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ORIGINAL RESEARCH

Characteristics of Patients Initiated on Budesonide/Glycopyrronium Bromide/Formoterol Fumarate Single Inhaler Triple Therapy for the Treatment of Chronic Obstructive Pulmonary Disease: A Population-Based Observational Study

Gaétan Deslee[1], Caroline Fabry-Vendrand[2], Elsa Salmi[2], Nolwenn Poccardi[2], Adrien Coriat[3], Idir Ghout[3], Caroline Eteve-Pitsaer[3], Nicola J Adderley[4], Henri Leleu[5]

[1]Service de Pneumologie, INSERM UMRS-1250, Centre Hospitalier Universitaire de Reims, Université Reims, Champagne-Ardenne, France; [2]AstraZeneca, Courbevoie, France; [3]Cegedim Group, Boulogne-Billancourt, France; [4]Department of Applied Health Sciences, University of Birmingham, Edgbaston, Birmingham, UK; [5]Public Health Expertise, Paris, Île-de-France, France

Correspondence: Adrien Coriat, Cegedim Group, 137 rue d'aguesseau, Boulogne-Billancourt, 92100, France, Tel +33 7 64 63 51 69, Email Adrien.coriat@cegedim.com

Background: Budesonide/glycopyrronium bromide/formoterol fumarate (BUD/GLY/FOR) single inhaler triple therapy became available to prescribe to patients with severe chronic obstructive pulmonary disease (COPD) in France in 2021. The characteristics of patients prescribed BUD/GLY/FOR triple therapy and guideline adherence have not been previously described in France.

Objective: To describe the characteristics of COPD patients initiated on BUD/GLY/FOR triple therapy, assess adherence to COPD management guidelines, and explore any differences by prescribing physician.

Materials and Methods: A cross-sectional study using data from The Health Improvement Network (THIN®) France database was conducted. Patients with ≥2 recorded diagnostic codes for COPD were included. Demographic characteristics, comorbidities, management, COPD-related characteristics, and guideline adherence (Société de Pneumologie de Langue Française (SPLF); Haute Autorité de Santé (HAS)), stratified by initiating physician speciality (general practitioner (GP) or pulmonologist) were described.

Results: A total of 263 patients initiating BUD/GLY/FOR triple therapy were included. Mean (SD) age was 68.8 (11.8) years; 53.6% were male. Mean (SD) COPD duration was 6.4 (5.5) years. Comorbidities were common, with slightly more cardiometabolic and mental health conditions recorded in the GP-initiated group, and more comorbid respiratory conditions recorded in the pulmonologist-initiated group. About 77.2% (n=203) of patients had at least one moderate or severe exacerbation in the 12 months before initiation. About 86.3% had a previous record of dual (n=117, 44.5%) or triple (n=110, 41.8%) therapy. About 68.8% had been initiated on BUD/GLY/FOR triple therapy in line with SPLF guidelines (62.4% and 72.4% in the GP- and pulmonologist-initiated groups, respectively); among those with a record of COPD severity, 75.2% were initiated in line with HAS guidelines (69.2% and 76.3% in the GP- and pulmonologist-initiated groups, respectively).

Conclusion: The majority of COPD patients are prescribed BUD/GLY/FOR triple therapy in accordance with current treatment guidelines, irrespective of whether the therapy is prescribed by a general practitioner or a pulmonologist.

Keywords: chronic obstructive pulmonary disease, triple therapy, budesonide/glycopyrronium bromide/formoterol fumarate, management

Introduction

Chronic obstructive pulmonary disease (COPD) is a common lung condition characterised by chronic respiratory symptoms and airflow obstruction, leading to disability and a significant deterioration in quality of life at all stages of

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the disease.[1] COPD affected 8.7% of the French adult population aged over 40 in 2005, with a projected increase in prevalence to 9.6% by 2025.[2] COPD was responsible for over 18,000 deaths in France in 2014.[3]

The management of COPD is multidisciplinary and encompasses lifestyle and dietary measures, in particular supporting smoking cessation, promoting physical activity, and nutritional monitoring; pulmonary rehabilitation; psycho-social support including recognition of disability; pharmacological management; and screening and management of comorbidities.[4] Pharmacological management primarily involves treatment with inhaled short- and long-acting bronch-odilators (beta-2 agonists, antimuscarinics) and corticosteroids, and, for severe cases, long-term oxygen therapy.[4,5] The therapeutic escalation and de-escalation strategy has been outlined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[4] group and Société de Pneumologie de Langue Française (French Language Respiratory Society, SPLF).[5]

