Improvements in lung function with budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler versus dual therapies in patients with COPD: a sub-study of the ETHOS trial

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Abstract

Background: In the phase III, 52-week ETHOS study in patients with moderate to very severe chronic obstructive pulmonary disease (COPD), triple therapy with budesonide/glycopyrrolate/formoterol fumarate (BGF), at two inhaled corticosteroid dose levels, resulted in significantly lower moderate/severe exacerbation rates versus glycopyrrolate/formoterol fumarate (GFF) and budesonide/formoterol fumarate (BFF). Here, we report results from the ETHOS pulmonary function test (PFT) sub-study, which assessed lung function in a subset of ETHOS patients.

Methods: ETHOS (NCT02465567) was a randomized, double-blind, multi-center, parallel-group study in patients with moderate to very severe COPD who had experienced ≥1 moderate/severe exacerbation in the previous year. Patients received BGF 320/18/9.6 µg, BGF 160/18/9.6 µg, GFF 18/9.6 µg, or BFF 320/9.6 µg twice daily via a single metered dose Aerosphere inhaler for 52 weeks. A subset of patients participated in the 4-hour PFT sub-study; primary endpoints were change from baseline in morning pre-dose trough forced expiratory volume in one second (FEV₁) versus GFF and FEV₁ area under the curve from 0 to 4 hours [AUC₀–₄] versus BFF at week 24.

Results: The PFT modified intent-to-treat population included 3088 patients (mean age 64.4 years; mean reversibility post-albuterol 16.7%; mean post-albuterol FEV₁% predicted 42.8). BGF 320/18/9.6 µg and 160/18/9.6 µg significantly improved morning pre-dose trough FEV₁ at week 24 versus GFF (p ≤ 0.0035 for both). Improvements in trough FEV₁ were also observed at week 52 for BGF 320/18/9.6 µg and 160/18/9.6 µg versus GFF (p ≤ 0.0005 for both). For FEV₁, AUC₀–₄ at week 24, BGF 320/18/9.6 µg and 160/18/9.6 µg showed significant improvements versus BFF (p < 0.0001 for both). Improvements were maintained at week 52 (p < 0.0001).

Conclusions: BGF 320/18/9.6 µg and 160/18/9.6 µg significantly improved trough FEV₁ versus GFF and FEV₁ AUC₀–₄ versus BFF at week 24. The lung function benefits with both doses of BGF were maintained following 52 weeks of treatment.

The reviews of this paper are available via the supplemental material section.

Keywords: BGF metered dose inhaler, chronic obstructive pulmonary disease, inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β₂-agonist (ICS/LAMA/LABA), pulmonary function, triple therapy

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Introduction
Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation and is ranked as the third leading cause of mortality worldwide. In 2017, COPD had a global prevalence of approximately 300 million cases, associated with approximately 3.2 million deaths, and was ranked as the seventh leading cause of disability worldwide.

The use of inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β₂-agonist (ICS/LAMA/LABA) triple therapy is recommended for patients with COPD who experience persistent exacerbations, defined as an acute worsening of respiratory symptoms resulting in the need for additional therapy, or symptoms despite the use of dual LAMA/LABA, or ICS/LABA inhaled therapies. In such patients, triple therapies have been shown to improve lung function and symptoms and reduce the frequency of COPD exacerbations relative to dual combination therapies.

In the ETHOS study (NCT02465567), the efficacy and safety of the ICS/LAMA/LABA triple fixed-dose combination therapy budesonide/glycopyrrolate/formoterol fumarate (BGF), at two ICS dose levels, delivered twice daily via a single metered dose Aerosphere inhaler, was assessed over a 52-week treatment period in symptomatic patients with moderate to very severe COPD, who had experienced at least one moderate or severe exacerbation in the previous 12 months. Moderate exacerbations were defined as those treated with corticosteroids with or without an antibiotic, and severe exacerbations were defined as those resulting in hospitalization or death. Treatment with BGF showed a significant reduction in the rate of moderate/severe COPD exacerbations, and improved symptoms and quality of life compared with glycopyrrolate/formoterol fumarate (GFF) and budesonide/formoterol fumarate (BFF). In addition, BGF 320/18/9.6 μg significantly reduced mortality versus GFF [hazard ratio 0.51, 95% confidence interval (CI) 0.33–0.80; unadjusted p-value 0.0035].

