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FULFIL Trial: Once-Daily Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease

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At a Glance Commentary:

Although inhaled triple pharmacologic therapy is recommended for patients with advanced chronic obstructive pulmonary disease and is often used clinically as step-up treatment, few randomized controlled trials have assessed the benefit of triple therapy compared with dual inhaled corticosteroid/long-acting β_2-agonist therapy. Results from the FULFIL study demonstrated the clinical benefit of once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) combination therapy using a single inhaler compared with twice-daily budesonide/formoterol (BUD/FOR) combination therapy. Once-daily FF/UMEC/VI improved lung function and health-related quality of life, as well as reducing exacerbation frequency, compared with twice-daily BUD/FOR.

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Abstract

Rationale: Randomized data comparing triple therapy with dual inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) therapy in patients with chronic obstructive pulmonary disease (COPD) are limited.

Objectives: We compared the effects of once-daily triple therapy on lung function and health-related quality of life with twice-daily ICS/LABA therapy.

Methods: FULFIL was a randomized, double-blind, double-dummy study comparing 24 weeks of once-daily triple therapy (fluticasone furoate/umeclidinium/vilanterol 100 µg/62.5 µg/25 µg; ELLIPTA® inhaler) with twice-daily ICS/LABA therapy (budesonide/formoterol 400 µg/12 µg; Turbuhaler®). A patient subgroup remained on blinded treatment for up to 52 weeks. Co-primary endpoints were change from baseline in trough forced expiratory volume in 1 second (FEV_1) and in St George's Respiratory Questionnaire (SGRQ) Total score, at Week 24.

Measurements and Main Results: In the intent-to-treat population (N = 1,810) at Week 24 for triple therapy (n = 911) and ICS/LABA therapy (n = 899): mean change from baseline in FEV_1 was 142 mL (95% confidence interval [CI], 126,158) and -29 mL (95% CI, -46,-13), respectively; mean change from baseline SGRQ was -6.6 units (95% CI, -7.4,-5.7) and -4.3 units (95% CI, -5.2,-3.4), respectively. For both endpoints, the between-group differences were statistically significant ($P < 0.001$). There was a statistically significant reduction in moderate/severe exacerbation rate with triple versus ICS/LABA therapy (35% reduction, 95% CI, 14,51; $P = 0.002$). The safety profile of triple therapy reflected the known profiles of the components.

Conclusions: These results support the benefits of single inhaler triple therapy compared with ICS/LABA therapy, in patients with advanced COPD.

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Introduction

The use of inhaled triple pharmacologic therapy by patients with chronic obstructive pulmonary disease (COPD) is common; a UK study found that after 2 years, 46% of patients initially prescribed a long-acting bronchodilator and 39% of those prescribed an inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) or ICS plus long-acting muscarinic antagonist (LAMA) progressed to triple therapy (1). In a US study, 25.5% of patients with COPD, who had received at least one LAMA, LABA, ICS, or phosphodiesterase-4 inhibitor, received triple therapy within 2 years of being diagnosed (2). The Global Initiative for Chronic Obstructive Lung Disease strategy document recommends inhaled triple pharmacologic therapy (ICS/LAMA/LABA) for patients with advanced COPD with persistent symptoms and risk of exacerbations (3).

Despite the current widespread use of triple therapy, there are few randomized controlled trials demonstrating a sustained benefit on lung function and patient reported outcome measures compared with ICS/LABA alone (4). Recently, a once-daily single inhaler triple therapy of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100 µg/62.5 µg/25 µg has been developed for patients with moderate to very severe COPD. This ‘closed triple’ therapy may offer clinically important improvements in lung function and quality of life compared with ICS/LABA dual therapy, as well as eliminating the need for delivering the medications using multiple inhalers. Single inhaler triple therapy may reduce the risk of medication errors and may help to ensure that a patient receives all three medications.

FULFIL (Lung FUnction and quality of LiFe assessment in COPD with closed trIpLe therapy) is the first study to compare once-daily single inhaler triple therapy (ICS/LABA/LAMA) with twice-daily dual therapy (ICS/LABA) in patients with

advanced, symptomatic COPD, who are at risk of exacerbations. It was designed in part to support the registration of once-daily FF/UMEC/VI in Europe and other countries globally. In consultation with European regulators, the sponsor was asked to provide a comparison with an ICS/LABA dual combination product indicated to treat patients with COPD, which was well known and well understood by physicians. BUD/FOR was chosen as it is a commonly prescribed medication for patients with COPD. The study provides comparative information not just between classes of therapies but also between different molecules with different dosing regimens.

