






Characteristics of Patients Receiving Budesonide/Glycopyrronium/Formoterol for Chronic Obstructive Pulmonary Disease in Spain: The AURA Study

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Background: Single-inhaler triple therapy with budesonide/glycopyrronium/formoterol fumarate (BGF; Trixeo Aerosphere[®]) was approved in the European Union in December 2020 for maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by dual therapy, and has been available in Spain since February 2022. This real-world, observational, retrospective cohort study, AURA Spain, describes the demographics, clinical characteristics, and healthcare resource utilization of patients initiating single-inhaler BGF triple therapy.

Methods: Electronic medical records in the Spanish Healthcare System anonymized, integrated BIG-PAC[®] database were analyzed to identify COPD patients aged ≥ 40 years initiating single-inhaler BGF between 1 February 2022 and 31 January 2023.

Results: Patients (N=482) had a mean (standard deviation, SD) age of 71.5 (10.0) years, mean BMI of 29.6 (6.2) kg/m², most were aged ≥ 65 years (73.7%) and male (62.5%). Most were former (62.7%) or current (24.5%) smokers. Applying GOLD FEV₁ thresholds, severity of COPD was moderate in 49.8% of patients, severe (41.9%), and very severe (6.5%). The most common comorbidities were hypertension (62.2%), dyslipidemia (56.8%), and anxiety (42.5%), and 85.9% had one or more cardiovascular-related comorbidity. Overall, 57.3% experienced at least one moderate or severe exacerbation in the 12-month baseline period, 9.5% visited the emergency department for COPD-related reasons; and 12.7% were hospitalized for COPD (median length of stay 7 [interquartile range: 6–8] days). Patients initiating single-inhaled BGF triple therapy escalated from monotherapy (2.3%) or dual therapy (62.7%), switched from other triple therapies (31.3%), or were treatment-naïve (3.7%).

Conclusion: Single-inhaler BGF triple therapy was initiated mostly as an escalation from dual maintenance therapy, with many switching from triple therapy, in patients with a high burden of disease, as demonstrated by their frequent exacerbation profile, advanced COPD severity (moderate to very severe obstruction) and the high frequency of several comorbidities, including cardiovascular diseases.

Keywords: budesonide/glycopyrronium/formoterol, chronic obstructive pulmonary disease, exacerbations, real-world data, single-inhaler triple therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms such as dyspnea, cough, sputum production and/or acute respiratory events (exacerbations), and persistent, often progressive, restricted airflow.¹ Globally, COPD accounted for 3.23 million deaths in 2019.²

The estimated prevalence of COPD in Spain, assessed by spirometry evaluation of more than 9000 subjects in the general population aged 40 years or older is 11.8% and is higher in males (14.6%) than females (9.4%).³ This equates to



approximately 3.3 million people (1.9/1.4 million males/females) living with COPD.⁴ National epidemiological studies suggest that COPD is significantly underdiagnosed (by approximately 78%) in Spain, especially in women and younger populations.^{3,5} In Spain, COPD is the third leading cause of death (behind ischemic heart disease and stroke), accounting for over 7% of all deaths nationally in 2019, ie, more than 31,000 deaths. Despite advances in therapy, COPD-related deaths have increased by 42% from 1990 (47.7 per 100,000) to 2019 (67.9 per 100,000).⁶

GOLD guidelines recommend triple therapy with an inhaled corticosteroid (ICS), long-acting muscarinic antagonist (LAMA) and long-acting β 2-agonist (LABA) as first-line pharmacological treatment for patients with COPD with ≥ 2 moderate exacerbations or ≥ 1 exacerbation leading to hospitalization and with an eosinophil count ≥ 300 cells/ μ L. The use of inhaled triple therapy has been recommended as a treatment escalation strategy in COPD patients who, despite receiving dual therapy, still have clinically significant symptoms that adversely impact their quality of life or those who have a higher risk of exacerbation. Triple therapy improves lung function, patient-reported outcomes and reduces exacerbations when compared to LAMA alone, LAMA + LABA, and LABA + ICS.^{1,7} Spanish COPD guidelines (GesEPOC) also recommend ICS/LAMA/LABA triple therapy in patients with exacerbations despite treatment with LABA/LAMA.⁸ Single-inhaler triple therapy (SITT) improves adherence and persistence compared with multiple-inhaler triple therapy (MITT)^{9–11} and reduces healthcare resource utilization and improves cost-effectiveness compared with multiple inhalers.^{11,12}