A previous study of BGF, KRONOS, assessed symptomatic patients with moderate to very severe COPD without a requirement for a history of exacerbations (NCT02497001); primary endpoints were change from baseline in morning pre-dose trough forced expiratory volume in one second (FEV₁) versus GFF and FEV₁ area under the curve from 0 to 4 hours post-dose (AUC₀₋₄) versus BFF at week 24. In the KRONOS study, BGF 320/18/9.6 μg significantly improved FEV₁ AUC₀₋₄ at week 24 compared with BFF; however, the improvement in the change from baseline in morning pre-dose trough FEV₁ at week 24 for BGF 320/18/9.6 μg compared with GFF did not reach statistical significance.

Here, we report data from the ETHOS pulmonary function test (PFT) sub-study, which assessed the effect of BGF relative to GFF and BFF on lung function, including the effect on the rate of decline, in a subset of patients in the ETHOS study, throughout the 52-week treatment period. In addition, we performed subgroup analyses based on FEV₁ severity and blood eosinophil count at baseline.

Methods

Study design
Details of the primary ETHOS study design have been published. Briefly, ETHOS was a 52-week, randomized, double-blind, parallel-group trial conducted across 26 countries. Patients received twice daily dosing with BGF 320/18/9.6 μg, BGF 160/18/9.6 μg, GFF 18/9.6 μg, or BFF 320/9.6 μg. All treatments were administered via oral inhalation from a single metered dose Aerosphere inhaler; doses represent the sum of two actuations.

Eligible patients for the ETHOS study were 40–80 years of age, with symptomatic COPD (COPD assessment test score ≥10 at screening despite receiving ≥2 inhaled maintenance therapies), had a post-bronchodilator FEV₁ 25–65% of predicted normal, and had a smoking history of ≥10 pack-years. If post-bronchodilator FEV₁ was <50% of predicted normal, patients required a history of ≥1 moderate or severe COPD exacerbation in the previous year, and if post-bronchodilator FEV₁ was ≥50% of predicted normal, a history of ≥2 moderate or ≥1 severe COPD exacerbations was required. Patients with a current diagnosis of asthma, respiratory disease other than COPD, or other significant uncontrolled diseases (including cardiac disease and cancer) were excluded.

A subset of study sites was designated for participation in the PFT sub-study, which was
conducted concurrently with the full study. For inclusion in the PFT sub-study, the average of the 60- and 30-minute pre-dose FEV₁ assessments was required to be <65% predicted normal value at visit 4. In addition, patients were excluded from the PFT sub-study if they failed to meet American Thoracic Society/European Respiratory Society spirometry criteria for acceptability and repeatability. In order to ensure that baseline FEV₁ values were stable and reflective of their true COPD severity during the screening period but prior to randomization, patients who did not meet FEV₁ baseline stability criteria were also excluded; this was defined as the average of the 60- and 30-minute pre-dose FEV₁ assessments at the randomization visit being within ±20% or 200 mL of the mean pre-dose FEV₁ obtained at the two previous visits.

Lung function endpoints and assessments
Primary endpoints of the PFT sub-study included change from baseline in morning pre-dose trough FEV₁ at week 24 and over 24 weeks for BGF versus GFF, and FEV₁ AUC₀₋₄ post-dose at week 24 and over 24 weeks for BGF versus BFF. Endpoints at week 24 were part of the US Food and Drug Administration (FDA) registration requirements and endpoints over 24 weeks were part of the European Medicines Agency (EMA) registration requirements. Other lung function endpoints included change from baseline in morning pre-dose trough FEV₁ over 52 weeks, FEV₁ AUC₀₋₄ over 52 weeks, the onset of action (defined as the first time point at which the mean change from baseline in FEV₁ exceeded 100 mL), and the rate of decline in pre-dose FEV₁ and FEV₁ AUC₀₋₄ over 52 weeks. Baseline for all FEV₁ analyses was calculated as the mean of 60- and 30-minute pre-dose FEV₁ values obtained at randomization.

During the PFT sub-study, spirometry assessments were obtained at day 1 and weeks 4, 12, 24, 36, and 52. At these visits, spirometry assessments were conducted at 60 minutes and 30 minutes pre-dose and 5 (day 1 only), 15, and 30 minutes, and 1, 2, and 4 hours post-dose.

The FEV₁ AUC₀₋₄ was calculated using the trapezoidal rule, after first having subtracted the baseline FEV₁ value, and the AUC was transformed into a weighted average by dividing by the time in hours from dosing to the last measurement included (typically 4 hours).