The role of single inhaler triple therapies in fixed combinations (inhaled corticosteroids (ICS), long-acting beta-2 agonist (LABA), long-acting muscarinic antagonists (LAMA)) has been well documented in recent years.[6,7] According to SPLF guidelines on COPD management, the ICS/LAMA/LABA triple therapy combination should be reserved for patients who continue to experience dyspnea and/or exacerbations (≥2 moderate or ≥1 severe) despite treatment with dual therapy, in the absence of prior adverse effects from ICS.[5] The 2019 haute Autorité de Santé (French National Authority for Health, HAS) guidelines restrict the step-up from dual therapy to patients with severe COPD.[8] In the GOLD 2021 guidelines, triple therapy is recommended as a step-up treatment in patients treated with LABA and ICS who continue to experience exacerbations, and can be considered in patients treated with LABA and LAMA who continue to experience exacerbations if blood eosinophil count is ≥100 cells/µL.[4] The most recent GOLD 2025 guideline also suggests that clinicians consider ICS/LAMA/LABA triple therapy for COPD patients treated with LABA and ICS who continue to experience dyspnea/high symptom load.[9] The guidance on the use of triple therapy draws in particular on two large randomised controlled trials conducted in symptomatic COPD patients with a history of frequent and/or severe exacer-bations, IMPACT[10,11] and ETHOS,[7] which found a significant reduction in all-cause mortality among patients prescribed single inhaler ICS/LAMA/LABA triple therapy compared to dual LABA+LAMA therapy. There is some evidence indicating that medication persistence is improved in patients prescribed single inhaler triple therapy compared to multiple inhaler triple therapy.[12]

In December 2020, budesonide/glycopyrronium bromide/formoterol fumarate (160/9/5 µg) (BUD/GLY/FOR) Aerosphere, a new single inhaler (fixed dose) triple therapy, obtained European market authorization for COPD treatment.[13] In March 2021, the HAS Commission de la Transparence (Transparency Commission, CT), responsible for evaluating drugs that have been granted market authorization, concluded that, similar to other single inhaler triple therapies for COPD, BUD/GLY/FOR triple therapy offers no clinical added value in the management of patients with severe COPD who have not been successfully treated with ICS/LABA or LABA/LAMA dual therapy.[14] The HAS CT also raised concerns about the potential misuse of treatments containing ICS for COPD patients following a 2007 report from the Directorate General of Health,[15] which indicated a prescription rate of ICS by general practitioners of 40%, compared to an expected rate of 20% based on COPD epidemiological data in France and the 2007 GOLD recommendations.[16] To address this risk, the initiation of single inhaler triple therapies for COPD patients (including BUD/GLY/FOR) was restricted to pulmonologists, and a Post-Inscription-study was requested by the CT to describe the disease history, COPD characteristics, and previous treatments of patients prescribed triple therapy. The HAS CT subsequently removed the restriction on their initiation in June 2023, allowing any physician to initiate single inhaler triple therapy in patients with severe COPD who experienced persistent exacerbations or symptoms despite dual therapy with ICS and LABA or LABA and LAMA.[17] The CT also stipulated that the prescription of BUD/GLY/FOR triple therapy should only be initiated when lung function tests confirming the existence of obstructive airway disease had been performed in the year preceding initiation, and recommended that follow-up by a pulmonologist should be performed during the year following the initial prescription in order to confirm that ICS are necessary.

The aim of this study was to use real-world, routinely collected healthcare data in France to describe the profile of COPD patients initiated on BUD/GLY/FOR Aerosphere single inhaler triple therapy, to compare this profile between different prescribing physicians (general practitioners (GPs) and pulmonologists), and to explore adherence to national and international guidelines for the management of COPD. The primary objective of the study was to describe the characteristics of COPD patients at the time of initiation of BUD/GLY/FOR triple therapy, including demographic characteristics, comorbidities, management, and COPD-related characteristics (severity and previous treatments). The secondary objective was to describe the percentage of patients who had been initiated on BUD/GLY/FOR triple therapy according to SPLF 2021, HAS 2019 and GOLD 2021 guidelines.

Materials and Methods

Study Design

This study is a real-world, observational, cross-sectional study using both retrospective routinely collected healthcare data and additional data collected via questionnaire. The study period was for 2 years from the approximate date BUD/GLY/FOR triple therapy became available in the French market, September 2021 until September 2023.

Data Source

Study data were obtained from The Health Improvement Network (THIN®) France, a Cegedim database. Cegedim databases are anonymized in compliance with currently applicable data protection laws, regulations, and policies. THIN is an unobtrusive medical data collection scheme that collects anonymized patient data from electronic health records of participating general practitioners (GPs) and clinical specialists. For the THIN database in France, several audits were conducted by Commission Nationale de l'Informatique et des Libertés – the French authority responsible for the protection of personal data – and the database is approved for research purposes and does not require patient consent for specific studies.

THIN France contains anonymized electronic patient records from a pool of 2,000 GPs and 1,000 clinical specialists, including 65 pulmonologists (private practice). The records comprise demographic details and medical information including diagnoses, drug prescriptions, diagnostic tests, hospitalizations, hospital outpatient consultations, and specialist referrals. THIN is representative of the French population in terms of age, gender, and geographic distribution. All diagnoses are coded according to the International Classification of Diseases, tenth revision, Clinical Modification (ICD-10-CM). Drug prescriptions include information on trade names, formulations, and active substances, and are coded according to their Anatomical Therapeutic Chemical (ATC) classification. The pool of physicians is selected from across the entire territory of France, excluding overseas departments and territories, using a quota sampling method to ensure representativeness of the French medical population in terms of age, gender, region, and practice mode. The pool is adjusted annually to account for changes in medical demographics reported by the DREES (Direction de la Recherche, des Études, de l'Évaluation et des Statistiques).