Single-inhaler budesonide/glycopyrronium/formoterol fumarate (BGF; Trixeo Aerosphere[®]) was efficacious when compared with the corresponding dual therapies for symptomatic patients with moderate to very severe COPD.¹³ Furthermore, in the 52-week ETHOS clinical trial of patients with moderate to very severe COPD who had experienced ≥ 1 moderate/severe exacerbation in the previous year, single inhaler BGF at two dose levels of inhaled glucocorticoid (budesonide, 320 or 160 μ g) reduced the rate of moderate or severe COPD exacerbations and improved lung function compared to glycopyrronium-formoterol or budesonide-formoterol dual therapy.^{14,15} In the Phase 3 ETHOS clinical trial, single inhaler higher-dose glucocorticoid BGF (320 μ g budesonide) reduced all-cause mortality compared with glycopyrronium/formoterol.¹⁶ In addition, recent results from the SKOPOS-MAZI retrospective study showed that BGF reduced the risk of all-cause mortality compared with MITT in a real-world setting.¹⁷ Fixed-dose triple therapy with BGF was approved in the European Union (EU) in December 2020 for maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an ICS + LABA, or a combination of a LABA + LAMA.¹⁸ BGF is the third fixed, triple combination therapy approved in the EU for COPD and has been available in Spain since February 2022.

Since the launch of BGF, there is a lack of real-world data on characteristics of patients initiating BGF triple therapy. This retrospective, non-interventional, observational study (AURA Spain) aimed to evaluate demographics, clinical characteristics, and healthcare resource utilization among patients with COPD in Spain who initiated BGF triple therapy.

Methods

Study Design

This was a real-world, retrospective, observational cohort study comprising longitudinal analyses of electronic medical records (EMRs). This study was approved by the Ethics Committee of Consorci Sanitari of Terrassa on 24th of July 2023. The study used secondary, fully anonymized data, and consequently there was no need to obtain patient consent.

Objectives

The primary objective of the AURA Spain study was to describe the demographics, clinical characteristics, and healthcare resource utilization of patients with COPD initiating triple therapy with single-inhaler BGF.

Data Source

EMRs contained in the Spanish National Healthcare System integrated BIG-PAC[®] database were analyzed to identify COPD patients aged ≥ 40 years initiating single-inhaler BGF triple therapy between 1 February 2022 and

31 January 2023. The anonymized database includes EMRs of approximately 2 million patients and contains information on diagnoses, treatment prescriptions, procedures, and analytical data. The database is certified by Spanish Agency of Medicines and Medical Devices and has age distribution and sex profiles which are similar to the Spanish population.¹⁹

Study Population

Patients with COPD aged 40 years or older, and diagnosed by one or more ICD-9 (491.x, 492.x and 496) or ICD-10 codes (J41.x, J42, J43.x, and J44.x) ([Supplementary Table 1](#)), who initiated single-inhaler BGF triple therapy between 1 February 2022 and 31 January 2023, were included in the study. Patients were required to have a minimum patient history of 12 months before the index date.

Study Measures

Study measures were patient demographics; clinical characteristics and healthcare resource utilization during the 12-month baseline period (12 months prior to the index date); treatment history and index prescriber specialty.

Acute Exacerbation Definitions

A moderate acute exacerbation of COPD was defined as an outpatient visit to the general practitioner (GP) or pulmonologist with a diagnosis code for COPD; and a dispensation for an oral corticosteroid (OCS [glucocorticoids]; ATC codes H02AB) and/or antibiotics (ATC code J01) within 5 days following the visit, for a maximum duration of 15 days. A severe acute exacerbation of COPD was defined as an emergency department visit or hospitalization, and with a primary or secondary discharge diagnosis code for acute exacerbation of COPD (ICD-9: 491.21; ICD-10: J44.0 or J44.1).

