Rescue medication use before, during, and after an exacerbation of chronic obstructive pulmonary disease: post-hoc analysis of the ETHOS study

368

Scan QR code for e-poster, video narration, and ETHOS methods summary

John R Hurst,[1] Gary T Ferguson,[2] Klaus F Rabe,[3] Patrick Darken,[4] Mehul Patel,[5] Paul Dorinsky[6]
Presented by Jonathan Marshall (AstraZeneca, Cambridge, UK)

UCL Respiratory, University College London, London, UK[1]; Pulmonary Research Institute of Southeast Michigan, Farmington Hills, MI, USA[2]; LungenClinic Grosshansdorf and Christian-Albrechts University Kiel, Airway Research Center North, Member of the German Center for Lung Research (DZL), Grosshansdorf, Germany[3]; AstraZeneca, Gaithersburg, MD, USA[4]; AstraZeneca, Cambridge, UK[5]; Formerly of AstraZeneca, Durham, NC, USA[6]

Introduction

- Patients with chronic obstructive pulmonary disease (COPD) commonly use short-acting β_2-agonist (SABA) rescue therapy to relieve acute symptoms.[1,2]
- Use of SABA rescue medication tends to increase with worsening symptoms, and higher SABA use can be an indicator of an impending COPD exacerbation.[1,3]
- 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.[4]
- 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 with lower (≤4 puffs/day) and higher (>4 puffs/day) SABA use at baseline, with greater benefits in those using >4 puffs/day.[5]
- This post-hoc analysis evaluated rescue SABA use in direct proximity to a COPD exacerbation to determine whether rescue SABA use increased prior to an exacerbation.

Methods

Study design

- Full details of the ETHOS study design, including patient inclusion and exclusion criteria, have been published[4,6]; 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 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 over 52 weeks, via a single metered-dose Aerosphere™ inhaler.

Analyses

- In this post-hoc analysis, rescue SABA use was evaluated for 30 days before, on the first day of, and for 30 days after the start of the first moderate or severe exacerbation, first moderate exacerbation, and first severe exacerbation.
  - 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.
  - The analyses focussed on the first exacerbation so that each patient was only considered once.
- An exacerbation was defined as a change in the patient's usual COPD symptoms that lasted ≥2 days, was beyond normal day-to-day variation, was acute in onset, and warranted a change in regular medication.
  - Symptom changes must have included ≥1 major symptom (dyspnoea, sputum volume, and sputum colour) and ≥1 other major symptom or minor symptom (cough, wheeze, sore throat, cold symptoms [rhinorrhoea or nasal congestion], and fever without other cause).
  - Moderate exacerbations were defined as those leading to treatment for ≥3 days with systemic corticosteroids and/or antibiotics. Severe exacerbations were defined as those resulting in hospitalization or death.
- The exacerbation start date was defined as the earliest of: medication start date (systemic corticosteroid and/or systemic antibiotic), hospitalization start date (if the exacerbation resulted in hospitalization), or date of death (if the exacerbation resulted in death).
  - Patients were included in the analysis regardless of whether the exacerbation start date was within the first 30 days of the study or if they discontinued within 30 days from the exacerbation start date.
- As this analysis used post-randomization information and the amount of rescue medication differed by treatment group, there is potential for confounding with treatment. Therefore, the analysis focussed on overall results across treatment groups, rather than on comparing treatment groups.