Additional data were collected prospectively using questionnaires sent to the participating pool of physicians, which were completed during consultations with COPD patients initiating BUD/GLY/FOR triple therapy. These questionnaires collected data on smoking status, forced expiratory volume in one second (FEV1; to assess COPD severity), dyspnea, and COPD duration at BUD/GLY/FOR initiation. Completion of the questionnaire was voluntary.

Study Population

All patients in the THIN France database with at least two recorded ICD-10 codes for COPD or chronic bronchitis (J41.x, J42.x, J43.x, J44.x) who initiated BUD/GLY/FOR Aerosphere triple therapy between September 2021 and September 2023 (first prescription by a participating physician without any prior reimbursement history for BUD/GLY/FOR triple therapy) were included in the study. Patients were required to have a computerised medical record history (integrated reimbursement history) for at least 12 months prior to initiation, in order to collect data on previous COPD prescriptions, exacerbations and other patient characteristics such as comorbidities. Patients with chronic bronchitis were included to increase the sensitivity of the study population (Figure 1); this definition is consistent with other European database studies.[12,18–20]

Patients with a dispensation of BUD/GLY/FOR triple therapy prior to the first prescription by a participating physician (ie initiation by another physician) or without a prescription by a participating physician were excluded. In

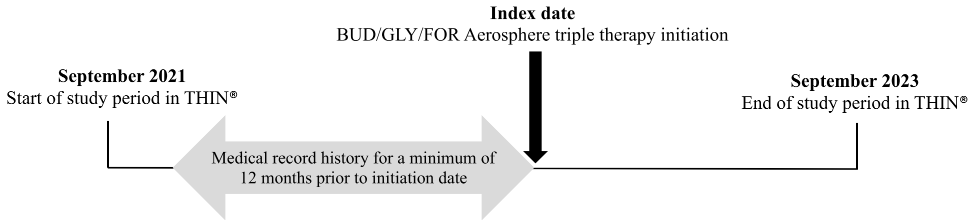

Figure 1 Schema of study period and participant inclusion.
Abbreviations: BUD/GLY/FOR, budesonide/glycopyrronium bromide/formoterol fumarate; THIN, The Health Improvement Network; ®, registered trademark.

order to confirm the initiation of BUD/GLY/FOR triple therapy, patients without computerised medical record/reimbursement history or with less than one year of history were excluded.

Outcomes

The primary outcomes were descriptive characteristics of patients prescribed BUD/GLY/FOR triple therapy, including demographic characteristics (age, gender); body mass index (BMI); smoking status; comorbidities (asthma (ever), active asthma (12 months before inclusion), hypertension, heart failure, diabetes (type 1 or type 2), sleep disorder, anxiety disorder, mood disorder, depressive disorder, osteoporosis, dysphonia, atopic dermatitis, allergic conjunctivitis, oral candidiasis, ear nose or throat cancer, glaucoma, cataract, tuberculosis, and Charlson comorbidity index); blood eosinophil count; patient management in the year prior to initiation (long-term oxygen therapy, blood count performed, spirometry performed, seen by a pulmonologist); COPD-related characteristics (exacerbations, previous treatments for COPD (including maintenance therapies, rescue treatments, and long-term oxygen therapy), severity of COPD at initiation (calculated from FEV1 measurements at the time of initiation), time since COPD diagnosis). Eosinophil count, measures of patient management, and exacerbations were measured in the previous 12 months prior to initiation. All characteristics were stratified by prescribing physician (GP or pulmonologist).

The secondary outcomes were to assess the proportion of COPD patients prescribed BUD/GLY/FOR triple therapy who were initiated according to clinical guidelines: SPLF 2021; HAS 2019; and GOLD 2021.

SPLF 2021 guidelines recommend the introduction of triple therapy as a step-up from dual therapy with LAMA and LABA or LABA and ICS in patients who develop further exacerbations and/or dyspnea while on maintenance dual therapy.[5] Data on dyspnea is not available in the THIN database, and additional data on dyspnea in the questionnaire were poorly completed by participating physicians; therefore, it was not possible to calculate the proportion of patients who were stepped-up from dual therapy with dyspnea (modified Medical Research Council dyspnea scale [mMRC] $\geq$ 2). Therefore, the adherence to SPLF guidelines as previous prescription for dual therapy with at least 2 moderate or 1 severe exacerbation in the previous year, or previous prescription for another triple therapy was described.

HAS 2019 guidelines recommend that the initiation of triple therapy should be reserved for patients with severe COPD who develop further exacerbations while on maintenance dual therapy.[8] The HAS 2019 guidelines, which were in use during the study period, recommend that single inhaler (fixed dose) triple therapy should only be initiated by a pulmonologist; however, the guidance was updated in 2023 to authorize GPs to initiate single inhaler triple therapy.[17] Therefore, HAS guideline adherence in both specialties was calculated.

The GOLD 2021 guidelines recommend triple therapy as a follow-up treatment in patients with exacerbations on LABA and ICS, and considered in patients with exacerbations on LABA and LAMA if blood eosinophils are ≥100 cells/μL.[4]

Statistical Analysis

Patient characteristics were described for the full study population and stratified by the prescribing physician (GP or pulmonologist). Continuous variables were described using mean and standard deviation (SD) for normally distributed variables, and the median and range for skewed data. Categorical variables were described using numbers and percentages.