Statistical Analysis

The database was searched using customized SQL scripts, and retrieved data were validated by frequency distribution and careful review to identify possible recording or coding errors.

Continuous variables were described by mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum, and categorical variables by number and percentage. Data were analyzed using RStudio, version 4.3.1 and Microsoft Excel.

Results

Patients initiating single-inhaler BGF triple therapy ($N = 482$) had a mean (SD) age of 71.5 (10.0) years, most were aged ≥ 65 years (73.7%) and were mainly male (62.5%). Most BGF initiators were former (62.7%) or current (24.5%) smokers, and patients with available data had a mean (SD) BMI of 29.6 (6.2) kg/m^2 ($n = 283$); FEV₁ predicted of 50.8 (14.5) and FEV₁/FVC of 0.6 (0.1) ($n = 430$); and an eosinophil count of 293.6 (98.4) cells/ μL ($n = 422$). Applying GOLD FEV₁ thresholds,⁷ almost half of patients with available data (214/430; 49.8%) had moderate COPD (FEV₁ predicted 50–79%), 41.9% had severe (FEV₁ predicted 30–49%) and 6.5% very severe (FEV₁ predicted $<30\%$) COPD. The most common comorbidities were hypertension (62.2%), dyslipidemia (56.8%), anxiety (42.5%), and diabetes (27.8%). Overall, 85.9% of the cohort had one or more cardiovascular-related comorbidity. Mean Charlson Comorbidity Index (CCI) and Elixhauser Comorbidity Index (ECI) values were 1.9 and 7.6, respectively ([Table 1](#)).

More than half of all patients (57.3%; $n = 276$) experienced at least one moderate or severe exacerbation in the previous 12 months. The mean (SD) number of moderate/severe exacerbations among all initiators was 1.6 (1.9), and 23.9% of patients experienced ≥ 3 moderate/severe exacerbations. A total of 232 patients (48.1%) experienced one or more moderate exacerbations and the mean (SD) number of moderate exacerbations per patient was 1.3 (1.8). At least one severe exacerbation was experienced by 86 patients (17.8%) and the mean (SD) number of severe exacerbations per patient was 0.2 (0.6) ([Table 2](#)).

Healthcare resource utilization during the 12-month baseline period is shown in [Table 3](#). Nearly all patients (99.2%) visited a GP and the mean (SD) number of visits to a GP was 15.4 (11.9). In contrast, less than half of all patients visited a pulmonologist (45.9%) and had a mean (SD) number of 0.8 (0.9) visits per patient. Approximately a tenth of all

Table 1 Demographics and Baseline Clinical Characteristics of Cohort (N = 482)

Characteristic	Value
Age at index (years), mean (SD); median (IQR)	71.5 (10.0); 72.3 (13.9)
Sex, n (%)	
Female	181 (37.6)
Male	301 (62.5)
BMI [†] (kg/m ²): mean (SD); median (IQR)	29.6 (6.2); 29.7 (8.2)
Smoking status, n (%)	
Current smoker	118 (24.5)
Former smoker	302 (62.7)
Non-smoker	62 (12.9)
FEV ₁ predicted [‡] , mean (SD)	50.8 (14.5)
≥80%	8 (1.9)
50–79%	214 (49.8)
30–49%	180 (41.9)
<30%	28 (6.5)
FEV ₁ /FVC [‡] , mean (SD)	0.6 (0.1)
Eosinophil count (cells/μL) [§] , mean (SD)	293.6 (98.4)
<100 cells/μL, n (%)	7 (1.5)
≥300 cells/μL, n (%)	203 (42.1)
Comorbidities, n (%)	
Hypertension	300 (62.2)
Dyslipidemia	274 (56.8)
Anxiety	205 (42.5)
Diabetes	134 (27.8)
Arrhythmias (including cardiac arrhythmias)	106 (22.0)
Heart failure	104 (21.6)
Depression	76 (15.8)
Asthma	60 (12.4)
Cerebrovascular disease	46 (9.5)
Myocardial infarction	39 (8.1)
Lung cancer	13 (2.7)
Venous thromboembolism	11 (2.3)
Gastro-esophageal reflux disease	7 (1.5)
Pulmonary hypertension	6 (1.2)

(Continued)

Table 1 (Continued).