Statistical analyses
The PFT sub-study population was a subset of the patients in the modified intent-to-treat (mITT) population of the ETHOS study. The overall mITT population included all patients who were randomly assigned and treated and had post-randomization data obtained before discontinuation of treatment. The change from baseline in morning pre-dose trough FEV₁ and differences between treatment groups in FEV₁ AUC₀₋₄ were analyzed using a repeated measures linear mixed model. The model included baseline FEV₁, log baseline blood eosinophil count, and percentage reversibility to bronchodilator as continuous covariates, and visit, treatment, treatment by visit interaction, and ICS use at baseline as categorical covariates. Other endpoints were analyzed using a similar repeated measures linear mixed model such as morning pre-dose trough FEV₁. The rates of decline in morning pre-dose trough FEV₁ and FEV₁ AUC₀₋₄ were analyzed with a linear mixed model with random patient slopes of FEV₁ versus time, and random patient intercepts. The rate of decline (the negative of the slope) was estimated and compared between treatments. The model included similar covariates to the analysis of trough FEV₁ but with time in weeks as a continuous covariate in place of visit, smoking status as an additional categorical covariate and interactions between time and treatment, smoking status and baseline FEV₁. Rate of decline analyses used changes from the week 4 visit. In addition, patients were stratified into subgroups based on post-bronchodilator FEV₁ predicted (<50% and ≥50%) and baseline blood eosinophil count (<150 cells/mm³ versus ≥150 cells/mm³) to evaluate the potential impact of intrinsic or extrinsic factors on the results.

The primary endpoints were part of a type I error control procedure used for reporting the full ETHOS study. Other endpoints were not multiplicity controlled and were reported in terms of unadjusted p-values. Interpretation of results in subgroups relied on estimation and CIs.

In order to examine further the potential impact of lung function severity and eosinophil counts on lung function decline over one year, we performed an exploratory analysis of lung function decline in a pooled cohort of ICS-containing therapies (BGF 320/18/9.6 µg, BGF 160/18/9.6 µg, and BFF 320/9.6 µg) versus the non-ICS-containing therapy cohort (GFF 18/9.6 µg). As ICS may
modulate lung function decline, the ICS-containing therapies were combined into a single group to reduce variability and increase overall sample size of the lung function severity and eosinophil subgroups.

Results

Study population
A total of 3088 patients were included in the 4-hour PFT sub-study (36.3% of the total ETHOS mITT population; mean age 64.4 years; mean reversibility post-albuterol 16.7%; mean post-albuterol FEV₁% predicted, 42.8%; Table 1). Patient demographics were generally similar to those of the overall ETHOS mITT population.10

Morning pre-dose trough FEV₁
BGF 320/18/9.6 μg treatment resulted in significant improvements in least squares (LS) mean change from baseline morning pre-dose trough FEV₁ at week 24 compared with GFF (35 mL; p-value 0.0025; Table 2) and BFF (76 mL; unadjusted p-value < 0.0001; Table 2). Treatment with BGF 160/18/9.6 μg also significantly improved LS mean change from baseline in morning pre-dose trough FEV₁ at week 24 compared with GFF (33 mL; p-value 0.0035; Table 2) and BFF (74 mL; unadjusted p-value < 0.0001; Table 2).

Significant improvements in morning pre-dose trough FEV₁ were maintained at week 52 for BGF 320/18/9.6 μg and BGF 160/18/9.6 μg versus BFF and GFF (unadjusted p-value ⩽ 0.0005; Table 2). Improvements in FEV₁ AUC₀–₄ with both doses of BGF versus BFF and GFF were sustained throughout the 52-week treatment period (Figure 1). While there was no appreciable difference between BGF doses at week 24, there was a small numerical difference in favor of BGF 320/18/9.6 μg versus both GFF and BFF (unadjusted p-value 0.0005; Table 2).

FEV₁ AUC₀–₄
BGF 320/18/9.6 μg treatment resulted in significant improvements in LS mean FEV₁ AUC₀–₄ at week 24 compared with BFF (119 mL; p-value < 0.0001; Table 2) and GFF (53 mL; unadjusted p-value < 0.0001; Table 2). Treatment with BGF 160/18/9.6 μg also significantly improved LS mean FEV₁ AUC₀–₄ at week 24 compared with BFF (109 mL; p-value < 0.0001) and GFF (43 mL; unadjusted p-value 0.0004; Table 2). There were small numerical differences in favor of BGF 320/18/9.6 μg versus BGF 160/18/9.6 μg both at week 24 and over 24 weeks (Figure 2; Table 2).

Analyses by FEV₁ % predicted at baseline (<50% versus ⩾50%)
The effects of BGF versus GFF and BFF on morning pre-dose trough FEV₁ and FEV₁ AUC₀–₄ at week 24 in patients with post-bronchodilator FEV₁ <50% and ⩾50% predicted were directionally consistent with the overall findings but with slightly larger estimated benefits in the subgroup with post-bronchodilator FEV₁ ⩾50% (Table 3).