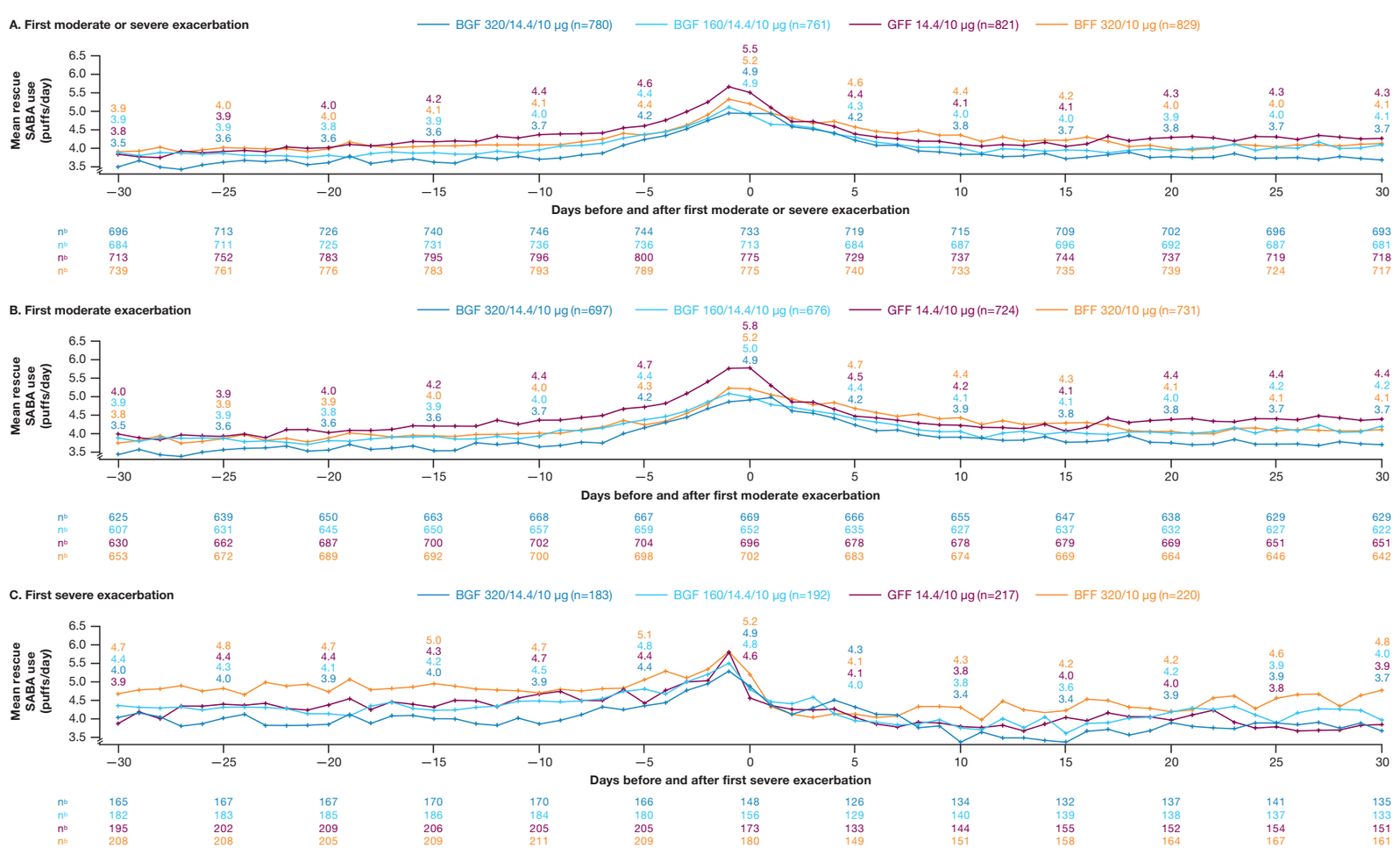
Table 1. Baseline demographics and clinical characteristics (SABA users[a])

	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/mm^3	882 (61.7)	854 (61.4)	866 (62.3)	885 (61.9)
≥300 cells/mm^3	225 (15.7)	227 (16.3)	214 (15.4)	238 (16.7)
FEV_1 % 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)
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 (3.0)	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 3 was used, 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; FEV_1, forced expiratory volume in 1 second; GFF, glycopyrronium/formoterol fumarate dihydrate; ICS, inhaled corticosteroids; mITT, modified intent-to-treat; SABA, short-acting β_2-agonist; SD, standard deviation.

Figure 1. Rescue SABA use surrounding the first A) moderate or severe exacerbation, B) moderate exacerbation, and C) severe exacerbation (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).
[b]Missing data were for patients who had a first exacerbation but were missing SABA diary counts for that day.

BFF, budesonide/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; GFF, glycopyrronium/formoterol fumarate dihydrate; mITT, modified intent-to-treat; SABA, short-acting β_2-agonist.