Characteristic	Value
Pulmonary oedema	4 (0.8)
History of revascularization	4 (0.8)
Any cardiovascular-related comorbidity	414 (85.9)
Charlson Comorbidity Index, mean (SD)	1.9 (1.2)
Elixhauser Comorbidity Index, mean (SD)	7.6 (5.7)

Notes: †n = 283; ‡n = 430; §n = 422. Includes myocardial infarction, pulmonary oedema, pulmonary hypertension, venous thromboembolism, heart failure, arrhythmias (including cardiac arrhythmias), disorders of lipoprotein metabolism, diabetes, hypertensive diseases and history of revascularization comorbidities.

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; SD, standard deviation.

Table 2 Patients with Moderate/Severe Exacerbations in the Previous 12 months (N = 482)

Parameter	Value
Patients with moderate/severe exacerbations, n (%)	276 (57.3)
Mean (SD) number of moderate/severe exacerbations (per patient)	1.6 (1.9)
1 exacerbation, n (%)	86 (17.8)
2 exacerbations, n (%)	75 (15.6)
≥3 exacerbations, n (%)	115 (23.9)
Patients with moderate exacerbations only, n (%)	232 (48.1)
Mean (SD) number of moderate exacerbations (per patient)	1.3 (1.8)
1 exacerbation, n (%)	69 (14.3)
2 exacerbations, n (%)	62 (12.9)
≥3 exacerbations, n (%)	101 (21.0)
Patients with severe exacerbations only, n (%)	86 (17.8)
Mean (SD) number of severe exacerbations (per patient)	0.2 (0.6)
1 exacerbation, n (%)	61 (12.7)
2 exacerbations, n (%)	20 (4.2)
≥3 exacerbations, n (%)	5 (1.0)

Abbreviation: SD, standard deviation.

Table 3 Healthcare Resource Utilization During the 12-month Baseline Period (N = 482)

Parameter	Value
General practitioner (GP) visits	
Patients with ≥1 GP visit, n (%)	478 (99.2)
Number of GP visits (per patient), mean (SD); median (IQR)	15.4 (11.9); 12.5 (7–20)

(Continued)

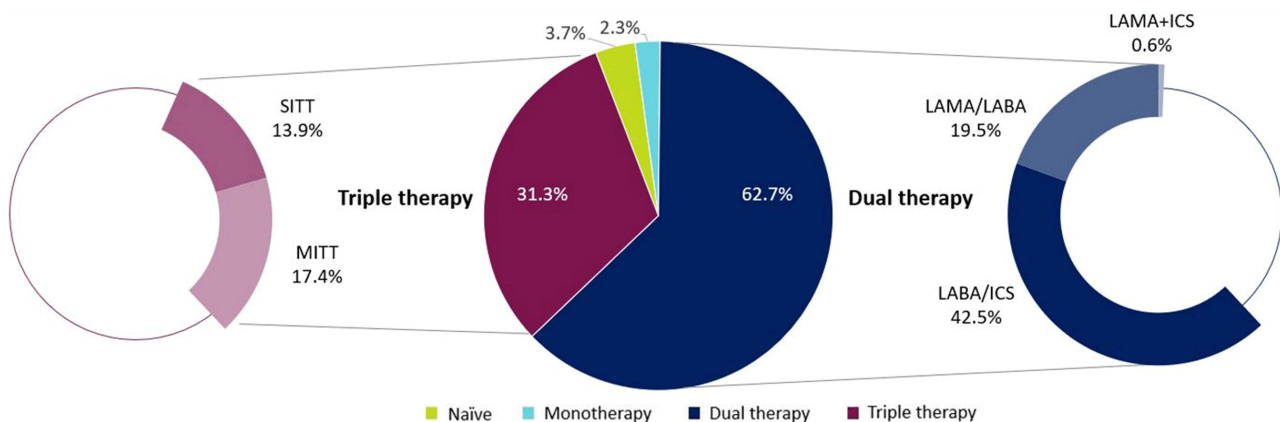
Table 3 (Continued).