Analyses by baseline blood eosinophil count (<150 cells/mm³ versus ⩾150 cells/mm³)
Similarly, the effects of BGF versus GFF and BFF on morning pre-dose trough FEV₁ and FEV₁ AUC₀–₄ at week 24 in patients with blood eosinophil count <150 cells/mm³ and ⩾150 cells/mm³ were directionally consistent with the overall findings but with slightly larger estimated benefits in the subgroup with blood eosinophil count ⩾150 cells/mm³ (Table 4).

The change from baseline in morning pre-dose trough FEV₁ and FEV₁ AUC₀–₄ at week 24 for both doses of BGF versus GFF and BFF in patients with blood eosinophil counts <100 cells/mm³, 100–<300 cells/mm³, and ⩾300 cells/mm³ is shown in Supplemental Table 1. Larger changes from baseline in morning pre-dose trough FEV₁ and FEV₁ AUC₀–₄ at week 24 were seen for both doses of BGF versus GFF from blood eosinophil counts ⩾100 cells/mm³, which increased as baseline blood eosinophil count increased. Benefits were seen in morning pre-dose trough FEV₁ and FEV₁ AUC₀–₄ at week 24 for both doses of BGF versus BFF, although these did not vary across eosinophil levels to the extent observed for BGF versus GFF.
Onset of action
Improvements in FEV₁ were achieved rapidly with post-dose changes from baseline in FEV₁ being >100 mL for all four treatment groups at the 5-minute post-dose measurement (Figure 3).

Analyses of ICS-containing therapies versus GFF on lung function decline
A trend for a lower rate of decline in morning pre-dose trough FEV₁ over 52 weeks was observed in the BGF treatment groups relative to GFF (Supplemental Table 2). However, no consistent effects were observed for a lower rate of decline in FEV₁ AUC₀⁻⁴ for BGF relative to BFF (Supplemental Table 2).

Patients treated with ICS-containing therapies were pooled to assess whether benefits versus the non-ICS-containing therapy, GFF, were driven by acute ICS withdrawal in patients who received ICS prior to randomization and to increase the

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Table 1. Demographics and baseline characteristics (PFT sub-study mITT population).

|                          | BGF 320/18/9.6 µg n=747 | BGF 160/18/9.6 µg n=807 | GFF 18/9.6 µg n=779 | BFF 320/9.6 µg n=753 |
|--------------------------|--------------------------|--------------------------|---------------------|-----------------------|
| Age, years, mean (SD)    | 64.3 (7.5)               | 64.4 (7.6)               | 64.8 (7.6)          | 64.3 (7.5)            |
| Male, n [%]              | 397 (53.1)               | 441 (54.6)               | 386 (49.6)          | 407 (53.9)            |
| CAT score, mean (SD)²    | 20.2 (6.5)               | 20.5 (6.6)               | 20.3 (6.8)          | 20.4 (6.7)            |
| Body mass index, kg/m², mean (SD)² | 28.4 (6.6) | 28.3 (6.9) | 28.6 (6.6) | 27.9 (6.9) |
| Current smoker, n [%]    | 331 (44.3)               | 351 (43.5)               | 336 (43.1)          | 339 (44.9)            |
| No. pack-years smoked, c median (range) | 44.0 (10.0–150.0) | 44.6 (10.0–187.5) | 43.0 (10.0–168.0) | 44.0 (10.0–250.0) |

Baseline eosinophil count, n [%]

| <100 cells/mm³          | 106 (14.2)               | 120 (14.9)               | 95 (12.2)           | 100 (13.2)            |
| ≥100 cells/mm³          | 641 (85.8)               | 687 (85.1)               | 684 (87.8)          | 655 (86.8)            |
| <150 cells/mm³          | 255 (34.1)               | 303 (37.5)               | 266 (34.1)          | 247 (32.7)            |
| ≥150 cells/mm³          | 492 (65.9)               | 504 (62.5)               | 513 (65.9)          | 508 (67.3)            |

Exacerbation history, n [%]

| 1                        | 349 (46.7)               | 371 (46.0)               | 352 (45.2)          | 343 (45.4)            |
| ≥2                       | 398 (53.3)               | 436 (54.0)               | 427 (54.8)          | 412 (54.6)            |

Post-albuterol FEV₁, % of predicted normal, mean (SD)

| 43.1 (10.4)               | 42.5 (10.4)               | 43.0 (10.3)           | 42.7 (10.5)          |

Reversibility post-albuterol FEV₁, %, mean (SD)³

| 17.4 (16.6)               | 16.3 (16.3)               | 17.3 (15.9)          | 15.8 (15.4)          |

Reversible, n [%]

| 264 (35.3)               | 257 (31.8)               | 280 (35.9)           | 251 (33.2)           |

Use of ICS at screening, n [%]

| 562 (75.2)               | 628 (77.8)               | 598 (76.8)           | 573 (75.9)           |

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Notes: BGF 320/18/9.6 µg n = 745; BGF 160/18/9.6 µg n = 806.
GFF 18/9.6 µg n = 778; BFF 320/9.6 µg n = 753.

