

# Budesonide/Glycopyrrolate/Formoterol for the Management of COPD in a UK Primary Care Population: Real-World Use and Early Medication Success

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**Purpose:** Real-life research is needed to evaluate the effectiveness of budesonide/glycopyrrolate/formoterol (BGF) in routine COPD primary care management. We assessed the frequency of medication success among patients with COPD who initiated BGF using real-world data.

**Patients and Methods:** Patients with a recorded diagnostic COPD code who started BGF with  $\geq 2$  prescriptions within 90-days were identified in the UK Optimum Patient Care Research Database and followed from first prescription until censoring at the end of follow-up (180-days), death, leaving database or end of data at 24/10/2022. The primary outcome was medication success at 90-days post-BGF initiation, defined as no major cardiac or respiratory event (ie no complicated COPD exacerbation, hospitalization for any respiratory event, myocardial infarction, new/hospitalized heart failure, and death) and no incidence of pneumonia. Medication success was also assessed at 180-days post-BGF initiation. Overall real-life medication success was claimed if the lower 95% confidence interval (CI) for the proportion of patients meeting the primary outcome was  $\geq 70\%$  (defined a priori).

**Results:** Two hundred eighty-five patients were included. Prior to BGF initiation, these patients often had severe airflow obstruction (mean ppFEV<sub>1</sub>: 54.5%), were highly symptomatic (mMRC  $\geq 2$ : 77.9% (n = 205/263); mean CAT score: 21.7 (SD 7.8)), with evidence of short-acting  $\beta_2$ -agonist (SABA) over-use ( $\geq 3$  inhalers/year: 62.1%, n=179/285), repeat OCS prescriptions ( $\geq 2$  courses/year: 33.0%, n = 95/285) and multiple primary care consultations ( $\geq 2$  visits/year: 61.1%, n = 174/285). Overall, 39.6% of patients (n = 113/285) switched from previous triple therapies. Real-life medication success was achieved by 96.5% of patients (n = 275/285 [95% CI: 93.6, 98.3]) during 90-days treatment with BGF and by 91.8% (n = 169/184 [95% CI: 86.9, 95.4]) of patients at 180-days. The prescribed daily dose of SABA remained stable over the study period.

**Conclusion:** The majority of patients initiating BGF experienced real-life medication success reflecting the absence of severe cardiopulmonary events. These benefits were apparent after 90-days of treatment and sustained over 180-days.

**Keywords:** death, exacerbation, heart failure, myocardial infarction, pneumonia

## Introduction

Worldwide, 10.3% of the population aged 30–79 years are living with chronic obstructive pulmonary disease (COPD),<sup>1,2</sup> ranked as the third leading cause of death globally (responsible for 3.23 million deaths in 2019), and the 7<sup>th</sup> leading cause of poor health.<sup>3</sup> In the UK, COPD affects approximately 1.8–2.0% of the population of England and Scotland in 2011,<sup>4</sup> has one of the worst age-standardised years of life lost from COPD in Europe,<sup>5</sup> and has an annual direct healthcare cost estimated to increase to \$2.32 billion in England alone by 2030.<sup>4</sup> Patients with COPD are also frequently affected by other comorbidities, particularly cardiovascular disease (CVD)<sup>6</sup> and have a 2–3 fold increased risk of coronary artery disease and other

cardiovascular comorbidities.<sup>7–9</sup> The presence of CVD is associated with increased hospitalisation risk, length of hospital stay, and all-cause COPD-related mortality.<sup>6</sup> There is still substantial scope to improve COPD assessment and to optimize treatment to reduce patients' overarching cardiopulmonary risk.<sup>10</sup>

COPD is preventable and treatable.<sup>1,3</sup> Triple therapy (ie inhaled corticosteroid (ICS)/long-acting muscarinic antagonist (LAMA)/long-acting  $\beta_2$ -agonist (LABA)) is recommended as an initial treatment option for patients with  $\geq 2$  moderate exacerbations (or  $\geq 1$  exacerbation leading to hospitalization) with blood eosinophil count (BEC)  $\geq 300$  cells/ $\mu\text{L}$ , and as follow-up treatment for those with persistent exacerbations while treated with either LABA or LAMA (plus BEC  $\geq 300$  cells/ $\mu\text{L}$ ) or with LABA+LAMA (plus BEC  $\geq 100$  cells/ $\mu\text{L}$ ).<sup>1</sup> The Global Initiative for chronic obstructive Lung Disease (GOLD) recognizes that single inhaler therapy (ie, fixed dose inhalers) may be more convenient and effective than multiple inhalers.<sup>1</sup> Budesonide/glycopyrrolate/formoterol (BGF; BREZTRI/TRIXEO, AstraZeneca, Cambridge, UK) is one such fixed dose triple combination therapy, and approved by the European Medicines Agency (EMA) in 2020 for the maintenance treatment in adult patients with moderate-to-severe COPD, who are not adequately treated with ICS+ LABA or LABA+LAMA.<sup>11</sup>

The efficacy and safety of BGF has been evaluated in patients with moderate to very severe COPD in two multi-centre, randomized controlled trials (RCTs), including COPD patients symptomatic while receiving two or more daily maintenance therapies (ie, ETHOS and KRONOS).<sup>12,13</sup> In both studies, BGF treatment significantly reduced the annual rate of on-treatment moderate/severe exacerbations versus LAMA+LABA comparators; a 24% and 52% lower rate of moderate-to-severe exacerbations versus LAMA/LABA in ETHOS and KRONOS, respectively,<sup>12,13</sup> and was associated with a 46–49% lower mortality compared with LAMA/LABA in ETHOS.<sup>12,14</sup> BGF treatment also significantly improved on-treatment lung function versus dual-therapy comparators, an effect which was sustained for the study duration, and reduced dyspnoea scores, improved disease-specific health status and reduced use of rescue medication.<sup>12,13</sup>