Parameter	Value
Pulmonologist visits	
Patients with ≥ 1 visits, n (%)	221 (45.9)
Number of specialist visits (per patient), mean (SD); median (IQR)	0.8 (0.9); 0 (0–2)
COPD-related emergency department visits	
Patients with ≥ 1 visit, n (%)	46 (9.5)
Number of COPD emergency visits (per patient), mean (SD)	0.1 (0.3)
COPD-related hospitalizations	
Patients with ≥ 1 hospitalization, n (%)	61 (12.7)
Number of hospitalizations, mean (SD)	0.2 (0.4)
Length of stay among hospitalized patients (days), median (IQR)	7 (6–8)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation.

patients (9.5%) visited the emergency department for COPD-related reasons, but a higher proportion (12.7%) were hospitalized for COPD. The median length of stay in hospital was 7 (interquartile range, IQR: 6–8) days.

Physicians prescribing SITT/MITT were mainly GPs (52.7%; $n = 254$) and pneumologists (44.2%; $n = 213$), with fewer prescribers in internal medicine (2.7%; $n = 13$) and emergency departments (0.4%; $n = 2$). Patients initiating single-inhaled BGF triple therapy escalated from monotherapy ($n = 11$; 2.3%) or dual therapy ($n = 302$; 62.7%), switched from SITT ($n = 67$; 13.9%) or MITT ($n = 84$; 17.4%), or were treatment-naïve ($n = 18$; 3.7%) (Figure 1). Short-term treatment included use of short-acting beta agonists (SABA) (41.70%; $n = 201$) or OCS (45.2%; $n = 205$). Mean (SD) annual total cumulative dose of OCS among patients with ≥ 1 OCS prescription ($n = 218$) was 432.4 (629.3) mg, and while most patients (80.3%) received an OCS dose of <500 mg, 19.7% of patients received ≥ 500 mg OCS during the 12-month baseline period.

**Figure 1** Previous treatment.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting $\beta 2$ -agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy.

Discussion

This real-world retrospective cohort study describes baseline characteristics, COPD treatment patterns, history of exacerbations, and healthcare resource use in patients with COPD initiating single-inhaler BGF triple therapy, during the first year since its launch in Spain in February 2022.

Most patients in the study were aged ≥ 65 years, male, overweight, and had a history of smoking. The prevalence of individual comorbidities, together with CCI and ECI values indicated the presence of multiple long-term conditions, notably cardiovascular-related disorders, with 85.9% of the cohort having at least one cardiovascular-related comorbidity. Cardiovascular disease (CVD) is known to be a common interlinked condition to COPD and COPD patients with CVD have a worse health status, a higher risk of hospitalization, and a poorer prognosis. COPD patients frequently die of respiratory (exacerbations) and cardiovascular causes;^{20,21} real-world evidence from the EXACOS-CV studies in Spain²² and Italy²³ has shown that patients with COPD are at high risk of severe cardiovascular events following exacerbations. Based on GOLD FEV₁ thresholds,⁷ nearly half of the cohort in the current study (48.4%) had severe to very severe COPD and 50% had moderate COPD when initiating BGF. In addition, eosinophil cell counts were high (≥ 300 cells/ μ L) in many patients (42.1%).

A significant proportion of patients (57.3%) had at least one exacerbation during the 12-month baseline period, with 48.1% having at least one moderate exacerbation and 17.8% having one or more severe exacerbation. However, these numbers may be underestimated as exacerbations may not be fully recorded in EMRs.²⁴ Furthermore, patients are known to underreport exacerbations and, whether unreported or reported, exacerbations have negative health implications.²⁵ As over half of all patients had one or more exacerbation during the 12-month baseline period, this suggests that their treatment was not optimal, and they may have benefited from earlier treatment escalation. Almost all patients had at least one GP visit and less than half (45.9%) visited a pulmonologist during the 12-month baseline period. This may indicate a lack of access to specialist care and, therefore, delays in timely initiation of BGF or other therapies. Approximately 13% of patients were admitted to hospital for COPD-related reasons, with a median length of stay of 7 days. These results emphasize the high disease burden of COPD prior to the initiation of BGF triple therapy. The AURA USA real-world study of COPD patients initiating BGF also found a high disease burden among patients.²⁶ Despite current therapy, many patients in AURA USA experienced exacerbations and respiratory symptoms, and chronic comorbidities, especially cardiopulmonary-related, were common.²⁶ In a retrospective study of COPD patients initiating SITT (fluticasone furoate/umeclidinium/vilanterol) in the USA, most users experienced persistent symptoms or a history of exacerbations despite dual maintenance therapy, prior to initiating triple therapy.²⁷ The EPOCONSUL 2021 audit of Spanish COPD patients found that triple therapy in high-risk COPD patients was used as escalation therapy in patients with high clinical impact.²⁸ Furthermore, an observational retrospective analysis of Italian administrative healthcare data from the Fondazione Ricerca e Salute database showed that COPD patients receiving triple therapy were older and had more comorbidities, particularly CVD, than patients receiving other treatments, highlighting the high disease burden of these COPD patients.²⁹