BFF, budesonide/formoterol fumarate; BGF, budesonide/glycopyrrolate/formoterol fumarate; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; GFF, glycopyrrolate/formoterol fumarate; ICS, inhaled corticosteroid; mITT, modified intent-to-treat; PFT, pulmonary function test; SD, standard deviation.
The sample size of the subgroup. Pooling patients treated with ICS-containing therapies showed lower annual rates of decline in pre-dose trough FEV\(_1\) versus GFF [treatment difference −16.4 mL (95% CI −36.4 mL, 3.6 mL); Table 5]. A smaller reduction in the annual rate of decline was also seen for FEV\(_1\) AUC\(_{0-4}\) in patients treated with ICS-containing therapies versus GFF [treatment difference −7.5 mL (95% CI −26.5 mL, 11.6 mL); Table 5]. Patients with moderate airflow obstruction (FEV\(_1\) ≥50% predicted at baseline) and blood eosinophil counts ≥100 cells/mm\(^3\) had a greater reduction in the adjusted annual rates of decline in morning pre-dose trough FEV\(_1\) and FEV\(_1\) AUC\(_{0-4}\) when treated with ICS-containing therapies versus GFF (Figure 4).

|                | BGF 320/18/9.6 µg versus GFF 18/9.6 µg | BGF 160/18/9.6 µg versus GFF 18/9.6 µg | BGF 320/18/9.6 µg versus BFF 320/9.6 µg | BGF 160/18/9.6 µg versus BFF 320/9.6 µg |
|----------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| Change from baseline in morning pre-dose trough FEV\(_1\), mL\(^c\) |                                      |                                      |                                      |                                      |
| At week 24     | 35 (12, 57)                           | 33 (11, 55)                           | 76 (54, 99)                           | 74 (52, 96)                           |
| p-value        | 0.0025                               | 0.0035                               | <0.0001                              | <0.0001                              |
| Over 24 weeks  | 43 (25, 60)                           | 30 (12, 47)                           | 76 (58, 94)                           | 63 (46, 81)                           |
| p-value        | <0.0001                              | 0.0009                               | <0.0001                              | <0.0001                              |
| At week 52     | 55 (30, 79)                           | 43 (18, 67)                           | 65 (40, 89)                           | 53 (29, 77)                           |
| p-value        | <0.0001                              | 0.0005                               | <0.0001                              | <0.0001                              |
| Over 52 weeks  | 46 (27, 64)                           | 36 (18, 54)                           | 72 (54, 90)                           | 62 (45, 80)                           |
| p-value        | <0.0001                              | <0.0001                              | <0.0001                              | <0.0001                              |
| FEV\(_1\) AUC\(_{0-4}\), mL\(^c\) |                                      |                                      |                                      |                                      |
| At week 24     | 53 (29, 77)                           | 43 (19, 66)                           | 119 (95, 143)                         | 109 (85, 132)                         |
| p-value        | <0.0001                              | 0.0004                               | <0.0001                              | <0.0001                              |
| Over 24 weeks  | 49 (31, 66)                           | 34 (17, 51)                           | 99 (82, 117)                          | 85 (67, 102)                          |
| p-value        | <0.0001                              | <0.0001                              | <0.0001                              | <0.0001                              |
| At week 52     | 66 (40, 92)                           | 55 (30, 80)                           | 108 (82, 133)                         | 97 (71, 122)                          |
| p-value        | <0.0001                              | <0.0001                              | <0.0001                              | <0.0001                              |
| Over 52 weeks  | 53 (35, 71)                           | 41 (23, 59)                           | 102 (84, 120)                         | 90 (72, 108)                          |
| p-value        | <0.0001                              | <0.0001                              | <0.0001                              | <0.0001                              |

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Table 2. Change from baseline\(^a\) in morning pre-dose trough FEV\(_1\) and FEV\(_1\) AUC\(_{0-4}\) [efficacy estimand; PFT sub-study mITT population\(^b\)].

\(^a\)Baseline was defined as the mean of the 30- and 60-minute values prior to dosing on day 1, if available; otherwise, the mean of the 30- and 60-minute pre-bronchodilator assessments at visit 3 were used, if available; otherwise, the mean of the 30- and 60-minute pre-bronchodilator assessments at visit 2 were used.