Missing data for all relevant variables (BMI, COPD severity (FEV1), time between COPD diagnosis and BUD/GLY/FOR triple therapy initiation, adherence to HAS guidelines) were reported as a missing category. Where there were missing data, means were calculated among those for whom data were available, and proportions were calculated using the number of people with available data as the denominator. Smoking status was included in the questionnaire sent to GPs and pulmonologists, but this was poorly recorded by participating physicians and is therefore not reported in the results.

All statistical analyses were performed using SAS (Version 9.4, SAS Institute, North Carolina, USA) or R 3.5.3.

Results

Study Population

A total of 121,117 patients with a diagnosis of COPD were identified in THIN France database between September 2021 and September 2023. A total of 623 patients with COPD were initiated on BUD/GLY/FOR triple therapy during this period. Of these, 263 patients had a reimbursement history of at least 12 months in THIN and were initiated by participating pulmonologists or GPs; these patients formed the study population (Figure 2).

Characteristics of COPD Patients Initiated on BUD/GLY/FOR Triple Therapy by Prescribing Physician Speciality

Demographic characteristics were broadly similar between COPD patients prescribed BUD/GLY/FOR triple therapy by GPs and by pulmonologists: the mean age of patients was 69 years, and just over half were male (Table 1). Median COPD duration at the time of initiation was 5 years. A total of 156 (59.3%) patients had a record of spirometry, and the recorded use of spirometry was higher among patients prescribed by a pulmonologist compared to those prescribed by a GP group (67.6% vs 44.1%, respectively).

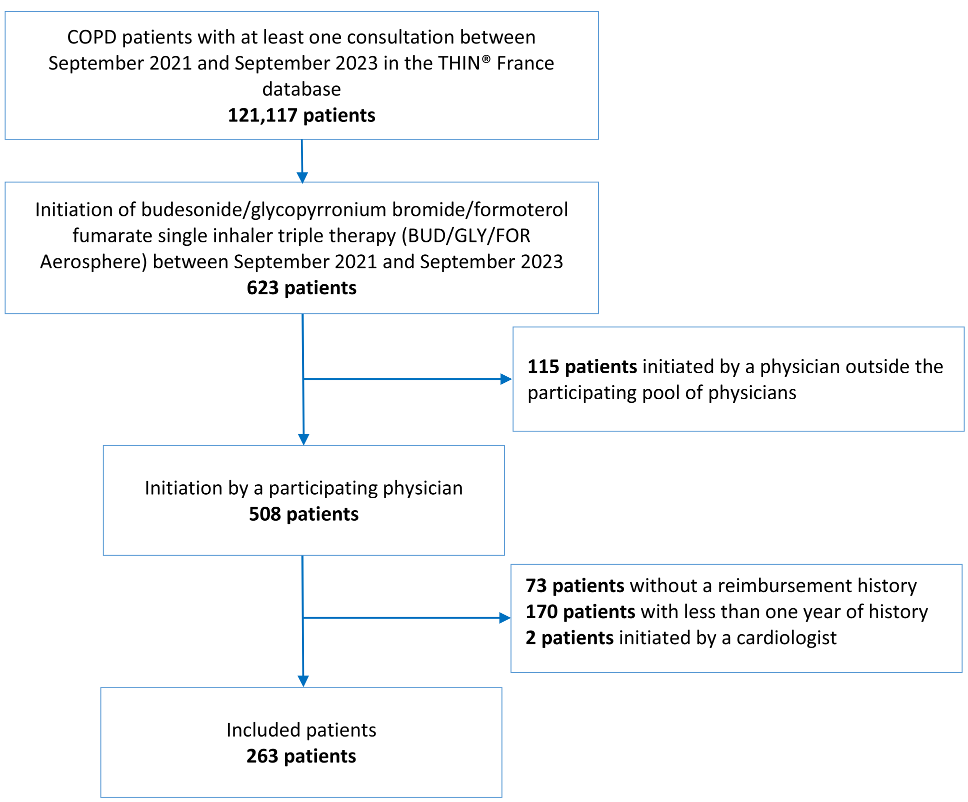

Figure 2 Flow diagram of the included study population.
Abbreviations: COPD, chronic obstructive pulmonary disease; THIN, The Health Improvement Network; ®, registered trademark.

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Table 1 Demographic Characteristics and Comorbidities of Patients Prescribed Budesonide/Glycopyrronium Bromide/Formoterol Fumarate Single Inhaler Triple Therapy, Stratified by Initiating Physician Speciality