Although these RCTs convincingly demonstrated the efficacy and safety of BGF,<sup>12–14</sup> they included homogenous and rigidly defined patient populations, not necessarily representative of the general COPD population. It has been estimated that as few as 23% of real-life COPD patients seen in primary care in the UK would be eligible for inclusion into COPD clinical trials of inhaled long-acting bronchodilators.<sup>15</sup> Although providing vital evidence of cause and effect, RCTs are considered insufficient by themselves to provide holistic evidence of the benefit/risk ratio of interventions when offered, initiated or used in a heterogeneous patient population and care settings that exist outside the trial environment.<sup>16</sup> It is, therefore, necessary to assess their generalizability and applicability to the general patient population and to specific subgroups usually excluded by RCTs.<sup>16</sup> The observational study design, including a broad population and free ecology of care,<sup>17</sup> offers the opportunity to study interventions in real-life, providing an insight into how therapies are used and how they perform outside the tight confines and rigours of RCTs. According to the EMA, observational studies are a fundamental part of epidemiological research, and can complement knowledge from RCTs and fill certain gaps, particularly where clinical trials cannot be conducted.<sup>18</sup>

As a relatively new medication, real-life evidence of the safety, acceptability and effectiveness of BGF is limited. Real-life research is needed to reflect patient experience when switching to BGF, and to evaluate the effectiveness of BGF in routine COPD management, thus providing reassurance to health care providers considering stepping up patients to triple therapy or when switching from one triple therapy to another. This is particularly important when one considers that switching inhaler regimens is a complex issue and can have highly variable clinical consequences.<sup>19</sup> The electronic medical records (EMRs) collected within the UK Optimum Patient Care Research Database (OPCRD) provide a source of up-to-date real-world data to investigate these questions.<sup>20,21</sup> The aim of our study was to assess the frequency of real-life medication success among patients with COPD initiating treatment with BGF using real-world data. The abstract of this paper was presented at the 2023 European Respiratory Society International Congress as an abstract presentation with interim findings. The poster's abstract was published in "Poster Abstracts" in the European Respiratory Journal ([https://erj.ersjournals.com/content/62/suppl\\_67/PA1319](https://erj.ersjournals.com/content/62/suppl_67/PA1319); doi: 10.1183/13993003.congress-2023.PA1319).

## Material and Methods

### Study Design

This was a historical cohort study, including a real-life population of patients with a recorded Quality and Outcomes Framework (QoF) diagnostic code for COPD, who were early adopters of BGF (ie BGF prescription within 2 years of

launch) and registered at General Practitioner clinics in the UK. Patients were followed from first BGF prescription until censoring at the end of follow-up at 180 days, death, leaving the database or end of data collection on 24<sup>th</sup> October 2022. The current study protocol was approved by the Anonymised Data Ethics & Protocol Transparency committee (ADEPT0123), performed and reported in compliance with Good Clinical Practice and Good Pharmacoepidemiology Practice, STrengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines, and the real-life evidence assessment tool (RELEVANT)<sup>22</sup> and registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; EUPAS104156).<sup>23</sup>

## Data Source

Patients' EMRs were extracted from the OPCRd, which currently contains data from 1100 general practices within the UK, providing de-identified data from more than 23 million patients.<sup>20,21</sup> Within the OPCRd, patients have a mean duration of 11.7 years' follow-up (standard deviation [SD] 17.50), with a majority having key summary data from birth to last data entry.<sup>21</sup> Patients prescribed BGF had a mean of 21.4 (SD 17.9) years in the database (median: 18.6 years, IQR 6.6–31.2). GP practices provided consent for OPCRd to collect their patients' de-identified data. Individual patients could opt-out of contributing data to OPCRd. No patient identifiable information was available to the study team. See [online supplement 1](#) for additional information about OPCRd.

## Patients

Patients were required to have a recorded QoF diagnostic code for COPD (see [online supplement 2](#) for QoF criteria),  $\geq 1$  prescription of BGF from the start of data availability up to 90 days prior to the date of data extraction, and  $\geq 1$  further prescription of BGF without any other LABA-, LAMA-/ICS-containing prescription within 90 days of the first BGF prescription (ie, continuous users with  $\geq 2$  BGF prescriptions within 90 days). Patients were also required to be  $\geq 40$  years old, current or ex-smokers, and have  $\geq 1$  year of continuous practice data prior to BGF initiation. Those with other chronic lower respiratory conditions were excluded. Those with asthma were not excluded as asthma diagnosis in patients with COPD is commonly found in real-world data. This reflects similarities in clinical presentation. It is also challenging to precisely ascertain which patients acquired asthma as a part of the diagnostic pathway to COPD (ie initially diagnosed with asthma and then corrected to COPD) and which patients have a true combination of phenotypic features of both diseases. We did, however, conduct sensitivity analyses in those with and without asthma (see below).