FULFIL was specifically designed to have a close resemblance to real-world clinical practice. It compared a once-daily triple pharmacologic therapy to a current standard-of-care ICS/LABA, and the run-in period allowed patients to continue on their pre-study maintenance therapy up to randomization to mimic switch scenarios in clinical practice. FULFIL also allowed inclusion of patients with commonly observed comorbidities who are often excluded from other trials. The patient's perspective was carefully evaluated using a health-related quality of life co-primary endpoint. Some of the results have been previously reported in the form of an abstract (5).

Methods

Trial Design and Oversight

FULFIL was a phase III, randomized, double-blind, double-dummy, parallel-group, multicenter study (ClinicalTrials.gov number, NCT02345161; GSK study CTT116853). Patients were randomized to receive 24 weeks of once-daily

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FF/UMEC/VI (100 µg/62.5 µg/25 µg) using a single ELLIPTA® inhaler and twice-daily placebo using the Turbuhaler®, or twice-daily budesonide/formoterol (BUD/FOR) (400 µg/12 µg) using the Turbuhaler® and once-daily placebo using the ELLIPTA® inhaler. Twice-daily BUD/FOR using the Turbuhaler® was the comparator, as this ICS/LABA is commonly used in this patient population. All patients took one inhalation from the ELLIPTA® inhaler in the morning and two inhalations (one in the morning and one in the evening) from the Turbuhaler® to minimize the impact of different dosing regimens.

There was a 2-week run-in period, during which medications at screening were unchanged, followed by a 24-week treatment period. A subset of the first 430 patients to enroll in the trial and consent to longer-term treatment remained on blinded study treatment for up to 52 weeks. To minimize loss of data, patients who permanently discontinued study treatment (but did not withdraw consent) were not required to withdraw from the study, but could continue to have certain safety and efficacy assessments conducted.

The primary objectives were to evaluate the effects of once-daily single inhaler triple therapy (FF/UMEC/VI) on lung function and health-related quality of life compared with twice-daily dual ICS/LABA therapy (BUD/FOR) at 24 weeks.

The institutional review boards for human studies approved the protocol and written consent was obtained from the subjects or their surrogates as required by the institutional review boards.

Study Endpoints

The co-primary endpoints were change from baseline in trough forced expiratory volume in 1 second (FEV_1) and change from baseline in St George's Respiratory

Questionnaire (SGRQ) Total score, at Week 24. Supportive analyses for the primary endpoints included: proportion of patients with a clinically meaningful change from baseline in trough FEV_1 (≥ 100 mL) and change from baseline SGRQ Total score (≥ 4 unit decrease); change from baseline in Evaluating Respiratory Symptoms in COPD score (E-RS: COPD; formerly EXACT RS) over 24 weeks and the proportion of responders. Population pharmacokinetic analyses were conducted on serial and sparse blood samples collected from a subset of patients (n = 74) to assess FF, UMEC, and VI systemic exposure from a single inhaler.

Efficacy and safety endpoints were analyzed up to Week 24 in the intent-to-treat (ITT) population and up to Week 52 in the extension (EXT) population.

Patients

FULFIL enrolled patients with COPD aged ≥ 40 years defined as Global Initiative for Chronic Obstructive Lung Disease Group D: FEV_1 < 50% and COPD Assessment is Test™ ≥ 10, ***or*** patients with FEV_1 ≥ 50–< 80% and COPD Assessment Test™ ≥ 10, and either ≥ 2 moderate exacerbations in the past year or ≥ 1 severe exacerbation in the past year. Patients were required to be receiving daily maintenance therapy for COPD for ≥ 3 months. Patients were excluded if they had a current diagnosis of asthma causing their symptoms, or unresolved pneumonia or severe COPD exacerbation. Demographic and disease characteristics were recorded at screening.

Efficacy Assessments

Spirometry was performed in all patients at baseline and at Weeks 2, 4, 12, 24, and at Weeks 36 and 52 in the EXT population, using standardized equipment according to the American Thoracic Society-European Respiratory Society criteria (6). The

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SGRQ for COPD patients was completed using a patient-held eDiary at Day 1 and at Weeks 4 and 24 (and Week 52 for the EXT population). Potential COPD exacerbations were identified based on symptoms reported using the eDiary, which triggered follow-up with the investigator, who confirmed any exacerbations based on an interaction with the patient. Mild exacerbations were defined as worsening symptoms of COPD that were self-managed by the patient (*e.g.* increase in albuterol use) and not associated with the use of corticosteroids or antibiotics. A moderate exacerbation was defined as having worsening symptoms of COPD that required treatment with oral/systemic corticosteroids and/or antibiotics. A severe exacerbation was defined as worsening symptoms of COPD that required treatment with in-patient hospitalization. The E-RS: COPD questionnaire was completed each evening using the eDiary.