Patient Characteristic	General Practitioner (N=93)	Pulmonologist (N=170)	Total (N=263)
Age, mean (SD) years	70.0 (10.6)	68.2 (12.3)	68.8 (11.8)
Gender, n (%)			
Female	38 (40.9)	84 (49.4)	122 (46.4)
Male	55 (59.1)	86 (50.6)	141 (53.6)
Body mass index			
Mean (SD) kg/m^2	28.2 (5.7)	27.7 (7.7)	28.0 (6.4)
Missing, n (%)	66 (71.0)	154 (90.6)	220 (83.7)
Follow-up time in THIN, median (range) years	7.3 (1.1–24.8)	7.0 (1.1–24.8)	7.0 (1.1–24.8)
COPD duration*			
Mean (SD) years	5.7 (5.3)	6.8 (5.7)	6.4 (5.5)
Median (range) years	4.5 (0.0–23.5)	5.3 (0.0–19.7)	5.1 (0.0–23.5)
Management in year prior to inclusion, n (%)			
Long-term oxygen therapy	0 (0)	0 (0)	0 (0)
Blood count performed	61 (65.6)	124 (72.9)	185 (70.3)
Spirometry performed	41 (44.1)	115 (67.6)	156 (59.3)
Seen by pulmonologist	36 (38.7)	–	–
Comorbidities, n (%)			
Any long-term illness	75 (80.6)	130 (76.5)	205 (77.9)
Charlson comorbidity index			
<5	49 (52.7)	114 (67.1)	163 (62.0)
≥5	44 (47.3)	56 (32.9)	100 (38.0)
Asthma (ever)	31 (33.3)	88 (51.8)	119 (45.2)
Active asthma (12 months before inclusion)	12 (12.9)	56 (32.9)	68 (25.9)
Hypertension	53 (57.0)	32 (18.8)	85 (32.3)
Heart failure	13 (14.0)	1 (0.6)	14 (5.3)
Type 1 or type 2 diabetes	27 (29.0)	17 (10.0)	44 (16.7)
Sleep disorder	37 (39.8)	49 (28.8)	86 (32.7)
Anxiety disorder	28 (30.1)	22 (12.9)	50 (19.0)
Mood disorder	27 (29.0)	15 (8.8)	42 (16.0)
Depressive disorder	27 (29.0)	15 (8.8)	42 (16.0)
Osteoporosis	11 (11.8)	0 (0.0)	11 (4.2)
Dysphonia	9 (9.7)	1 (0.6)	10 (3.8)
Atopic dermatitis	5 (5.4)	1 (0.6)	6 (2.3)
Allergic conjunctivitis	2 (2.2)	3 (1.8)	5 (1.9)
Oral candidiasis	5 (5.4)	0 (0.0)	5 (1.9)
Ear, nose or throat cancer	3 (3.2)	3 (1.8)	6 (2.3)
Glaucoma	4 (4.3)	1 (0.6)	5 (1.9)
Cataract	3 (3.2)	1 (0.6)	4 (1.5)
Tuberculosis	4 (4.3)	5 (2.9)	9 (3.4)

Notes: *As recorded in THIN.
Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

The proportion of patients with long-term illness was slightly higher among the GP-initiated group compared to pulmonologist-initiated patients (80.6% vs 76.5%, respectively), and the overall recorded comorbidity burden was greatest in the GP-initiated group (47.3% vs 32.9% of patients with a Charlson comorbidity index of 5 or more, respectively) (Table 1). However, there were notable differences in the distribution of specific comorbidities between the two groups. Among GP-initiated patients, there was a greater proportion with a recorded diagnosis of cardiometabolic conditions and mental health conditions, including hypertension 57.0% in the GP group compared to 18.8% in the pulmonologist group; diabetes 29.0% vs 10.0%; anxiety disorder 30.1% vs 12.9%; and depressive disorder 29.0% vs 8.8%. Conversely, there was a greater proportion of COPD patients in the pulmonologist-initiated group with a history of asthma: 33.3% in the GP group compared to 51.8% in the pulmonologist group (Table 1).

Approximately three-quarters (77.2%) of patients in the study population had a recorded moderate or severe exacerbation in the year prior to the initiation of BUD/GLY/FOR triple therapy (Table 2). Almost two-thirds of the COPD patients had presented with 2 or more moderate exacerbations in the previous year. The number of participants

Table 2 COPD-Related Characteristics of Patients Prescribed Budesonide/Glycopyrronium Bromide/Formoterol Fumarate Single Inhaler Triple Therapy, Stratified by Initiating Physician Speciality