## Study Variables

Study variables included patient demographic and COPD clinical characteristics ([Tables 1 and 2](#)), major cardiac and respiratory events (MACRE) and incidence of pneumonia. See [S-Table 1](#) for a full list of variables collected, including definitions and categorizations. Our MACRE definition was based on that previously published by the Collaboration on Quality Improvement Initiative for Achieving Excellence in Standards of COPD<sup>24</sup> and included a new diagnosis of heart failure or hospitalization for heart failure, myocardial infarction, hospitalization for any respiratory event, complicated COPD exacerbation or death (all-cause). A complicated COPD exacerbation was one which required hospitalization or treatment with acute oral corticosteroid (OCS) and/or antibiotics between 8 and 28 days after the date of COPD exacerbation coding. Pneumonia was required to be physician-diagnosed and confirmed by chest x-ray or hospital admission within 1 month of diagnosis (as defined previously).<sup>25</sup>

## Study Outcomes

The primary outcome was real-life medication success at 90 days post-BGF initiation (early medication success), a binary, composite outcome defined as no MACRE and no incidence of pneumonia (ie modified MACRE). It thus comprised both safety and efficacy outcomes, the former including incidence of heart failure, myocardial infarction, pneumonia and mortality, and the latter including incidence of hospitalization for respiratory events or complicated COPD exacerbations. The term overall real-life medication success was claimed if  $\geq 70\%$  of patients met the above criteria (ie, if the lower 95% confidence interval (CI) for the % of patients with medication success was  $\geq 70\%$ ). Previously published asthma studies have defined this as a clinically meaningful limit.<sup>26,27</sup> The secondary outcome

**Table 1** Demographic and Clinical Characteristics for Patients with COPD Initiating BGF

	<b>New BGF users (N=285)</b>
<b>Age</b>	
Median (IQR)	69.8 (62.7–77.3)
40 to < 60 yrs, n (%)	51 (17.9)
60 to < 80 yrs, n (%)	185 (64.9)
80 to < 100 yrs, n (%)	49 (17.2)
<b>Sex</b>	N=284
Female, n (%)	153 (53.9)
<b>BMI</b>	N=284
Mean (SD)	28.4 (7.3)
0 to < 18.5, underweight n (%)	18 (6.3)
18.5 to < 25, healthy weight n (%)	84 (29.6)
25 to < 30, overweight n (%)	82 (28.9)
>30, obese n (%)	100 (35.2)
<b>Smoking status</b>	N=284
Current, n (%)	105 (36.8)
Ex, n (%)	180 (63.2)
<b>Index of Multiple Deprivation Decile<sup>A</sup></b>	N=279
1–4, n (%)	144 (51.6)
5–7, n (%)	103 (36.9)
8–10, n (%)	32 (11.5)
<b>Race</b>	N=267
White, n (%)	255 (95.5)
Asian, n (%)	4 (1.5)
Mixed/Others, n (%)	8 (3.0)
<b>Comorbidities</b>	
Active asthma (within 1 year prior to BGF initiation), n (%)	88 (30.9)
Asthma prior to 40 yrs old, n (%)	36 (12.6)
Validated COPD diagnosis, n (%)	96 (33.7)
Ischemic heart disease, n (%)	35 (12.3)
Heart failure, n (%)	27 (9.5)
Depression or anxiety, n (%)	167 (58.6)
<b>Time since first validated COPD diagnosis, years</b>	N=171
Median (IQR)	7.9 (4.4–11.7)
<b>FEV<sub>1</sub> (within 2 years prior to BGF initiation), L</b>	N=70
Mean (SD)	1.5 (0.7)
<b>FEV<sub>1</sub>% predicted (within 2 years prior to BGF initiation)</b>	N=50
Mean (SD)	54.5% (22.6)
<b>GOLD stage (2022 version)</b>	N=50
0 <30, n (%)	6 (12.0)
30 <50, n (%)	19 (38.0)
50 <80, n (%)	15 (30.0)
80 <110, n (%)	10 (20.0)

(Continued)

Table 1 (Continued).

	New BGF users (N=285)
<b>mMRC Score (nearest and within 2 years prior to BGF initiation)</b>	N=263
0, n (%)	8 (3.0)
1, n (%)	50 (19.0)
2+, n (%)	205 (77.9)
<b>GOLD 2022 group<sup>B</sup></b>	
A, n (%)	9 (3.2)
B, n (%)	23 (8.1)
C, n (%)	49 (17.2)
D, n (%)	182 (63.9)
Missing, n (%)	22 (7.7)
<b>CAT score (nearest and prior to BGF initiation)</b>	N=218
Mean (SD)	21.7 (7.8)
<b>Exacerbations</b>	
Any, n (%)	100 (35.1)
<b>Moderate exacerbations (within a year prior to BGF initiation)</b>	
Mean (SD)	0.79 (1.5)
I+, n (%)	100 (35.1)
<b>Complicated exacerbations (within a year prior to BGF initiation)</b>	
Exacerbations, mean (SD)	0.15 (0.53)
I+, n (%)	27 (9.5)

**Notes:** <sup>A</sup>The Index of Multiple Deprivation is the official measure of relative deprivation for small areas in England. The IMD combines information from the seven domains (income, employment, education, health, crime, housing and service, environment) to produce an overall relative measure of deprivation. <sup>B</sup>COPD groups defined as follows: A: 0 or 1 moderate or severe exacerbations (not leading to hospitalization), mMRC 0–1 and CAT <10; B: 0 or 1 moderate or severe exacerbations (not leading to hospitalization), mMRC ≥2 and CAT ≥10. C: ≥2 moderate or severe exacerbations (≥1 leading to hospitalization), mMRC 0–1 and CAT <10; D: ≥2 moderate or severe exacerbations (≥1 leading to hospitalization), mMRC ≥2 and CAT ≥10.

**Abbreviations:** BGF, beclometasone/glycopyrrolate/formoterol; BMI, body mass index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in one second; GOLD, Global Obstructive Lung Disease; IQR, inter-quartile range; mMRC, modified Medical Research Council; SD, standard deviation.

