, baseline SGRQ total score, baseline post-bronchodilator percentage

predicted $FEV_1$, and percentage reversibility to bronchodilator and the categorical covariates of treatment, visit, treatment-by-visit interaction, and ICS use at screening (yes/no). Exacerbation rates were analyzed using negative binomial regression, adjusting for study, baseline post-bronchodilator percentage predicted $FEV_1$, baseline COPD exacerbation history (0, 1, ≥2), log baseline blood eosinophils, region, and ICS use at screening (yes/no). The logarithm of time at risk of experiencing an exacerbation was used as an offset variable in the model.

This pooled, post hoc, subgroup analysis was not pre-specified, powered, or adjusted for multiplicity and, as such, should be considered exploratory; p-values are provided for informational purposes only, and cannot be used to determine if there are significant differences or not.

# Results

## Study Population

Despite patients with a current asthma diagnosis being excluded from the studies, 6.2% (98/1578) and 4.9% (314/6388) of the mITT populations of KRONOS and ETHOS, respectively, had phenotypic features of asthma (a degree of reversibility and relatively elevated eosinophils) and were included in this analysis. ICS use at screening was representative of the full cohorts in both studies (Table 1).[16,17]

## Efficacy

### Lung Function

Improvements in lung function, as assessed by changes from baseline in pre-dose trough $FEV_1$ and post-dose $FEV_1$ $AUC_{0–4}$, were estimated to be greater with BGF versus both GFF (LSM difference [95% confidence interval (CI)] 125 [39–211] mL, p = 0.0048 and 153 [59–247] mL, p = 0.0016) and BFF (LSM difference [95% CI] 118 [30–207] mL, p = 0.0094 and 146 [49–243] mL, p = 0.0033) over weeks 12–24 (Figure 1).

**Table 1** Demographic and Baseline Clinical Characteristics of Patients with COPD and Phenotypic Features of Asthma, [a]Pooled KRONOS and ETHOS mITT Populations (n = 412)

| | BGF (n=142) | GFF (n=140) | BFF (n=130) |
|---|---|---|---|
| Age (years), mean (SD) | 63.6 (7.5) | 63.3 (8.1) | 64.4 (7.4) |
| Sex, n (%) | | | |
| Female | 33 (23.2) | 32 (22.9) | 35 (26.9) |
| Male | 109 (76.8) | 108 (77.1) | 95 (73.1) |
| Current smoker, n (%) | 48 (33.8) | 53 (37.9) | 47 (36.2) |
| Blood eosinophils | | | |
| Median cells/$mm^3$ (IQR) | 362.5 (325–440) | 375 (330–460) | 405 (340–485) |
| Moderate/severe exacerbations in the previous year | | | |
| Mean (SD) | 1.4 (1.1) | 1.4 (1.1) | 1.7 (1.0) |
| 0, n (%) | 28 (19.7) | 31 (22.1) | 13 (10.0) |
| 1, n (%) | 45 (31.7) | 50 (35.7) | 38 (29.2) |
| ≥2, n (%) | 69 (48.6) | 59 (42.1) | 79 (60.8) |
| Post-bronchodilator percentage reversibility, mean (SD) | 31.8 (16.6) | 31.4 (13.6) | 29.5 (11.9) |
| Total CAT score, mean (SD) | 20.3 (6.2) | 19.1 (6.2) | 19.5 (7.0) |
| Used ICS at screening, n (%) | 103 (72.5) | 114 (81.4) | 101 (77.7) |

**Note**: [a]Patients from the mITT population with reversibility to salbutamol (≥12% and ≥200 mL increase in $FEV_1$ after administration of salbutamol) and blood eosinophils ≥300 cells/$mm^3$ (KRONOS, n = 98; ETHOS, n = 314).

**Abbreviations**: BFF, budesonide/formoterol fumarate dihydrate 320/10 µg; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate 320/14.4/10 µg; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 second; GFF, glycopyrronium/formoterol fumarate dihydrate 14.4/10 µg; ICS, inhaled corticosteroid; IQR, interquartile range; mITT, modified intention-to-treat; SD, standard deviation.

