Relationship between on-treatment rescue medication use, exacerbation rates, and health-related quality of life in chronic obstructive pulmonary disease: post-hoc analysis of the ETHOS study

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Introduction

- Patients with chronic obstructive pulmonary disease (COPD) commonly use short-acting β_2-agonist (SABA) rescue therapy to relieve acute symptoms.[1,2]

- SABA rescue medication use tends to increase with increasing symptomatic burden,[1] and high SABA use can be an indicator of increased COPD exacerbation risk.[1,3,4] Furthermore, increased need for rescue medication is associated with worsening health-related quality of life (HRQoL).[5]

- In the Phase III, 52-week ETHOS study (NCT02465567), treatment with the triple fixed-dose combination inhaled corticosteroid (ICS)/long-acting muscarinic antagonist/long-acting β_2-agonist of budesonide/glycopyrronium/formoterol fumarate dihydrate (BGF) at two ICS dose levels (320 µg and 160 µg) significantly reduced the frequency of moderate or severe COPD exacerbations versus dual therapies in patients with moderate-to-very severe COPD.[6]

- In a previous post-hoc analysis, benefits of BGF 320/14.4/10 µg on exacerbation rates versus dual therapy with glycopyrronium/formoterol fumarate dihydrate (GFF) 14.4/10 µg or budesonide/formoterol fumarate dihydrate (BFF) 320/10 µg in ETHOS were seen both in patients using ≤4 and >4 puffs/day of SABA at baseline (pre-randomization), with benefits being greater in those using >4 puffs/day.[7]

- The current post-hoc analysis evaluated relationships between on-treatment SABA use, exacerbation rates, and HRQoL, while exploring the potential benefits of BGF.

Methods

Study design

- Full details of the ETHOS study design, including patient inclusion and exclusion criteria, have been published[6,8]; a summary of ETHOS methods is available via the **QR code link**.

- In brief, ETHOS was a randomized, double-blind, parallel-group, Phase III study in patients with moderate-to-very severe COPD who were symptomatic and had a history of ≥1 moderate or severe exacerbation in the past year.

- All patients must have been taking ≥2 inhaled maintenance therapies for the management of their COPD for ≥6 weeks prior to screening.

  — As-needed treatment with a SABA was provided as rescue medication throughout the study.

- Patients were randomly assigned 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, via a single metered-dose Aerosphere™ inhaler.

Analyses

- In this post-hoc analysis, COPD exacerbation rates over 52 weeks and change from baseline St George's Respiratory Questionnaire (SGRQ) total score over 24 weeks were assessed in patients with on-treatment SABA use of ≤1 versus >1 canister every 2 months.

  — One 200-puff SABA canister every 2 months is equivalent to approximately 3.3 puffs/day.

- The analysis was supplemented by generalized additive models predicting exacerbation rates and changes from baseline SGRQ total score using on-treatment mean SABA puffs/day as a continuous variable.

- The analysis was performed in patients with average baseline rescue SABA use ≥1.0 puff/day in the modified intent-to-treat (mITT) population (randomized and treated patients with on-treatment data) of the ETHOS study. This approach was chosen to focus on settings where SABAs are commonly prescribed to patients with COPD and to avoid skewing the results with data from parts of the world where SABAs are not prescribed to patients with COPD.

Results

- Of the 8509 patients in the mITT population, 5639 (66.3%) were included in the SABA rescue use population (i.e., those with average baseline SABA use of ≥1.0 puff/day).

- In the SABA rescue use population, baseline demographics and clinical characteristics were similar across treatment groups (**Table 1**).

- Across treatment groups, rates of moderate or severe exacerbations, and rates of severe exacerbations, were higher in patients with higher on-treatment rescue SABA use (**Table 2**, **Figure 1A**, and **Figure 1B**).

- Across treatment groups, improvements in SGRQ total score were smaller in patients with higher on-treatment rescue SABA use (**Table 3** and **Figure 1C**).