\(^b\)mITT population: BGF 320/18/9.6 µg, \(n = 747\); BGF 160/18/9.6 µg, \(n = 807\); GFF 18/9.6 µg, \(n = 779\); BFF 320/9.6 µg, \(n = 755\).

\(^c\)The pre-specified treatment comparisons of interest were both doses of BGF versus GFF (for trough FEV\(_1\)), and both doses of BGF versus BFF (for FEV\(_1\) AUC\(_{0-4}\)). Results in bold were type I error-controlled; all other comparisons were not adjusted for multiplicity.

AUC\(_{0-4}\), area under the curve from 0 to 4 hours post-dose; BFF, budesonide/formoterol fumarate; BGF, budesonide/glycopyrrolate/formoterol fumarate; CI, confidence interval; FEV\(_1\), forced expiratory volume in 1 second; GFF, glycopyrrolate/formoterol fumarate; LSM, least squares mean; mITT, modified intent-to-treat; PFT, pulmonary function test.
**Figure 1.** Change from baseline in morning pre-dose trough FEV₁ over study duration (efficacy estimand; PFT mITT sub-study population). Data are adjusted mean ± standard error.

BFF, budesonide/formoterol fumarate; BGF, budesonide/glycopyrrolate/formoterol fumarate; FEV₁, forced expiratory volume in 1 second; GFF, glycopyrrolate/formoterol fumarate; mITT, modified intent-to-treat; PFT, pulmonary function test.

**Figure 2.** FEV₁ AUC₀–₄ over study duration (efficacy estimand; PFT mITT sub-study population). Data are adjusted mean ± standard error.

AUC₀–₄, area under the curve from 0 to 4 hours post-dose; BFF, budesonide/formoterol fumarate; BGF, budesonide/glycopyrrolate/formoterol fumarate; FEV₁, forced expiratory volume in 1 second; GFF, glycopyrrolate/formoterol fumarate; mITT, modified intent-to-treat; PFT, pulmonary function test.
Table 3. Change from baseline in morning pre-dose trough FEV₁ and FEV₁ AUC₀–₄ at week 24 by post-bronchodilator FEV₁% predicted (efficacy estimand; PFT sub-study mITT population).

| % Predicted post-bronchodilator FEV₁ | BGF 320/18/9.6 µg versus GFF 18/9.6 µg | BGF 160/18/9.6 µg versus GFF 18/9.6 µg | BGF 320/18/9.6 µg versus BFF 320/9.6 µg | BGF 160/18/9.6 µg versus BFF 320/9.6 µg |
|--------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| Morning pre-dose trough FEV₁, mL     |                                        |                                        |                                        |                                        |
| <50% n = 2250                        | LSM [95% CI] 31 [7, 55]                 | 29 [5, 53]                             | 71 [47, 95]                           | 69 [45, 92]                           |
| p-value                              | 0.0118                                 | 0.0180                                 | <0.0001                               | <0.0001                               |
| ≥50% n = 838                         | LSM [95% CI] 47 [-4, 97]                | 47 [-2, 95]                            | 90 [39, 140]                          | 89 [40, 138]                          |
| p-value                              | 0.0705                                 | 0.0624                                 | 0.0006                                | 0.0004                                |
| FEV₁, AUC₀–₄, mL                     |                                        |                                        |                                        |                                        |
| <50% n = 2250                        | LSM [95% CI] 48 [22, 75]                | 39 [13, 65]                            | 112 [86, 138]                         | 103 [77, 129]                         |
| p-value                              | 0.0003                                 | 0.0036                                 | <0.0001                               | <0.0001                               |
| ≥50% n = 838                         | LSM [95% CI] 67 [16, 118]               | 57 [8, 107]                            | 135 [83, 186]                         | 125 [75, 175]                         |
| p-value                              | 0.0108                                 | 0.0241                                 | <0.0001                               | <0.0001                               |

AUC₀–₄, area under the curve from 0 to 4 hours post-dose; BFF, budesonide/formoterol fumarate; BGF, budesonide/glycopyrrolate/formoterol fumarate; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; GFF, glycopyrrolate/formoterol fumarate; LSM, least squares mean; mITT, modified intent-to-treat; PFT, pulmonary function test.

Figure 3. Change from baseline in FEV₁ over 4-hour post-dose interval at day 1 (efficacy estimand; PFT mITT sub-study population). Data are adjusted mean ± standard error.