Safety Assessments

The incidence of adverse events (AEs), serious AEs (SAEs), pneumonia and supporting radiography, cardiovascular events including pre-specified major cardiovascular events analysis, bone fractures, and other AEs of special interest (AESI) were evaluated in the study (AESI are listed in Table E1 in the online data supplement).

Statistical Analyses

Statistical analyses were carried out using SAS Version 9.3. Sample size was calculated based on the co-primary endpoints and previous experience with drugs of these classes. The ITT population, stratified by smoking status, comprised all randomized patients, excluding those who were randomized in error who did not

receive a dose of study medication. The EXT population comprised the subset of patients in the ITT population who were enrolled into the 52-week extension phase. The co-primary endpoints were analyzed using mixed model repeated measures and were adjusted for multiplicity using the Hochberg method.

Further details of the methods are provided in the online data supplement.

Results

Patients

In total, 1,810 patients were included in the ITT population (FF/UMEC/VI, n = 911; BUD/FOR, n = 899) and 430 in the EXT population (FF/UMEC/VI, n = 210; BUD/FOR, n = 220) (Figure E1 in the online data supplement). Overall, 94% of patients completed the study and 90% completed the study on investigational treatment; premature treatment discontinuations were most frequently due to patient decision (4%), AE, or lack of efficacy (both 3%). Patient and disease characteristics at baseline for the ITT and EXT populations are shown in Table 1. COPD medications used during the study run-in are provided in Table E2 in the online data supplement.

Co-Primary Endpoints

In the ITT population, FF/UMEC/VI demonstrated clinically meaningful improvements from baseline in trough FEV_1 at all time points over the 24-week treatment period (Figure 1A; Table 2). At Week 24, the mean change from baseline in trough FEV_1 was 142 mL (95% confidence interval [CI], 126,158) for FF/UMEC/VI and -29 mL

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(95% CI, -46,-13) for BUD/FOR; the difference between FF/UMEC/VI and BUD/FOR was statistically significant (171 mL; 95% CI, 148,194; *P* < 0.001) (Table 2). The treatment differences ranged from 123 to 171 mL and were statistically significant in favor of FF/UMEC/VI at all time points (*P* < 0.001).

In the ITT population, at Week 24, clinically meaningful improvements in SGRQ Total score were observed in both treatment groups. The change from baseline in SGRQ was -6.6 units (95% CI, -7.4,-5.7) with FF/UMEC/VI and -4.3 (95% CI, -5.2,-3.4) with BUD/FOR. The between-treatment difference in improvement in SGRQ Total score was statistically significant for FF/UMEC/VI (-2.2 units; 95% CI, -3.5,-1.0; *P* < 0.001) compared with BUD/FOR (Table 2).

Similar findings in change from baseline in trough FEV_1 were observed in the EXT population at Week 52 (Figure 1B; Table 2). The mean change from baseline in trough FEV_1 was 126 mL (95% CI, 92,159) for FF/UMEC/VI and -53 mL (95% CI, -87,-20) for BUD/FOR. The mean change from baseline in SGRQ Total score in the EXT population was -4.6 units (95% CI, -6.5,-2.6) with FF/UMEC/VI and -1.9 units (95% CI, -3.9,0.1) with BUD/FOR, and although the between-treatment difference was of a similar magnitude to that observed in the ITT population, it did not reach statistical significance (Table 2).

Selected Secondary and Other Endpoints

In the ITT population at Week 24, an increase of ≥ 100 mL from baseline in trough FEV_1 was achieved by a larger proportion of patients in the FF/UMEC/VI group (453; 50%) than in the BUD/FOR group (184; 21%). The odds ratio (OR) of achieving versus not achieving this increase was statistically significant in favor of FF/UMEC/VI (OR, 4.03; 95% CI, 3.27,4.97; *P* < 0.001).