Table 2 COPD Treatment and Consultation Burden for Patients with COPD Initiating Treatment with BGF

	New BGF users (N=285)
<b>Acute OCS prescription (within a year prior to BGF)</b>	
Mean (SD)	1.9 (3.7)
0, n (%)	158 (55.4)
1, n (%)	33 (11.6)
2, n (%)	20 (7.0)
3+, n (%)	74 (26.0)
<b>Antibiotic prescription within 3 days of a LRT infection (within a year prior to BGF initiation)</b>	
Mean (SD)	0.6 (1.6)
0, n (%)	204 (71.6)
1, n (%)	44 (15.4)
2, n (%)	17 (6.0)
3+, n (%)	20 (7.0)

(Continued)

Table 2 (Continued).

	New BGF users (N=285)
<b>Daily SABA Dose (<math>\mu\text{g}</math>, within a year prior to BGF initiation)</b>	
Mean (SD)	395.7 (415.3)
0 <100, n (%)	91 (31.9)
100 <200, n (%)	28 (9.8)
200 <300, n (%)	24 (8.4)
300 <400, n (%)	20 (7.0)
400 <3000, n (%)	122 (42.8)
<b>SABA Inhalers (within a year prior to BGF initiation)</b>	
Mean (SD)	7.1 (7.1)
0, n (%)	69 (24.2)
1–2, n (%)	39 (13.7)
3–6, n (%)	46 (16.1)
7–10, n (%)	43 (15.1)
11–15, n (%)	53 (18.6)
$\geq 16$ , n(%)	35 (12.3)
<b>COPD Primary Care Consultations (within a year prior to BGF initiation)</b>	
Mean (SD)	2.3 (1.9)
0, n (%)	26 (9.1)
1, n (%)	85 (29.8)
2–4, n (%)	143 (50.2)
5–6, n (%)	20 (7.0)
$\geq 7$ , n (%)	11 (3.9)
<b>Maintenance Treatment immediately prior to BGF initiation<sup>A</sup></b>	
None, n (%)	47 (16.5)
LAMA, n (%)	9 (3.2)
LABA, n (%)	1 (0.4)
LABA+LAMA, n (%)	48 (16.8)
ICS+LABA, n (%)	53 (18.6)
Free triple, separates, n (%)	81 (28.4)
Fixed triple, n (%)	32 (11.2)
Other Separate/Combinations, n (%)	14 (4.9)
<b>Maintenance Treatment (within a year prior to BGF initiation)<sup>B</sup></b>	
None, n (%)	58 (20.4)
LAMA, n (%)	3 (1.1)
LABA, n (%)	1 (0.4)
LABA+LAMA, n (%)	38 (13.3)
ICS+LABA, n (%)	104 (36.5)
Free triple, separates, n (%)	67 (23.5)
Fixed triple, n (%)	92 (32.3)

**Notes:** <sup>A</sup>The last combination of maintenance COPD treatments in the year prior to the index date, combination treatment containing separates occur on the same day (patients are only in one category). <sup>B</sup>All combinations of maintenance COPD treatments in the year prior to the index date, patients receiving individual separates on the same day are classed as combinations (patients can be in multiple categories).

**Abbreviations:** BGF, budesonide glycopyrrolate formoterol; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic antagonist; LRT, lower respiratory tract; OCS, oral corticosteroid; SABA, short-acting  $\beta_2$ -agonist; SD, standard deviation.

was real-life medication success assessed at 180 days post-BGF initiation Average daily short-acting  $\beta_2$ -agonist (SABA) dose (ie 0 to <101; 101 to <201; 201 to <301; 301 to <401 and >401 mcg/day) was assessed as an exploratory outcome, assessed in the year prior to the index date (baseline) and at 90- and 180-days post-BGF initiation.

## Statistical Analysis

The statistical analysis plan was pre-defined. Stata version 15.1 (College Station, TX, US) was used to conduct all statistical analyses. The sample size calculation was based on the primary outcome of medication success. Assuming 80% of patients had success, 285 patients were sufficient to achieve a 97.6% power to show a medication success rate  $\geq 70\%$  at the  $p < 0.025$  (one sided) level of significance. Patient demographic, COPD clinical characteristics and the proportion of patients achieving 90- and 180-day real-life medication success were summarized descriptively. Real-life medication success at 90 days was also described according to asthma status (ie, never, inactive or active), for those who stepped-up to BGF from previous non-triple or other triple therapies and according to pre-BGF exacerbation burden (ie, 0 or  $\geq 1$  COPD exacerbations/year).