BFF, budesonide/formoterol fumarate; BGF, budesonide/glycopyrrolate/formoterol fumarate; FEV₁, forced expiratory volume in 1 second; GFF, glycopyrrolate/formoterol fumarate; mITT, modified intent-to-treat; PFT, pulmonary function test.
Discussion

The findings of this 4-hour PFT sub-study of ETHOS demonstrated the benefit of BGF versus GFF and BFF on both morning pre-dose trough FEV$_1$ and FEV$_1$ AUC$_{0-4}$ for the first 24 weeks of treatment. These improvements in lung function were sustained at week 52. These findings are in line with the recommendations in the GOLD report, which notes that triple therapy can improve lung function versus dual LAMA/LABA and ICS/LABA therapies. While ETHOS was the first study of a triple fixed-dose combination therapy to evaluate two different ICS doses in the same study, it was not designed or powered to detect significant differences between the doses of BGF. Numerical trends in favor of BGF 320/18/9.6 µg over BGF 160/18/9.6 µg relative to GFF were observed for the PFT sub-study primary endpoints; however, these differences were not large. The effects of the ICS component of BGF, as reflected by improvements in trough FEV$_1$ with BGF versus GFF, were greatest in the subgroup of patients with FEV$_1$ $\geq$ 50% predicted and eosinophil counts $\geq$ 100 cells/mm$^3$.

The benefits of BGF 320/18/9.6 µg on lung function at week 24 observed in ETHOS are consistent with data from the KRONOS study, in which BGF demonstrated significant improvements in lung function relative to ICS/LABA dual therapy. As in ETHOS, a statistically significant improvement in FEV$_1$ AUC$_{0-4}$ at week 24 was also observed for BGF 320/18/9.6 µg compared with BFF in KRONOS. However, unlike ETHOS, the improvement in change from baseline in morning pre-dose trough FEV$_1$ at week 24 compared with GFF in KRONOS was numerical, but did not achieve statistical significance.

Nonetheless, it is important to note that analyses at week 24 with the attributable estimand in KRONOS, which factored in missing data, did demonstrate a significant difference between BGF 320/18/9.6 µg and GFF for trough FEV$_1$ (24 mL; unadjusted $p$-value = 0.0370). This suggested that missing data played an important role in the trough FEV$_1$ results for BGF 320/18/9.6 µg versus GFF in KRONOS.

As reported previously, lung function improvements with an ICS are known to be associated

| Baseline eosinophil count | BGF 320/18/9.6 µg versus GFF 18/9.6 µg | BGF 160/18/9.6 µg versus GFF 18/9.6 µg | BGF 320/18/9.6 µg versus BFF 320/9.6 µg | BGF 160/18/9.6 µg versus BFF 320/9.6 µg |
|---------------------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| Morning pre-dose trough FEV$_1$, mL | | | | |
| $<150$ cells/mm$^3$ $n = 1071$ | LSM (95% CI) | 12 [−24, 47] | −5 [−39, 29] | 71 [34, 107] | 54 [20, 89] |
| $p$-value | 0.5266 | 0.7828 | 0.0001 | 0.0022 |
| $\geq 150$ cells/mm$^3$ $n = 2017$ | LSM (95% CI) | 45 [17, 74] | 55 [26, 83] | 77 [49, 105] | 86 [58, 114] |
| $p$-value | 0.0019 | 0.0002 | $<0.0001$ | $<0.0001$ |
| FEV$_1$, AUC$_{0-4}$, mL | | | | |
| $<150$ cells/mm$^3$ $n = 1071$ | LSM (95% CI) | 31 [−7, 68] | 2 [−34, 37] | 117 [79, 155] | 88 [52, 124] |
| $p$-value | 0.1063 | 0.9317 | $<0.0001$ | $<0.0001$ |
| $\geq 150$ cells/mm$^3$ $n = 2017$ | LSM (95% CI) | 64 [33, 94] | 68 [37, 98] | 120 [89, 150] | 123 [93, 153] |
| $p$-value | $<0.0001$ | $<0.0001$ | $<0.0001$ | $<0.0001$ |

AUC$_{0-4}$, area under the curve from 0 to 4 hours post-dose; BFF, budesonide/formoterol fumarate; BGF, budesonide/glycopyrrolate/formoterol fumarate; CI, confidence interval; FEV$_1$, forced expiratory volume in 1 second; GFF, glycopyrrolate/formoterol fumarate; LSM, least squares mean; mITT, modified intent-to-treat; PFT, pulmonary function test.
Table 5. Adjusted rate of decline in morning pre-dose trough FEV₁ and FEV₁ AUC₀–₄ over 52 weeks by ICS-containing therapy (efficacy estimand; PFT sub-study mITT population).

|               | ICS-containing therapy N=2309 | GFF 18/9.6 µg N=779 |
|---------------|-------------------------------|---------------------|
| Morning pre-dose FEV₁, mL/year<sup>a</sup> |                               |                     |
| Adjusted rate of decline (SE)     | 37.7 (5.0)     | 54.0 (8.9)         |
| Treatment difference (95% CI)     | –               | −16.4 [−36.4, 3.6] |
| FEV₁ AUC₀–₄, mL/year<sup>b</sup>  |                               |                     |
| Adjusted rate of decline (SE)     | 56.1 (4.7)     | 63.6 (8.5)         |
| Treatment difference (95% CI)     | –               | −7.5 [−26.5, 11.6] |

<sup>a</sup>Rate of the decline of pre-dose trough FEV₁ is −1 multiplied by the average of the individual slope of pre-dose trough FEV₁ over 52 weeks across patients for the treatment.