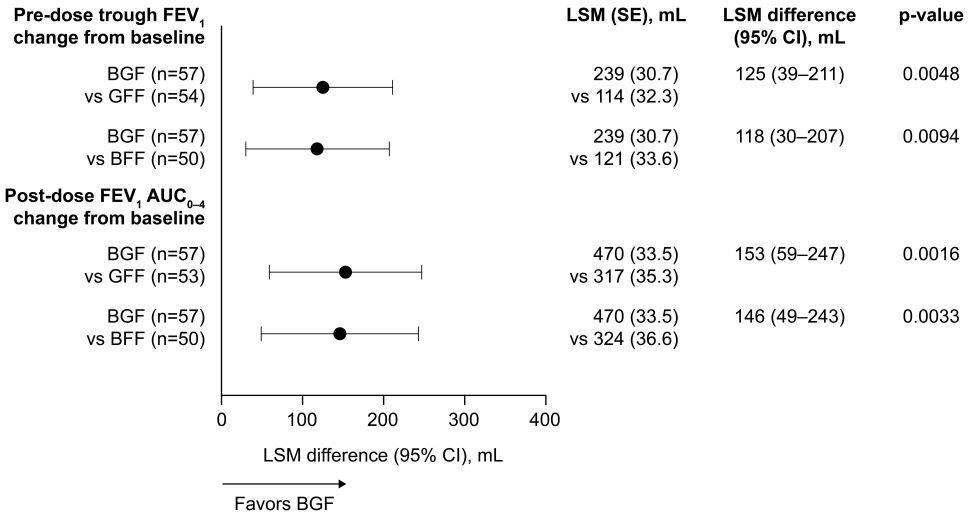


**Figure 1** Change from baseline in lung function over weeks 12–24 in patients with COPD and phenotypic features of asthma, [a]pooled KRONOS and ETHOS mITT populations (n = 412).

**Note**: [a]Patients from the mITT population with blood eosinophils ≥300 cells/mm$^3$ and reversibility to salbutamol (≥12% and ≥200 mL increase in $FEV_1$ after administration of salbutamol).

**Abbreviations**: $AUC_{0–4}$, area under the curve from hours 0 to 4; BFF, budesonide/formoterol fumarate dihydrate 320/10 µg; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate 320/14.4/10 µg; CI, confidence interval; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 second; GFF, glycopyrronium/formoterol fumarate dihydrate 14.4/10 µg; LSM, least squares mean; mITT, modified intention-to-treat; SE: standard error.

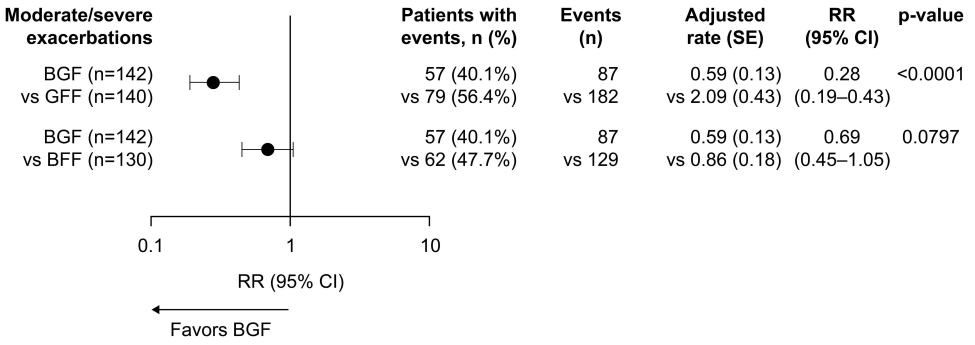


**Figure 2** Moderate/severe exacerbation rates over 24 weeks in patients with COPD and phenotypic features of asthma, [a]pooled KRONOS and ETHOS mITT populations (n = 412).

**Note**: [a]Patients from the mITT population with reversibility to salbutamol (≥12% and ≥200 mL increase in $FEV_1$ after administration of salbutamol) and blood eosinophils ≥300 cells/mm$^3$.

**Abbreviations**: BFF, budesonide/formoterol fumarate dihydrate 320/10 µg; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate 320/14.4/10 µg; CI, confidence interval; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 second; GFF, glycopyrronium/formoterol fumarate dihydrate 14.4/10 µg; mITT, modified intention-to-treat; RR, rate ratio; SE, standard error.

### Moderate/Severe Exacerbation Rates

BGF was estimated to reduce moderate/severe exacerbation rates over 24 weeks versus GFF by 72% (rate ratio [95% CI] 0.28 [0.19–0.43], p < 0.0001) and versus BFF by 31% (rate ratio [95% CI] 0.69 [0.45–1.05], p = 0.0797; Figure 2).