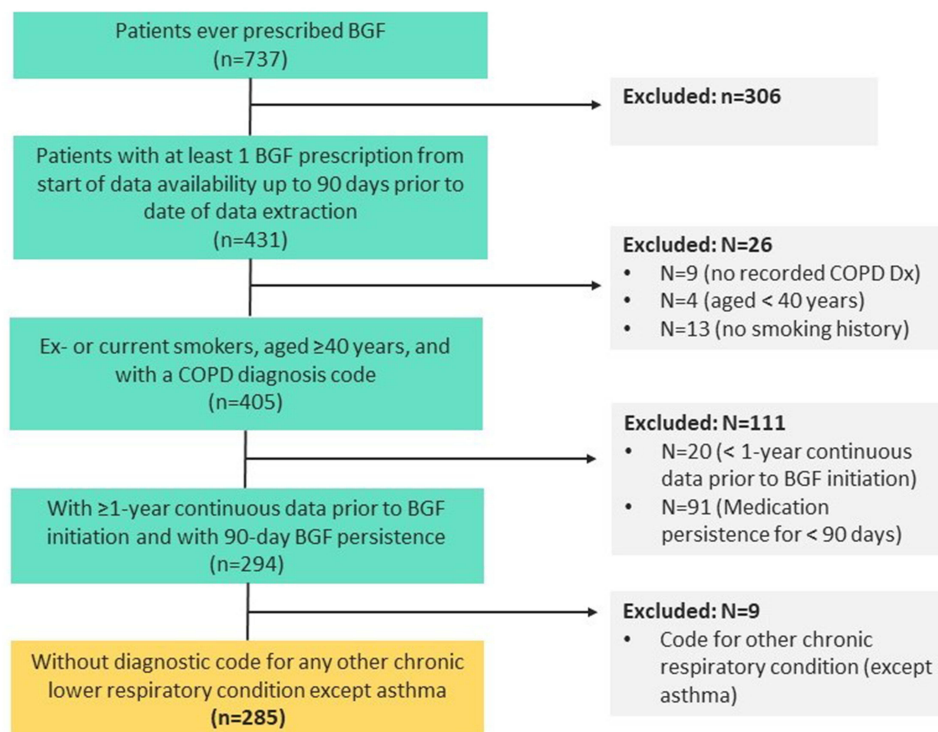
## Results

### Patients

Of 737 patients who had received a BGF prescription, 285 met all inclusion and exclusion criteria and were included in this study (Figure 1).

### Demographic and Clinical Characteristics

Patients were older adults (mean: 69.8 years) and were predominantly White (95.5%;  $n = 255/267$ ), female (53.9%;  $n = 153/284$ ), and overweight/obese (64.1%;  $n = 182/284$ ). All had a history of smoking, with 36.8% ( $n = 106/284$ ) continuing to smoke (Table 1). Almost 1/3 of patients (30.9%;  $n = 88/285$ ) had active asthma, 58.6% ( $n = 167/285$ ) had a history of depression or anxiety, 33.7% ( $n = 96/285$ ) had documented forced expiratory volume in one second ( $FEV_1$ )/forced vital capacity (FVC)  $< 0.7$ , and the median time since diagnosis was 7.9 years (IQR 4.4–11.7). Patients prescribed BGF tended to have a high symptom burden prior to BGF initiation as evidenced by their lung function, COPD Assessment Test (CAT) score (21.7; SD 7.8), modified Medical Research Council (mMRC) score ( $\geq 2$  for 77.9%;  $n = 205/263$ ) and proportion who had experienced  $\geq 1$  moderate COPD exacerbations/year (35.1%,  $n = 100/285$ ) (Table 1). Overall, 87.7% ( $n = 250/285$ ) of patients were classified as GOLD group



**Figure 1** Subject disposition.

**Abbreviations:** BGF, budesonide/glycopyrrolate/formoterol; COPD, chronic obstructive pulmonary disease; Dx, diagnosis.

E. Baseline characteristics for patients excluded due to non-continuous BGF use (ie, those with  $<2$  BGF prescriptions within a 90-day period) were similar (S-Table 2).

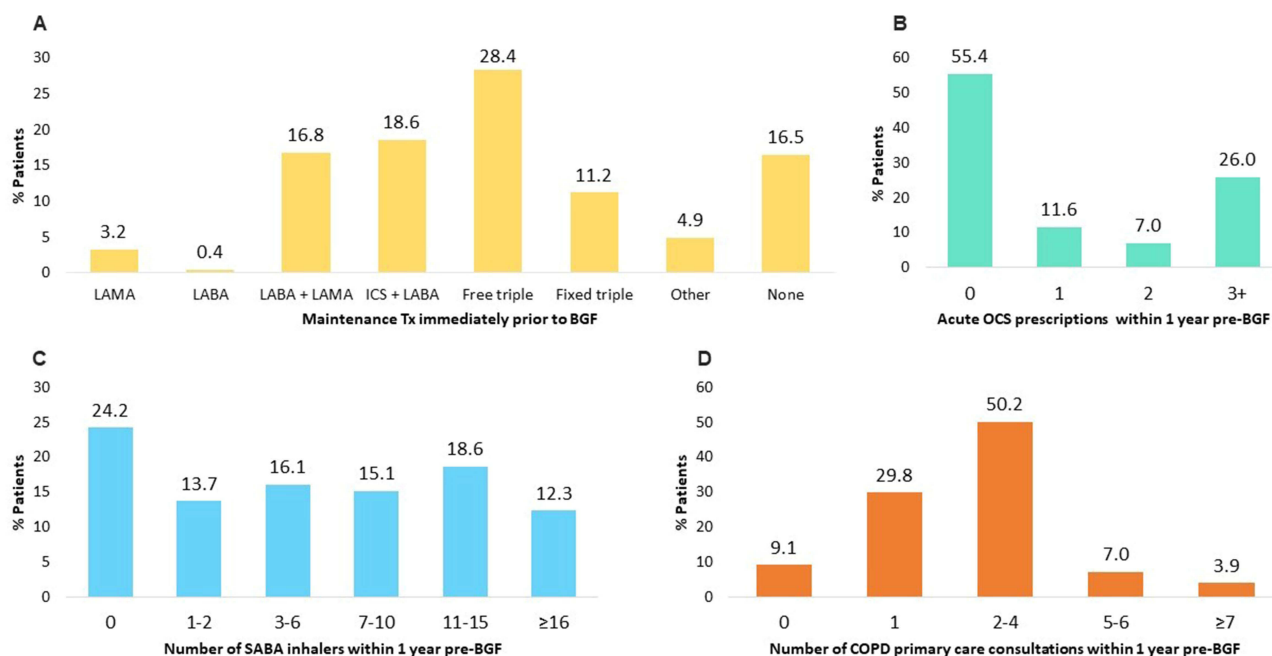
## COPD Treatment and Healthcare Resource Utilisation

COPD treatment burden and healthcare resource utilization (HCRU) were high in our patient population (Table 2). Overall, 39.6% ( $n = 113/285$ ) of patients had previously been treated with a triple combination therapy, 35.4% ( $n = 101/285$ ) had previously received a dual therapy, 3.6% ( $n = 4/285$ ) had received either LAMA or LABA alone, and 16.5% ( $n = 47/285$ ) had no record of any COPD prescription in their EMR (Figure 2A). One-third of patients (33.3%;  $n = 95/285$ ) had received  $\geq 2$  OCS prescriptions/year (Figure 2B), almost 2/3 (62.1% ( $n = 177/285$ )) had received  $\geq 3$  SABA prescriptions/year (Figure 2C) and 61.1% ( $n = 174/285$ ) had visited their primary care provider (PCP)  $\geq 2$  times in the year prior to BGF initiation (Figure 2D). Treatment burden and HCRU were also high for those excluded from the study due to non-continuous BGF use (S-Table 3).