- Although the magnitude of treatment differences should be interpreted with caution due to the use of post-randomization information, benefits of BGF 320 versus dual therapies on exacerbation rates were seen in both SABA use subgroups (**Table 2**).

  — Generalized additive models indicated differences between BGF and GFF on rates of moderate or severe exacerbations (**Figure 1A**) and on rates of severe exacerbations (**Figure 1B**), which increased with greater SABA use, an effect that was less apparent for change in SGRQ total score (**Figure 1C**).

Table 1. Baseline demographics and clinical characteristics (SABA users[a])

|	BGF 320/14.4/10 µg (N=1430)	BGF 160/14.4/10 µg (N=1391)	GFF 14.4/10 µg (N=1389)	BFF 320/10 µg (N=1429)
Age, mean years (SD)	64.3 (7.6)	64.5 (7.6)	64.5 (7.7)	64.5 (7.7)
Sex, n (%)				
Female	618 (43.2)	562 (40.4)	597 (43.0)	597 (41.8)
Male	812 (56.8)	829 (59.6)	792 (57.0)	832 (58.2)
Current smoker, n (%)	616 (43.1)	562 (40.4)	570 (41.0)	587 (41.1)
Moderate or severe exacerbations in the previous year, n (%)				
1	642 (44.9)	631 (45.4)	634 (45.6)	625 (43.7)
≥2	788 (55.1)	760 (54.6)	755 (54.4)	804 (56.3)
Blood eosinophil count, n (%)				
≥150 cells/mm³	882 (61.7)	854 (61.4)	866 (62.3)	885 (61.9)
≥300 cells/mm³	225 (15.7)	227 (16.3)	214 (15.4)	238 (16.7)
FEV₁ % predicted,[b] mean (SD)	36.6 (10.3)	35.9 (10.2)	36.3 (10.1)	36.2 (10.7)
Post-bronchodilator % reversibility, mean (SD)	16.5 (16.7)	16.1 (16.0)	17.0 (16.7)	15.9 (15.8)
SGRQ score, mean (SD)	53.8 (15.8)	54.0 (16.3)	53.1 (15.9)	53.2 (16.3)
CAT score, mean (SD)	20.7 (6.3)	20.5 (6.4)	20.3 (6.5)	20.4 (6.4)
Used ICS at screening, n (%)	1171 (81.9)	1137 (81.7)	1128 (81.2)	1141 (79.8)
SABA use, mean puffs/day (SD)	4.6 (3.1)	4.6 (2.9)	4.6 (2.9)	4.7 (3.1)

[a]Patients with average baseline rescue SABA use ≥1.0 puff/day in the mITT population (randomized and treated patients with on-treatment data).
[b]Baseline was defined as the mean of the 30- and 60-minute values prior to dosing on Day 1 (Visit 4), if available; otherwise, the mean of the 30- and 60-minute pre-bronchodilator assessments at Visit 2 was used.
BFF, budesonide/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; GFF, glycopyrronium/formoterol fumarate dihydrate; ICS, inhaled corticosteroids; mITT, modified intent-to-treat; SABA, short-acting β₂-agonist; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

Table 2. Exacerbation rates by on-treatment rescue SABA use (SABA users[a])