Patient Characteristic	General Practitioner (N=93)	Pulmonologist (N=170)	Total (N=263)
Exacerbations			
Moderate exacerbations in the year before initiation, n (%)			
0	27 (29.0)	33 (19.4)	60 (22.8)
1	7 (7.5)	28 (16.5)	35 (13.3)
2	12 (12.9)	21 (12.4)	33 (12.5)
>2	47 (50.5)	88 (51.8)	135 (51.3)
Severe exacerbations* in the year before initiation, n (%)			
0	90 (96.8)	169 (99.4)	259 (98.5)
1	2 (2.2)	1 (0.6)	3 (1.1)
2	1 (1.1)	0 (0)	1 (0.4)
At least 1 moderate or severe exacerbation* the year before initiation, n (%)	66 (71.0)	137 (80.6)	203 (77.2)
At least 2 moderate exacerbations or 1 severe exacerbation* the year before initiation, n (%)	59 (63.4)	109 (64.1)	168 (63.9)
Previous Treatment, n (%)			
None	3 (3.2)	4 (2.4)	7 (2.7)
Monotherapy	16 (17.2)	13 (7.7)	29 (11.0)
Dual therapy	45 (48.4)	72 (42.4)	117 (44.5)
LABA and LAMA (single or multiple inhaler)	26/45 (57.8)	34/72 (47.2)	60/117 (51.3)
LABA and ICS (single or multiple inhaler)	18/45 (40.0)	34/72 (47.2)	52/117 (44.4)
Other	1/45 (2.2)	4/72 (5.6)	5/117 (4.3)
Triple therapy	29 (31.2)	81 (47.6)	110 (41.8)
Single inhaler triple therapy	18/29 (62.1)	49/81 (60.5)	67/110 (60.9)
Multiple inhaler triple therapy	11/29 (37.9)	32/81 (39.5)	43/110 (39.1)
Severity of COPD at initiation, n (%)			
Mild ($FEV_1 \geq 80\%$)†	2 (7.7)	3 (2.2)	5 (3.0)
Moderate ($50\% \leq FEV_1 <80\%$)†	6 (23.1)	61 (43.9)	67 (40.6)
Severe ($30\% \leq FEV_1 <50\%$)†	13 (50.0)	62 (44.6)	75 (45.5)
Very severe ($FEV_1 <30\%$)†	5 (19.2)	13 (9.4)	18 (10.9)
Missing	67	31	98
Time since COPD diagnosis††, n (%)			
Less than 1 year†	2 (8.3)	1 (0.8)	3 (2.0)
Between 1 year and 2 years†	2 (8.3)	4 (3.3)	6 (4.1)
Between 3 years and 5 years†	4 (16.7)	19 (15.4)	23 (15.6)
Between 6 years and 10 years†	6 (25.0)	58 (47.2)	64 (43.5)
Between 11 years and 19 years†	4 (16.7)	37 (30.1)	41 (27.9)
≥20 years†	6 (25.0)	4 (3.3)	10 (6.8)
Missing	69	47	116

Notes: *Severe exacerbations may be underestimated as data on hospitalizations in public hospitals are not available via the Caisse Nationale d'Assurance Maladie integrated reimbursement history. †Percentage of those with a record. ††As reported by physicians completing the questionnaire.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist.

with recorded severe exacerbations was low (n=4, 1.5%). Exacerbations were similar between GP- and pulmonologist-initiated patients.

Almost half of the patients initiated on BUD/GLY/FOR triple therapy had been previously treated with dual therapy (44.5%), with the proportion being slightly higher for those initiated by a GP compared to a pulmonologist (48.4% vs 42.4%, respectively) (Table 2). Among those initiated on BUD/GLY/FOR by a GP, prior treatment with LABA and LAMA was more common than LABA and ICS (57.8% vs 40.0% of those prescribed dual therapy), whereas these two dual therapies were prescribed equally among patients initiated by a pulmonologist (47.2% for both LABA and LAMA, and LABA and ICS). Moreover, 41.8% of patients had been previously treated with another triple therapy prior to BUD/GLY/FOR initiation, with the proportion being higher among those initiated by a pulmonologist compared to a GP (47.6% vs 31.2%, respectively). About 60.9% of patients prescribed another triple therapy were treated with a single inhaler/fixed-dose triple therapy. Overall, most patients (86.3%) had previously been prescribed dual or triple therapy prior to the initiation of BUD/GLY/FOR triple therapy.

Completion rate of the questionnaire collecting data on COPD history and severity was low, particularly by GPs. Where data were available, more than half of patients (56.4%) initiated with BUD/GLY/FOR triple therapy had severe or very severe COPD (Table 2); the proportion of patients with severe/very severe COPD was slightly higher among those initiated by GPs compared to those initiated by pulmonologists (69.2% vs 54.0%). The majority of patients (78.2%) had a history of COPD of at least 6 years.

Initiation of BUD/GLY/FOR Triple Therapy According to Clinical Guidelines

About 68.8% of patients prescribed BUD/GLY/FOR triple therapy had been initiated in line with SPLF 2021 guidelines, defined as having been previously prescribed dual therapy with at least 2 moderate or 1 severe exacerbation in the previous year, or having switched from another triple therapy (Table 3). Adherence to guideline recommendations was slightly higher among pulmonologists (72.4%) compared to GPs (62.4%).

Among patients with a record of COPD severity, 75.2% were initiated with BUD/GLY/FOR triple therapy according to HAS guidelines, that is, in patients with severe COPD who developed further exacerbations while on maintenance dual therapy or having switched from another triple therapy. The proportion was again slightly higher in the pulmonologist-initiated group compared to the GP-initiated group (76.3% and 69.2%, respectively).

The number of patients with a record of eosinophil count was very low, therefore we were not able to assess the proportion of patients prescribed BUD/GLY/FOR triple therapy according to GOLD 2021 guidelines.