## Real-Life Medication Success at 90 Days (Early Success)

After 90 days BGF treatment, 275 patients (96.5%; 95% CI: 93.6%, 98.3%) achieved medication success, thus meeting the pre-defined criterion for overall real-life medication success. Reasons for failure to achieve success included new diagnosis of heart failure (0.4%,  $n = 1/285$ ), myocardial infarction (0.4%;  $n = 1/285$ ), hospitalization for respiratory events (1.1%;  $n = 3/285$ ) and complicated COPD exacerbation (1.8%;  $n = 5/285$ ).

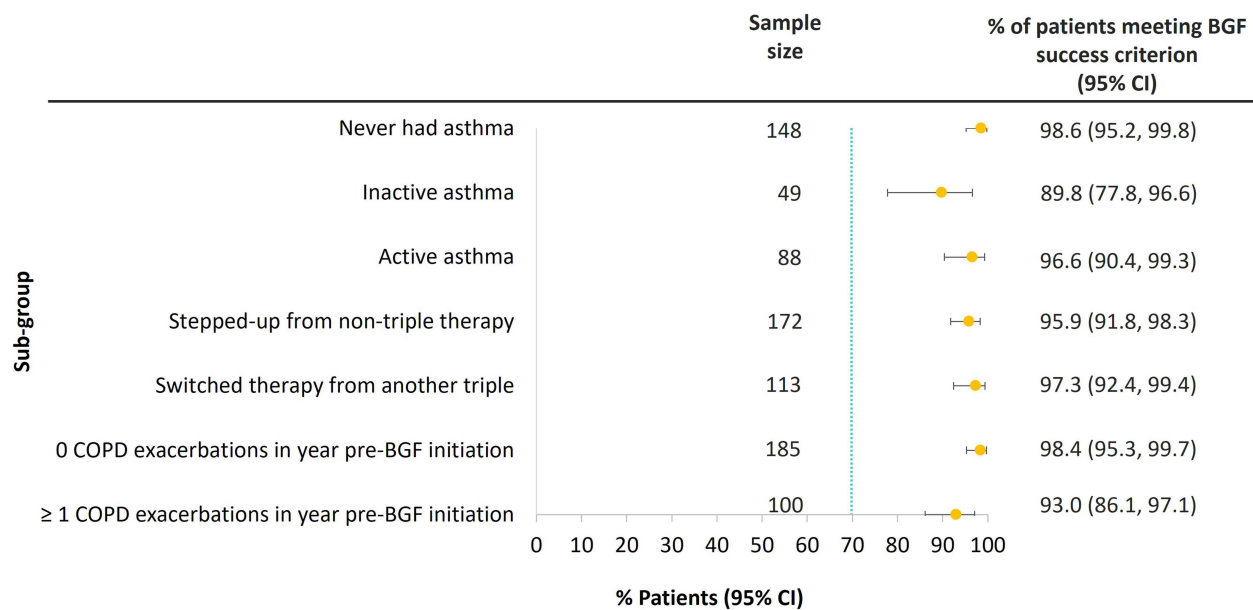
Real-life medication success was achieved in a high proportion of patients (89.8–98.6%) irrespective of asthma status, previous COPD treatment and exacerbation history; 98.6% ( $n = 146/148$ ) of patients who never had asthma, 89.8% ( $n = 44/49$ ) of patients with inactive asthma, 96.6% ( $n = 85/88$ ) of patients with active asthma, 95.9% ( $n = 165/172$ ) of patients who had stepped up from a non-triple therapy and 97.3% ( $n = 110/113$ ) of patients who switched from other triple therapies achieved early real-life medication success when treated with BGF (Figure 3). Similarly, 98.4% ( $n = 182/185$ ) and 93.0% ( $n = 93/100$ ) of patients who had experienced 0 or  $\geq 1$  exacerbations in the 1-year prior to BGF initiation, respectively, achieved real-life medication success at 90 days post-BGF initiation (Figure 3). Overlapping confidence



**Figure 2** (A) Maintenance medication use, (B) number of acute OCS prescriptions, (C) number of SABA inhalers and (D) number of COPD primary care consultations among COPD patients ( $n=285$ ) prior to BGF initiation.

**Abbreviations:** BGF, budesonide glycopyrrolate formoterol; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid; SABA, short-acting  $\beta_2$ -agonist; Tx, treatment.





**Figure 3** Proportion of patients with no MACRE and no incidence of pneumonia 90 days post-BGF initiation.

**Notes:** Medication success: no major cardiac and respiratory events and no incidence of pneumonia at 90 days post-BGF initiation and claimed if the lower 95% CI for the % of patients with medication success was  $\geq 70\%$ .

**Abbreviations:** BGF, budesonide glycopyrrolate formoterol; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MACRE, major cardiac and respiratory events.

intervals signified that these factors had relatively little impact on the proportion of patients achieving 90-day real-life medication success.