	BGF 320/14.4/10 µg	BGF 160/14.4/10 µg	GFF 14.4/10 µg	BFF 320/10 µg
On-treatment SABA use ≤1 canister every 2 months				
Patients, n	774	704	634	679
Moderate or severe exacerbations				
Patients with exacerbations, n (%)	373 (48.2)	333 (47.3)	325 (51.3)	329 (48.5)
Adjusted annual rate (SE)	1.06 (0.06)	0.96 (0.06)	1.28 (0.07)	1.07 (0.06)
Rate ratio (95% CI) [two-sided p-value]				
BGF 320 versus dual therapies	–	–	0.83 (0.71, 0.97) [0.0185]	0.99 (0.85, 1.16) [0.9126]
BGF 160 versus dual therapies	–	–	0.75 (0.64, 0.88) [0.0004]	0.89 (0.76, 1.05) [0.1706]
Severe exacerbations				
Patients with exacerbations, n (%)	72 (9.3)	82 (11.6)	79 (12.5)	67 (9.9)
Adjusted annual rate (SE)	0.12 (0.02)	0.12 (0.02)	0.17 (0.02)	0.13 (0.02)
Rate ratio (95% CI) [two-sided p-value]				
BGF 320 versus dual therapies	–	–	0.72 (0.51, 1.03) [0.0718]	0.90 (0.63, 1.27) [0.5423]
BGF 160 versus dual therapies	–	–	0.75 (0.53, 1.08) [0.1182]	0.93 (0.65, 1.33) [0.6966]
On-treatment SABA use >1 canister every 2 months				
Patients, n	653	686	755	748
Moderate or severe exacerbations				
Patients with exacerbations, n (%)	362 (55.4)	391 (57.0)	456 (60.4)	448 (59.9)
Adjusted annual rate (SE)	1.42 (0.08)	1.61 (0.09)	2.32 (0.12)	1.73 (0.09)
Rate ratio (95% CI) [two-sided p-value]				
BGF 320 versus dual therapies	–	–	0.61 (0.53, 0.71) [<0.0001]	0.82 (0.71, 0.95) [0.0101]
BGF 160 versus dual therapies	–	–	0.69 (0.60, 0.80) [<0.0001]	0.93 (0.80, 1.07) [0.3116]
Severe exacerbations				
Patients with exacerbations, n (%)	80 (12.3)	92 (13.4)	112 (14.8)	133 (17.8)
Adjusted annual rate (SE)	0.16 (0.02)	0.18 (0.02)	0.24 (0.02)	0.27 (0.03)
Rate ratio (95% CI) [two-sided p-value]				
BGF 320 versus dual therapies	–	–	0.68 (0.50, 0.92) [0.0130]	0.59 (0.44, 0.79) [0.0005]
BGF 160 versus dual therapies	–	–	0.75 (0.55, 1.01) [0.0553]	0.65 (0.49, 0.87) [0.0033]

[a]Patients with average baseline rescue SABA use ≥1.0 puff/day in the mITT population (randomized and treated patients with on-treatment data).
BFF, budesonide/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; CI, confidence interval; GFF, glycopyrronium/formoterol fumarate dihydrate; mITT, modified intent-to-treat; SABA, short-acting β₂-agonist; SE, standard error.