### SGRQ Total Score

BGF was estimated to improve SGRQ total score over 24 weeks versus GFF (LSM difference [95% CI] –5.18 [–8.11 to –2.24], p = 0.0006) and versus BFF (LSM difference [95% CI] –1.09 [–4.08 to 1.91], p = 0.4764; Figure 3).

## Discussion

This post hoc analysis of pooled data from the KRONOS and ETHOS studies examined the benefits of single-inhaler ICS/LAMA/LABA triple therapy with BGF 320/14.4/10/versus dual therapy with the LAMA/LABA GFF 14.4/10 µg or the ICS/LABA BFF 320/10 µg on lung function, exacerbations, and health-related quality of life in patients with COPD

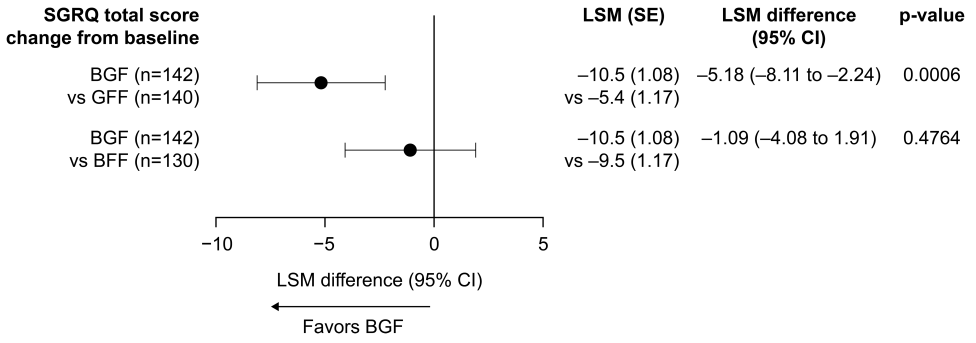


**Figure 3** Change in SGRQ total score over 24 weeks in patients with COPD and phenotypic features of asthma, [a]pooled KRONOS and ETHOS mITT populations (n = 412).
**Note**: [a]Patients from the mITT population with reversibility to salbutamol (≥12% and ≥200 mL increase in $FEV_1$ after administration of salbutamol) and blood eosinophils ≥300 cells/$mm^3$.
**Abbreviations**: BFF, budesonide/formoterol fumarate dihydrate 320/10 μg; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate 320/14.4/10 μg; CI, confidence interval; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 second; GFF, glycopyrronium/formoterol fumarate dihydrate 14.4/10 μg; LSM, least squares mean; mITT, modified intention-to-treat; SE, standard error; SGRQ, St George's Respiratory Questionnaire.

and phenotypic features of asthma (bronchodilator reversibility and blood eosinophils ≥300 cells/$mm^3$). With respect to lung function, BGF demonstrated superior treatment effects on morning pre-dose trough $FEV_1$ and post-dose $FEV_1$ $AUC_{0–4}$ compared with GFF and BFF. For moderate/severe exacerbation rate reductions and SGRQ total score improvements, BGF was estimated to have improvements versus both GFF and BFF. Considering that asthma features are associated with worse outcomes in terms of symptoms, lung function, and exacerbations in patients with COPD,[10] these findings indicate that BGF provides greater clinical benefit than LAMA/LABA dual therapy in these patients and suggest a benefit with BGF over ICS/LABA dual therapy.

These results are consistent with the findings of the overall KRONOS and ETHOS mITT populations of patients with moderate-to-very-severe COPD without a current diagnosis of asthma,[16–18] although the observed treatment benefit with BGF across lung function, exacerbation rates, and SGRQ total score in this analysis appears to be greater than that observed in the overall KRONOS and ETHOS populations. Treatment benefits were also observed in a previous post hoc analysis of KRONOS that evaluated lung function and exacerbations in patients who did not have phenotypic features of asthma (ie, no airway reversibility and blood eosinophils <300 cells/$mm^3$) and demonstrated that the overall findings of KRONOS were not driven by patients with asthma features.[25] Taken together, the previous post hoc analysis of patients in KRONOS who did not have phenotypic features of asthma and the current pooled post hoc analysis of patients from KRONOS and ETHOS with phenotypic features of asthma demonstrate that BGF provides benefits in lung function and exacerbation rates in patients both with and without phenotypic features of asthma. The available evidence also indicates that the benefits of BGF may be more pronounced among patients with COPD and phenotypic features of asthma compared with the overall study populations and those without phenotypic features of asthma. However, this post hoc analysis should be interpreted with caution due to its exploratory nature and relatively small sample size (<7% of either the KRONOS and ETHOS populations).