## Real-Life Medication Success at 180 Days

In total, 184 of 285 patients (64.6%) completed 180-day follow-up, and of these, 169 (91.8%; 95% CI: 86.9–95.4%) achieved real-life medication success. Reasons for failure to achieve 180-day medication success included new diagnosis of heart failure (1.1%,  $n = 2/184$ ), hospitalization for respiratory events (1.1%;  $n = 2/184$ ), pneumonia (0.5%;  $n = 1/184$ ) and complicated COPD exacerbations (5.4%;  $n = 10/184$ ).

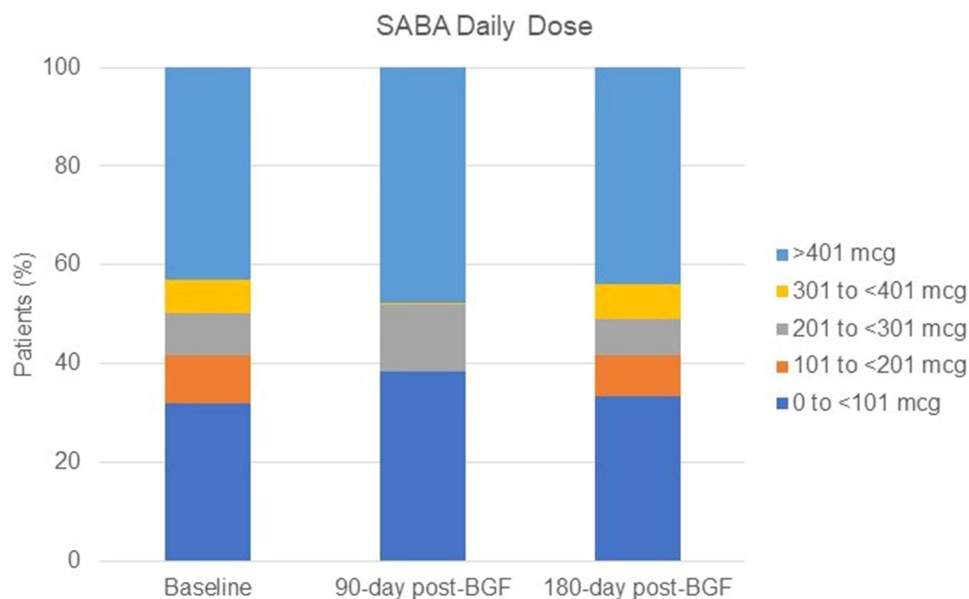
## Exploratory Outcome

The prescribed daily dose of SABA remained stable over the study period, with approximately 40% of patients prescribed  $<200$  mcg/day of SABA at both 90- and 180-days post BGF initiation (Figure 4).

## Discussion

Few clinical studies have investigated real-life use of BGF and patient experience, capturing both respiratory and non-respiratory endpoints in such a broad COPD population. Our data showcases the high symptomatic, treatment and HCRU burden of COPD in UK primary care and the need for triple therapy to manage those with moderate to very severe disease. Our findings complement efficacy and safety data obtained with BGF in RCTs and provide reassurance to PCPs that (i)  $>90\%$  of symptomatic COPD patients achieve early real-life medication success with BGF in real-life, (ii) this success rate is independent of asthma history or exacerbation burden and is sustained and (iii) patients can be transitioned to BGF from dual therapies and other triple therapies.

The term “real-life medication success” was used to describe a treatment which may be considered successful in a real-life setting in COPD patients with moderate to very severe disease, the majority of whom were already treated with dual and triple therapies and still experienced high symptom burden. The term “success” was coined a priori at protocol stage in compliance with RELEVANT,<sup>22</sup> accepted by ADEPT (ADEPT0123), registered with ENCePP and included as part of the published protocol in the EUPAS register (EUPAS104156). It was defined as an absence of key medical



**Figure 4** Average daily SABA dose (mcg) pre- and post-BGF initiation.  
**Abbreviations:** BGF, budesonide glycopyrrolate formoterol; SABA, short-acting  $\beta_2$ -agonist.

outcomes relevant to COPD that represent high burden to patients and health-care systems and comprises both safety and efficacy endpoints. The 70% medication success criterion was informed by two asthma studies, the first looking at real-life effectiveness of inhaler device switch from dry powder inhalers to pressurised metered dose inhalers in asthma patients treated with ICS/long-acting  $\beta_2$ -agonists,<sup>26</sup> and the second investigating the real-life effectiveness of initiating or changing to a fixed combination of fluticasone propionate/formoterol from fluticasone propionate/salmeterol.<sup>27</sup> This cut-off was set a priori and was far exceeded in the current study (ie 96.5% (95% CI: 93.6, 98.3)).

To date, only one other real-life study, investigating the effectiveness of BGF in COPD patients has been published (ie, the EROS study).<sup>28</sup> That study, also with a retrospective, observational, database design, incorporating >2000 patients with COPD who had a history of exacerbations in the previous year, found that promptly initiating BGF following an exacerbation (ie, within 30 days) was associated with a reduction in subsequent exacerbations, HCRU and costs. For every 30-day delay in BGF, the average number of post-index exacerbations in the following year increased by 5%.<sup>28</sup> Our study included patients irrespective of previous exacerbation burden or maintenance COPD treatment and found no increase in the incidence of pneumonia with BGF, as found in other studies which examined single inhaler triple vs dual therapies.<sup>12,29,30</sup> Furthermore, we showed that >90% of patients treated with BGF experienced neither heart failure, myocardial infarction, hospitalization or any respiratory event, complicated exacerbations nor mortality after 90- and 180-days treatment. Unlike previous studies, this benefit was noted in those with 0 and 1+ exacerbations, in those who stepped up to BGF from dual therapy or who switched from other triple therapies and in those without asthma history.