Figure 1. A) Annual rate of moderate or severe COPD exacerbations, B) annual rate of severe COPD exacerbations, and C) change from baseline in SGRQ total score by on-treatment rescue SABA use (SABA users[a])
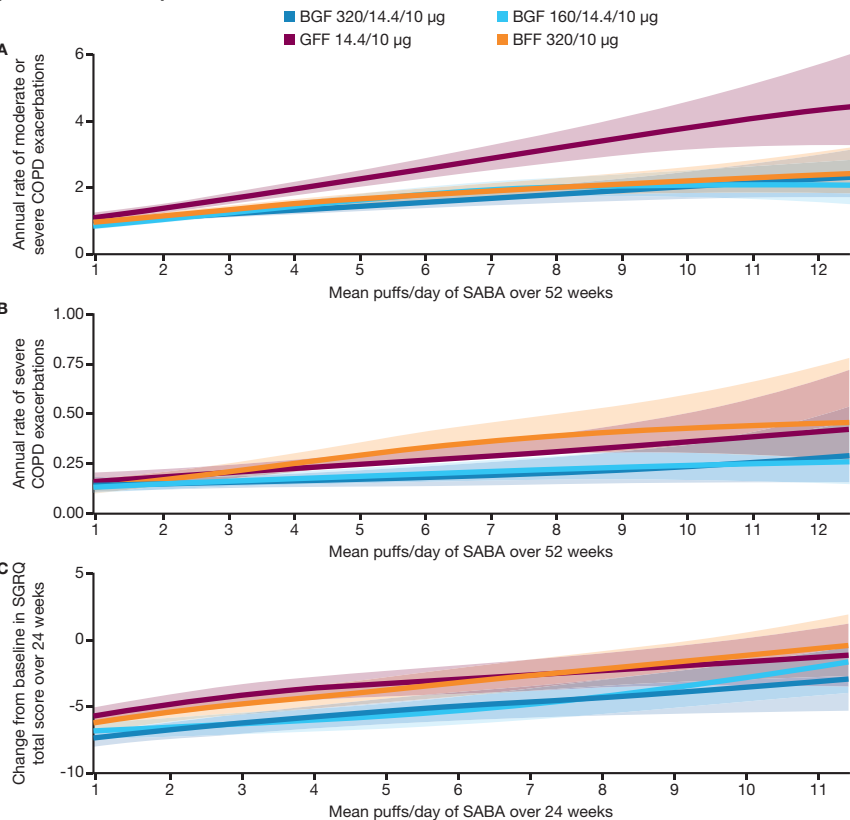
[a]Patients with average baseline rescue SABA use ≥1.0 puff/day in the mITT population (randomized and treated patients with on-treatment data).
Data from generalized additive models. Banded areas denote 95% CI.
BFF, budesonide/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFF, glycopyrronium/formoterol fumarate dihydrate; mITT, modified intent-to-treat; SABA, short-acting β₂-agonist; SGRQ, St George's Respiratory Questionnaire.

Table 3. Change from baseline in SGRQ total score over 24 weeks by on-treatment rescue SABA use (SABA users[a])

	BGF 320/14.4/10 µg	BGF 160/14.4/10 µg	GFF 14.4/10 µg	BFF 320/10 µg
Change from baseline in SGRQ total score over 24 weeks				
On-treatment SABA use ≤1 canister every 2 months				
Patients, n	774	704	634	679
LSM (SE)	−8.4 (0.41)	−7.6 (0.43)	−6.9 (0.45)	−7.4 (0.44)
LSM difference (95% CI) [p-value]				
BGF 320 versus dual therapies	–	–	−1.56 (−2.69, −0.43) [0.0068]	−1.06 (−2.17, 0.05) [0.0609]
BGF 160 versus dual therapies	–	–	−0.75 (−1.91, 0.40) [0.2007]	−0.25 (−1.39, 0.88) [0.6607]
On-treatment SABA use >1 canister every 2 months				
Patients, n	653	686	755	748
LSM (SE)	−4.9 (0.43)	−5.2 (0.43)	−3.4 (0.42)	−3.8 (0.41)
LSM difference (95% CI) [p-value]				
BGF 320 versus dual therapies	–	–	−1.49 (−2.58, −0.39) [0.0081]	−1.06 (−2.15, 0.03) [0.0566]
BGF 160 versus dual therapies	–	–	−1.78 (−2.87, −0.69) [0.0013]	−1.35 (−2.43, −0.28) [0.0138]

[a]Patients with average baseline rescue SABA use ≥1.0 puff/day in the mITT population (randomized and treated patients with on-treatment data).
BFF, budesonide/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; CI, confidence interval; GFF, glycopyrronium/formoterol fumarate dihydrate; LSM, least squares mean; SABA, short-acting β₂-agonist; SE, standard error; SGRQ, St George's Respiratory Questionnaire.

Conclusions

- BGF 320 reduced exacerbations and improved HRQoL, as measured by changes in SGRQ total score, versus dual therapies in patients with moderate-to-very severe COPD who used SABA rescue medication at either a low or high frequency during the treatment period.

- High SABA rescue medication use (i.e., >1 canister every 2 months) identifies patients at greater risk of exacerbations who may derive greater benefit from triple therapy relative to dual therapies.

- A limitation of this analysis is that it used post-randomization information and the amount of rescue medication differed by treatment group, so there is potential confounding with treatment.

References

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