Although GOLD 2024 no longer refers to asthma and COPD overlap, the co-occurrence of COPD and asthma is recognized as a COPD etiotype.[12] In instances where concomitant asthma is a possibility, GOLD 2024 recommends asthma treatment guidelines should be followed and would include mandatory use of an ICS.[12] The current data suggest ICS clearly suppresses exacerbations and the addition of ICS and LAMA is more effective than either dual therapy in this population of patients with COPD and phenotypic features of asthma. These observations support the GOLD 2024 recommendations,[12] and extend the benefits of ICS to those without a formal asthma diagnosis, as such a diagnosis was an exclusion criterion in both ETHOS and KRONOS.[16,17]

Some limitations should be considered when interpreting the current analysis. While ETHOS was a 52-week study, KRONOS was only 24 weeks in duration. Thus, this analysis was limited to assessing lung function only over weeks 12–24 and exacerbations over only 24 weeks. Also, this pooled post hoc analysis was not pre-specified, powered, or adjusted for multiplicity, and reported p-values are provided for informational purposes only. Further, patients were

considered to have phenotypic features of asthma based purely on the presence of relatively elevated blood eosinophils and bronchodilator reversibility at baseline given the data available within the cohort, and it is accepted that other features of asthma could also be considered when making clinical differentiation. Additionally, it is important to note that not all patients diagnosed with COPD and features of asthma exhibit blood eosinophils >300 cells/mm$^{311}$ and that eosinophilia is observed in other conditions.[26] However, for the purpose of the current analyses, combining high blood eosinophil levels with reversibility to salbutamol was used operationally to identify a subpopulation of patients with phenotypic features of asthma in a manner consistent with the published literature,[11,22,23] as both ETHOS and KRONOS excluded patients with an overt diagnosis of asthma.[16,17] Importantly, the KRONOS and ETHOS studies excluded patients with a current asthma diagnosis. Accordingly, the percentage of patients with phenotypic features of asthma in this analysis (6.2% in KRONOS and 4.9% in ETHOS among the analyzed treatment groups in the respective mITT populations) is much lower than in a non-restricted population (eg, 25% in a previous Japanese study[27]). Therefore, this was an opportunistic analysis within these limitations.

## Conclusions

The findings of this pooled post hoc analysis of patients from the KRONOS and ETHOS studies suggest there are benefits of BGF triple therapy versus LAMA/LABA and ICS/LABA dual therapies on lung function, exacerbations and health-related quality of life in patients with moderate-to-very-severe COPD and phenotypic features of asthma but without a current diagnosis of asthma. These findings may help inform decisions regarding initial therapy and the transition to triple therapy.

## Abbreviations

$AUC_{0–4}$, area under the curve from hours 0 to 4; BFF, budesonide/formoterol fumarate dihydrate (via MDI); BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; BUD/FORM, budesonide/formoterol fumarate (via dry powder inhaler); CI, confidence interval; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 second; GFF, glycopyrronium/formoterol fumarate dihydrate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; JRS, Japanese Respiratory Society; LABA, long-acting $\beta_2$-agonist; LAMA, long-acting muscarinic antagonist; LSM, least squares mean; MDI, metered-dose inhaler; mITT, modified intention-to-treat; NICE, National Institute for Health and Care Excellence; SGRQ, St George's Respiratory Questionnaire.

## Data Sharing Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

## Ethics Approval and Informed Consent

The KRONOS and ETHOS studies were performed in accordance with Good Clinical Practice, including the Declaration of Helsinki. The protocols and informed consent forms were approved by the appropriate institutional review boards or independent ethics committees (see Tables S1 and S2). All patients provided written consent before screening.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

SM has received lecture fees from AstraZeneca, GlaxoSmithKline, KYORIN Pharmaceutical, Nippon Boehringer Ingelheim, and Novartis Pharma. MS is an employee of AstraZeneca K.K. and holds stock and/or stock options in the company. JRH reports grants from AstraZeneca, consulting fees from AstraZeneca; speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Sanofi, and Takeda; travel support from AstraZeneca; and receipt of equipment from Nonin. DP, JM, KB, PFD, AM, and MP are employees of AstraZeneca and hold stock and/or stock options in the company. EAD is a former employee of AstraZeneca and held stock and/or stock options in the company.

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