<sup>b</sup>Rate of the decline of FEV₁ AUC₀–₄ is −1 multiplied by the average of the individual slope of FEV₁ AUC₀–₄ over 52 weeks across patients for the treatment.

AUC₀–₄, area under the curve from 0 to 4 hours post-dose; BFF, budesonide/formoterol fumarate; BGF, budesonide/glycopyrrolate/formoterol fumarate; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; GFF, glycopyrrolate/formoterol fumarate; ICS, inhaled corticosteroid; mITT, modified intent-to-treat; PFT, pulmonary function test; SE, standard error.

Figure 4. Adjusted rate of decline in pre-dose trough FEV₁ (a) and FEV₁ AUC₀–₄ (b) over 52 weeks.

Size of data point relative to size of patient cohort; n are for ICS-containing therapies and GFF 18/9.6 µg, respectively.

AUC₀–₄, area under the curve from 0 to 4 hours post-dose; CI, confidence interval; EOS, eosinophil; FEV₁, forced expiratory volume in 1 second; GFF, glycopyrrolate/formoterol fumarate; ICS, inhaled corticosteroid.
with blood eosinophil counts. In this regard, the percentage of patients with baseline blood eosinophil levels \(<150\text{ cells/mm}^3\) was 48.2% and 40.0% in the overall populations for KRONOS and ETHOS, respectively. The percentage of patients with blood eosinophil levels \(<150\text{ cells/mm}^3\) was considerably higher in KRONOS compared with ETHOS, which may explain the lower magnitude of benefit observed in pre-dose trough FEV$_1$ for BGF relative to GFF at week 24 in KRONOS. Nonetheless, the improvements observed in morning pre-dose trough FEV$_1$ at week 24 in ETHOS for BGF relative to GFF (35 mL) were consistent with values observed for the ICS component for this endpoint in other triple fixed-dose combinations at week 24 or week 26 (20 mL to 81 mL).

Although the current study was not designed to evaluate lung function decline, a trend for a lower rate of decline in morning pre-dose trough FEV$_1$ over 52 weeks was observed for both doses of BGF relative to GFF. No consistent effects were observed for rate of decline in FEV$_1$ AUC$_{0-4}$ over 52 weeks for BGF relative to BFF. However, exploratory analyses pooling ICS-containing therapies were also conducted to evaluate the effects of blood eosinophils and lung function severity on lung function decline, as these factors are known to modulate the lung function benefits of ICS in COPD. Results using the pooled data suggested that greater reductions in the annual rate of lung function decline relative to the LAMA/LABA occurred in patients with moderate airflow obstruction and those with a baseline blood eosinophil count \(\geq 100\text{ cells/mm}^3\). Although speculative, these findings suggest that there may be value in initiating ICS therapy to prevent lung function decline in COPD patients with eosinophil counts \(\geq 100\text{ cells/mm}^3\) and less severe lung function impairment, rather than waiting until a marked loss of lung function has already occurred. Clearly, prospective studies aimed at reducing the rate of lung function decline earlier in the COPD disease process are needed.

In conclusion, both BGF 320/18/9.6\(\mu\)g and BGF 160/18/9.6\(\mu\)g provided significant improvements in lung function at week 24 versus GFF and BFF in patients with moderate to very severe COPD. The benefits on lung function were sustained versus ICS/LABA and LAMA/LABA dual therapies over 52 weeks. The lung function improvements observed in this sub-study complement the improvements observed in exacerbations, symptoms, and quality of life in the overall ETHOS study in patients with moderate to very severe COPD.

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Author contributions

The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. All authors had full access to the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Klaus F Rabe, Fernando J Martinez, Dave Singh, Roopa Trivedi, and Magnus Aurivillius: Acquisition of data; data interpretation.

Martin Jenkins, Patrick Darken, and Paul Dorinsky: Conception/design; data analysis/interpretation.

Conflict of interest statement

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**Data availability**
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.

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**Supplemental material**
The reviews of this paper are available via the supplemental material section.

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