Results

- Of the 8509 patients in the mITT population, 5639 (66.3%) were included in the SABA rescue use population (i.e., those with an 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**).
- In all treatment groups, rescue SABA use increased in the 30 days leading up to, and decreased in the 30 days following, the first moderate or severe exacerbation (**Figure 1A**), the first moderate exacerbation (**Figure 1B**), and the first severe exacerbation (**Figure 1C**).
- Increases in mean SABA use were gradual from Day −30 to Day −7 before the exacerbation (**Figure 1A–C**).
  - For moderate or severe exacerbations, the range for mean (standard deviation [SD]) puffs/day of SABA use across treatments was 3.5 (3.5) to 3.9 (3.4) on Day −30, 3.9 (3.6) to 4.4 (3.6) on Day −7, and 4.9 (3.8) to 5.5 (4.2) on Day 0.
  - For moderate exacerbations, the range for mean (SD) puffs/day of SABA use across treatments was 3.5 (3.5) to 4.0 (3.4) on Day −30, 3.8 (3.5) to 4.5 (3.7) on Day −7, and 4.9 (4.1) to 5.8 (4.2) on Day 0.
  - For severe exacerbations, the range for mean (SD) puffs/day of SABA use across treatments was 3.9 (3.5) to 4.7 (3.9) on Day −30, 4.3 (4.1) to 4.8 (4.0) on Day −7, and 4.6 (4.1) to 5.2 (4.2) on Day 0.
  - More abrupt increases in rescue SABA use were seen in the 7 days before exacerbation onset (**Figure 1A–C**).
- Decreases in rescue SABA use in the days immediately following exacerbation onset appeared to be more abrupt for severe exacerbations than for moderate exacerbations (**Figure 1B–C**).
  - However, patients with severe exacerbations were hospitalized and may have received other interventions, including nebulized SABA, which were not captured in this analysis.
- Although treatment group comparisons were not the focus of the analysis, mean SABA use was numerically lower with BGF 320 versus GFF or BFF, both preceding and following the first moderate or severe exacerbation (**Figure 1A**) and the first moderate exacerbation (**Figure 1B**).
  - A similar trend was seen for first severe exacerbations, although there were relatively few events, making observations between treatment groups less clear (**Figure 1C**).

Conclusions

- While prospective studies are needed, the observed pattern of increased rescue SABA use preceding a COPD exacerbation may facilitate earlier detection and intervention by healthcare professionals to prevent or reduce the severity of COPD exacerbations.

Acknowledgements

The ETHOS study was supported by AstraZeneca. The authors thank all the patients and the team of investigators involved in ETHOS. Medical writing support, under the direction of the authors, was provided by Sarah Piggott, MChem, CMC Connect, a division of IPG Health Medical Communications, funded by AstraZeneca, in accordance with Good Publication Practice (GPP3) guidelines.[7]

References

1. Jenkins CR et al. BMC Pulm Med 2015; 15: 97.
2. Global Initiative for Chronic Obstructive Lung Disease. 2022 Report. Available at: https://goldcopd.org/2022-gold-reports-2/.
3. Maltais F et al. Respir Res 2020; 21: 280.
4. Rabe KF et al. N Engl J Med 2020; 383: 35–48.
5. Hurst JR et al. Eur Respir J 2021; 58 (Suppl 65): abstract PA790.
6. Rabe KF et al. Respir Med 2019; 158: 59–66.
7. Battisti WP et al. Ann Intern Med 2015; 163: 461–464.

Disclosures

Jonathan Marshall (presenter): employee of AstraZeneca and holds stock and/or stock options in the company. **John R Hurst**: consulting fees (AstraZeneca); speaker fees (AstraZeneca, Boehringer Ingelheim, Chiesi, Pfizer, and Takeda); travel support (AstraZeneca and GlaxoSmithKline). **Gary T Ferguson**: consultant (AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sunovion, Teva, Theravance, and Verona); advisory committee member (AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Sunovion, Theravance, and Verona); research grants (Amphastar, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Teva, Theravance, Sunovion, and Verona); speaker (AstraZeneca). **Klaus F Rabe**: grants (AstraZeneca and Boehringer Ingelheim); personal fees (AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, Regeneron, Roche, and Sanofi). **Patrick Darken** and **Mehul Patel**: employees of AstraZeneca and hold stock and/or stock options in the company. **Paul Dorinsky**: former employee of AstraZeneca and previously held stock and/or stock options in the company.

Primary Care Respiratory Society Conference, Telford, UK, September 22–24, 2022
(encore presentation from the American Thoracic Society International Conference, San Francisco, CA, USA, May 13−18, 2022)