Table 3 Patients Prescribed Budesonide/Glycopyrronium Bromide/Formoterol Fumarate Single Inhaler Triple Therapy in Accordance with Guidelines, Stratified by Initiating Physician Speciality

Guideline	General Practitioner (N=93)	Pulmonologist (N=170)	Total (N=263)
Patients initiated according to SPLF guidelines,* n (%)‡			
Yes	58 (62.4)	123 (72.4)	181 (68.8)
No	35 (37.6)	47 (27.6)	82 (31.2)
Patients initiated according to HAS guidelines, n (%)‡**			
Yes†	18 (69.2)	106 (76.3)	124 (75.2)
No†	8 (30.8)	33 (23.7)	41 (24.8)
Missing data	67 (72.0)	31 (18.2)	98 (37.3)

Notes: *Patients prescribed dual therapy with at least 2 moderate exacerbations or 1 severe exacerbation the year before initiation or patients switched from another triple therapy. **Patients with severe or very severe COPD and at least 2 moderate exacerbations or 1 severe exacerbation the year before initiation while on maintenance dual therapy or patients switched from another triple therapy. ‡Patients with triple therapy as previous treatment were considered following the SPLF and HAS guidelines even if the severity status was missing. †Percentage of those with a record of COPD severity.

Abbreviations: SPLF, Société de Pneumologie de Langue Française (French Language Respiratory Society) 2021; HAS, Haute Autorité de Santé (French National Authority for Health) 2019.

Discussion

This real-world study included 263 COPD patients who initiated BUD/GLY/FOR Aerosphere triple therapy following its commercialization in France in September 2021. Slightly more than half were male, the mean age was 69 years, and on average patients had had a diagnosis of COPD for more than 6 years. These COPD patients had multiple comorbidities; the most common were cardiometabolic conditions such as hypertension (32.3%) and diabetes (16.7%), sleep disorders (32.7%), and mental health conditions (anxiety 19.0%, depression 16.0%). A previous diagnosis of asthma was present in almost half of patients, with a quarter having active asthma. Patients initiated by a pulmonologist showed a higher prevalence of respiratory conditions and fewer non-respiratory comorbidities, which may reflect capture and recording of respiratory-related data within the clinical specialty rather than being a true indication of lower prevalence of non-respiratory conditions.

More than half of patients prescribed BUD/GLY/FOR triple therapy had severe or very severe COPD. Spirometry was performed for 59.3% of the patients in the year prior to initiation, with the proportion higher for patients initiated by a pulmonologist (44.1% in the GP group and 67.6% in the pulmonologist group). HAS guidelines recommend that BUD/GLY/FOR triple therapy should be initiated only among those with severe COPD and who have had lung function tests prior to initiation.[8,14,17]

Patient characteristics in this study were comparable to clinical trials of BUD/GLY/FOR Aerosphere in terms of age and sex.[7,10] In addition, patient characteristics were similar to characteristics of patients with severe COPD reported in similar real-world evidence studies in other countries[21] as well as in France.[22–25] In the study by Dalon et al,[24] which included a sample of patients from the French national health database, patients had an average age of 68 years and 67% were male; prevalence of comorbidities such as depression (20.5%) and diabetes (17.6%) were also similar to those observed in our study. In the OPTI study, which used THIN France database to describe the characteristics of COPD patients initiating triple therapy (single or multiple inhaler) in France, patients escalating to triple therapy were on average aged 67 years and 56% were male,[12] and the prevalence of comorbidities was also broadly similar to those observed in our study (asthma 45.6%, hypertension 44.4%, and sleep disorders 36.8%). The proportion of patients with a record of spirometry performed by the GP in the OPTI study was lower (33.4%) than in our study; our study data are more recent (2021–2023) compared to the OPTI study (2017–2019), and this difference may reflect changes in clinical practice in primary care settings with regard to the use of spirometry. Conversely, a lower proportion of patients had spirometry in the pulmonologist-initiated group in our study compared to the OPTI study (67.6% vs 92.2%, respectively); this may be explained in part by a significant proportion of the participants in our study switching from one triple therapy to another, rather than initiating a single or multiple inhaler triple therapy for the first time, which was the case in the OPTI study. The proportion of patients with severe/very severe COPD among those prescribed BUD/GLY/FOR triple therapy in our study was similar to another French study, TRILIFE that analyzed the real-world use of beclomethasone dipropionate/glycopyrronium bromide/formoterol (BECLO/GLY/FOR), in which 58% of patients had severe/very severe COPD at BECLO/GLY/FORM initiation.[26]

At the time of BUD/GLY/FOR triple therapy initiation, most patients in our study population had previously been treated with dual therapy (44.5%) or triple therapy (41.8%). Previous dual therapy was slightly more common among those initiated by a GP, while previous triple therapy was more common among those initiated by a pulmonologist. In patients escalated from dual therapy, previous treatment with LAMA and LABA was slightly more common than ICS and LABA. These results are in line with those presented in REFRAIN,[27] a retrospective study conducted using the Système national des données de santé (National Health Data System, SNDS) database in France to explore the use of the single inhaler triple therapy fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI), in which 39% of COPD patients were previously treated with a dual therapy and 43% with a triple therapy. Our results are also consistent with the TRILIFE study, in which 50% of patients had been previously treated with a dual therapy and 39% treated with a triple therapy prior to BECLO/GLY/FOR initiation.[26]

More than three-quarters of patients (77.2%) in our study had presented with at least one moderate or severe exacerbation in the year prior to initiation with BUD/GLY/FOR triple therapy, with the majority (63.9%) having experienced at least two moderate or one severe exacerbation. These characteristics were similar between both GP and pulmonologist prescribers. These results are in line with the OPTI study in which 74.9% of patients had experienced at least one moderate or severe exacerbation in the year before triple therapy initiation.[12] In the REFRAIN study, 20% to 25% of COPD patients had experienced a severe exacerbation and 68% of patients a moderate exacerbation in the 3 years prior to FF/UMEC/VI initiation.[27]