Reassuringly, we found that UK PCPs appeared to prescribe BGF mostly in line with its indication and GOLD recommendations.<sup>1,11</sup> Our patients had moderate to very severe disease (87.7% at GOLD E), with evidence of clinically significant dyspnea, exacerbations, and a negative impact on well-being and daily life. Overall, 39.6% and 25.4% of patients were treated with triple therapy or dual therapy, respectively, prior to BGF initiation. A cross-sectional observational study of COPD patients attending primary care in England including 3536 new users of single-inhaler triple therapy reported similar levels of breathlessness, lung function impairment and treatment history among those prescribed triple therapy; 65% of patients had an MRC dyspnea score  $\geq 3$ , 45% had predicted FEV<sub>1</sub> <50%, and 46%, 25% and 12% of patients had previously received multiple inhaler triple therapy, ICS/LABA or LABA/LAMA therapy, respectively, prior to triple therapy prescription.<sup>31</sup> Like our study, many patients appeared to have asthma in addition to

COPD, which may have been the reason for initiation of an ICS-containing therapy (25% with current asthma compared to 30.9% in our study).<sup>31</sup>

Our results highlighted some room for improvement in COPD diagnosis and optimization of treatment in the UK. We noted that only 33.7% had a spirometry confirmed COPD diagnosis. This low rate should be interpreted with caution, however, as it is likely a consequence of long-standing COPD diagnosis for many patients (ie possibility that FEV<sub>1</sub>/FVC was recorded prior to the 3-year look-back period employed in our study), a function of the multi-criteria nature of a QoF COPD diagnosis, and/or due to limited face-to-face consultations during the Covid-19 pandemic.<sup>32</sup> Additionally, we found some evidence of both under- and over-treatment; 16.5% of patients had received no treatment prior to BGF initiation, 33.3% had received  $\geq 2$  courses of OCS and 62.1% had received  $\geq 3$  SABA prescriptions in the previous year. These findings are relevant since OCS use has been associated with risk of adverse events and OCS-related comorbidities,<sup>33,34</sup> and overuse of SABA (defined as  $\geq 6$  cannisters) is independently associated with a higher risk of both moderate and severe exacerbations and of all-cause mortality.<sup>35</sup> Opportunities to optimize the management of COPD in primary care have been identified by others.<sup>10,36,37</sup> A recent opportunity analysis in a UK COPD cohort found that 40% of newly diagnosed COPD patients are diagnosed without spirometry and 7% of already diagnosed patients received no respiratory therapy despite being at high risk of exacerbating. Patients also waited a significant amount of time after an exacerbation to have their medication optimised.<sup>10</sup> The need for improvements in COPD management has been emphasised in the NHS long-term plan (2019),<sup>38</sup> and identified as a priority by both the Welsh and Scottish Governments.<sup>39,40</sup>

Limitations associated with our study include those common to observational studies, including missing data and being more prone to bias and confounding. The latter was mitigated in our study by adherence to STROBE quality standards for reporting of observational studies,<sup>41</sup> and also facilitated via implementation of a priori agreed protocol and data analysis plan. Other limitations included potential under-reporting of exacerbations and low number of patients with lung function data, likely due to the impact of the Covid-19 lockdown restrictions which caused widespread delay in accessing care, discontinuity and postponement of care and reductions in attendance at emergency departments.<sup>32,42</sup> Our study also did not include a comparator group. However, our objective was not to compare the effectiveness of triple vs dual therapy, which would have required larger patient numbers, patient-matching and a longer follow-up time, but rather to assess real-life use and initial treatment success following the introduction of BGF to the COPD treatment armamentarium in the UK. Further studies of longer duration and in larger data sets are warranted to compare the effectiveness of BGF with other COPD treatments in real-life. Strengths of our study are inclusion of a large heterogeneous cohort of COPD patients using the largest primary care database in the UK, providing data more representative of the UK COPD population than RCTs (although inclusion of those with milder disease may have increased medication success rate). We also assessed both early and sustained real-life medication success rate, overall and by subgroup, providing reassurances to PCPs concerning the value of BGF in routine clinical practice irrespective of asthma history, exacerbation burden or treatment history. However, studies of longer duration are warranted to ensure capture of all severe exacerbations and pneumonia, especially concerning seasonal variations. Further research is also needed to assess the impact of BGF (if any) on other COPD outcomes in real-life (eg COPD Assessment Test, COPD control, medication adherence, acceptance and exercise capacity). Such a study would require a larger dataset and standardization of assessment timings.

## Conclusion

In conclusion, we showed that the majority of patients initiating BGF experienced real-life medication success reflecting absence of severe cardiopulmonary events. These benefits were apparent after 90 days of treatment and sustained over 180 days.

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## Disclosure

Hana Müllerová, Stefan Franzén, Johann Castaneda, and Jonathan Marshall are employees of, and own stock in, AstraZeneca. Jeffrey Shi Kai Chan, Heath Heatley, Victoria Carter, John Townend, and Derek Skinner are employees of Observational and Pragmatic Research Institute. David Price has advisory board membership with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Viatris, Teva Pharmaceuticals; consultancy agreements with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Viatris, Teva Pharmaceuticals; consultancy and lecture fees from Medscape, Inside Practice paid to Observational and Pragmatic Research Institute; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Chiesi, Viatris, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Viatris, Novartis, Regeneron Pharmaceuticals and Sanofi Genzyme, Teva Pharmaceuticals; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Novartis, Teva Pharmaceuticals; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 92.61% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp which develops adherence monitoring technology; is peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation programme, and Health Technology Assessment; and was an expert witness for GlaxoSmithKline. The authors report no other conflicts of interest in this work.

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