The first prescription of BGF was made by GPs in over half of cases (52.7%) and by specialized care physicians, mainly pulmonologists, in the remainder. Dual therapy was the most common previous maintenance treatment prior to escalation to BGF (62.7%), whilst just under one-third of patients (31.3%) switched from other triple therapies (MITT or SITT). This may indicate a lack of effectiveness of these treatment options or a preference for single-inhaler BGF by patients and providers. A high proportion of patients used short-term treatment in the previous year, mainly SABA (41.7%) or OCS (45.2%). With regard to OCS, approximately one-fifth of patients (19.7%) had a dose >500 mg, suggesting that treatment was suboptimal. Although the mean annual cumulative OCS dose was relatively low (432.4 mg), any exposure of OCS in COPD patients significantly increases the risk of adverse outcomes compared with no OCS exposure.³⁰

There are several limitations of this study. Data from EMRs can be incomplete and of variable quality.³¹ This study validated data by frequency distribution analysis and by careful review to identify possible recording or coding errors. A second limitation is that previous symptoms (eg, dyspnea, cough, sputum production), which may also be a reason for treatment escalation, are not usually recorded by the treating physicians, especially in more severe patients (eg, previously treated with LABA + ICS) and therefore not captured by BIG-PAC[®]. Although, the presence of respiratory symptoms and/or exacerbations is a primary reason for escalation to triple therapy, the use of secondary data and the

descriptive nature of this study precluded any attempt to determine possible reasons for initiating or switching to single-inhaler BGF triple therapy. A third limitation is that while standard algorithms were used to define exacerbations, they may be prone to miscoding²⁴ and patients are known to underreport exacerbations.²⁵

In conclusion, these real-world data from Spain indicate that single-inhaler BGF triple therapy was initiated, mostly as an escalation from dual maintenance therapy, in patients with a high burden of disease, as shown by their frequent exacerbation profile, advanced severity of COPD (moderate to very severe obstruction) and the high frequency of several comorbidities, including cardiovascular-related diseases. Nearly a third of patients switched to BGF from other triple therapies, possibly indicating a lack of effectiveness or preference for single-inhaler BGF by patients and providers. Based on these characteristics, there may be merit in clinicians considering escalating to SITT earlier in the patient journey. Ongoing and future studies will aim to describe real-world clinical outcomes with single-inhaler BGF triple therapy.

Data Sharing Statement

All the data generated or analyzed during this study are included in the article. Requests for further information should be sent to the corresponding author.

Ethical Approval

This study was approved by the Ethics Committee of Consorci Sanitari of Terrassa on 24th of July 2023. The study used secondary, fully anonymized data, and consequently there was no need to obtain patient consent.

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Author Contributions

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

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Disclosure

M.C.R. has received speaker fees from AstraZeneca, Bial, Chiesi, CSL Behring, GlaxoSmithKline, Menarini and Grifols, and consulting fees from GlaxoSmithKline and Bial. J.A.T.C. has received speaker fees from AstraZeneca, Chiesi, GlaxoSmithKline, Menarini and Orion. P.C.B., L.E.H., M.P. and J.S-C. are employees of AstraZeneca and may hold stock and/or stock options in the company. I.H.S. is an employee of Atrys Health, which was contracted by AstraZeneca to conduct this study. The authors report no conflicts of interest in this work.

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