In evaluating the proportion of COPD patients who were initiated on BUD/GLY/FOR triple therapy according to French guidelines, a little over two-thirds of patients (68.8%) were initiated in line with SPLF guidelines, and three-quarters were initiated in line with HAS (75.2%) guidelines. In each case, the proportion was slightly higher among pulmonologists compared to GPs, however, in both physician groups the majority of COPD patients were prescribed according to guidelines. Unfortunately, it was not possible to assess adherence to GOLD guidelines due to the high level of missing data in blood eosinophil count. Overall, more patients in our study were prescribed BUD/GLY/FOR triple therapy by pulmonologists than by GPs, which reflects the HAS 2019 guidance in use for the majority of the study period, which stated that BUD/GLY/FOR triple therapy should only be prescribed by pulmonologists; the guidance was revised in June 2023 to permit initiation by any physician.[8,17]

This research was limited to a descriptive analysis of characteristics of COPD patients initiated on BUD/GLY/FOR triple therapy. Further research exploring treatment adherence and patient outcome measures using real-world data is recommended, including evaluation of differences in outcomes such as exacerbations, hospitalizations, and mortality between different treatment groups.

Strengths and Limitations

This study uses real-world data from a nationally representative database in France (THIN France). The participating physicians are representative of clinical practice in France. Prescription data is collected from linkage with pharmacy data, maximising capture of prescription information irrespective of the prescribing physician's specialty.

Nevertheless, there are several limitations. Firstly, it is possible that some comorbidities may be underestimated in this sample of patients; in particular, lower Charlson comorbidity index and prevalence of non-respiratory comorbidities in the pulmonologist group is likely to arise in part due to poorer recording of comorbidities in this group. Secondly, we were not able to report smoking status and dyspnea as the completion rate of these questions in the questionnaire sent to physicians was very low. The lack of dyspnea data meant that we were unable to calculate the proportion of patients who were stepped-up from dual therapy with dyspnea as per the SPLF guidelines; as a result, the proportion of patients prescribed BUD/GLY/FOR triple therapy in line with SPLF guidelines may have been underestimated. Thirdly, there was a high level of missing data for severity of COPD, again due to poor completion of the questionnaire, particularly among those initiated by GPs; this meant that HAS guideline adherence could not be assessed for all patients in the study population. Similarly, there was a very high level of missing data for eosinophil count, and it was therefore not possible to assess adherence to GOLD guidelines. Fourthly, severe exacerbations may be underestimated as data on hospitalizations in public hospitals are not available via the Caisse Nationale d'Assurance Maladie (National Health Insurance Fund) integrated reimbursement history and are therefore not captured in the THIN data. Fifthly, participants initiated on BUD/GLY/FOR triple therapy between 2021 and 2023 were included in the study; patients initiated in more recent years are not captured. Finally, although data has been collected from a representative pool of physicians in France, no information was available for hospital-based pulmonologists within THIN, potentially resulting in some selection bias.

Conclusions

This real-world evidence study demonstrates that the characteristics of patients initiating BUD/GLY/FOR triple therapy in France are consistent with previous published studies for other triple therapies for COPD. The majority of COPD patients are prescribed BUD/GLY/FOR triple therapy in accordance with current treatment guidelines, irrespective of whether the therapy is prescribed by a general practitioner or a pulmonologist.

Abbreviations

BECLO/GLY/FOR, beclomethasone dipropionate/glycopyrronium bromide/formoterol; BUD/GLY/FOR, budesonide/glycopyrronium bromide/formoterol fumarate; COPD, chronic obstructive pulmonary disease; CT, Commission de la

Transparence (Transparency Commission); FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GP, general practitioner; ICS, inhaled corticosteroids; FEV1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HAS, Haute Autorité de Santé (French National Authority for Health); LAMA, long-acting muscarinic antagonist; LABA, long-acting beta-2 agonist; mMRC, Medical Research Council dyspnea scale; SD, standard deviation; SNDS, Système national des données de santé (National Health Data System); SPLF, Société de Pneumologie de Langue Française (French Language Respiratory Society).

Data Sharing Statement

Data cannot be shared publicly because of legal restrictions. Data are available from the GERS SAS for researchers who meet the criteria for access to confidential data.

Ethics Approval and Informed Consent

Research using THIN database in France is compliant with current regulations, including GDPR. Ethical approval for this project was granted by the THIN EuroBoard scientific review committee (protocol number 2024-24). THIN® is a European medical database network of electronic health records; no identifiable personal data was used in this study, and informed consent was not required.

Author Contributions

AC and IG performed data management and statistical analyses. NJA and AC created the initial draft of the manuscript. 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

GD reports personal fees from Chiesi, Boehringer Ingelheim, GSK, Sanofi and AstraZeneca. CFV, ES and NP are employees of AstraZeneca. AC and CEP are employees of Cegedim. NJA is an independent consultant at the University of Birmingham. She also reports personal fees from Cegedim, during the conduct of the study; grants from the National Institute for Health Research, outside the submitted work.

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