A larger proportion of patients in the FF/UMEC/VI group (448; 50%) than in the BUD/FOR group (368; 41%) experienced a clinically meaningful improvement from baseline (≥ 4 unit decrease) in SGRQ Total score in the ITT population at Week 24. The OR of response versus non-response was statistically significant in favor of FF/UMEC/VI (OR, 1.41; 95% CI, 1.16,1.70; *P* < 0.001) (Table 2).

The incidence of moderate/severe COPD exacerbations over the 24-week treatment period was 10% (n = 95) and 14% (n = 126) for FF/UMEC/VI and BUD/FOR, respectively. The mean annualized rate of moderate/severe exacerbations was 0.22 and 0.34 for FF/UMEC/VI and BUD/FOR, respectively, and the reduction in the annualized rate was statistically significant (35%; 95% CI, 14,51%; *P* = 0.002) based on data up to 24 weeks in the ITT population (Table 3). Similar statistically significant results were observed for mild/moderate/severe exacerbations (Table 3). Fewer patients were hospitalized for exacerbations in the FF/UMEC/VI treatment group (12 [1%]) than in the BUD/FOR group (22 [2%]).

For the ITT population, at each 4-week interval over the 24-week treatment period, FF/UMEC/VI produced greater reductions from baseline in E-RS: COPD total score compared with BUD/FOR and the treatment differences were statistically significant (*P* < 0.001) (Figure 2). The ORs for response versus non-response for each 4-week interval were statistically significant in favor of FF/UMEC/VI (OR ranging 1.59,1.76; *P* < 0.001). Similar results were observed for each E-RS: COPD subscale (breathlessness; cough and sputum; chest symptoms).

The results for the secondary and other endpoints described here were also observed up to 52 weeks in the EXT population (see respective tables and figures).

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Safety Analyses

The incidence of on-treatment AEs in the ITT population up to Week 24 was 38.9% in the FF/UMEC/VI group and 37.7% in the BUD/FOR group; the most common AEs were nasopharyngitis (7% and 5% for FF/UMEC/VI and BUD/FOR, respectively) and headache (5% and 6% for FF/UMEC/VI and BUD/FOR, respectively) (Table 4). A similar pattern was observed in the EXT population up to Week 52; the most common AEs were nasopharyngitis (11% and 10% for FF/UMEC/VI and BUD/FOR, respectively) and headache (8% and 10% for FF/UMEC/VI and BUD/FOR, respectively). COPD worsening was one of the most common AEs in the BUD/FOR group (10%), but was less common in the FF/UMEC/VI group (2%) in the EXT population up to Week 52.

For FF/UMEC/VI and BUD/FOR, respectively: the incidence of on-treatment SAEs in the ITT population up to Week 24 was 5.4% and 5.7%; the most common on-treatment SAEs were COPD exacerbation (1.3% and 2.3%) and pneumonia (1.0% and 0.3%). There were 12 on-treatment deaths in this study (six in each treatment group), which was in line with expectations for patients with advanced COPD and multiple comorbidities. The incidence of adjudicated on-treatment non-fatal SAEs in the ITT population was 4.9% in the FF/UMEC/VI group and 5.2% in the BUD/FOR group. Of these (for FF/UMEC/VI and BUD/FOR, respectively), COPD exacerbations (1.5% and 2.4%) and pneumonia and/or respiratory tract infection without COPD exacerbation (0.9% and 0.3%) were the most common. An overview of the rate of drug-related AEs and SAEs is provided in the Results section of the online data supplement.

The incidence of pre-specified AESIs in the ITT population was also investigated. For FF/UMEC/VI and BUD/FOR, respectively: cardiovascular effects

were reported by 4.3% and 5.2% of patients and the incidence of pneumonia was 2.2% and 0.8% in the ITT population up to Week 24 (Table 4).

The incidence of on-treatment SAEs in the EXT population was 10.0% in the FF/UMEC/VI group and 12.7% in the BUD/FOR group. In the EXT population up to Week 52, for FF/UMEC/VI and BUD/FOR, respectively, cardiovascular effects as AESI were reported by 8.6% and 10.0% of patients, and the incidence of pneumonia as an AESI was 1.9% and 1.8% (Table 4).

The incidence of major cardiovascular events was 0.4% and 0.8% in the ITT population up to Week 24, and 2.4% and 0.9% in the EXT population up to Week 52, for FF/UMEC/VI and BUD/FOR, respectively. There were no clinically significant differences between treatment groups in vital signs, electrocardiograms, Holter findings, or laboratory values.

Population pharmacokinetic analyses showed that systemic drug levels of FF, UMEC, and VI following FF/UMEC/VI administration using a single inhaler (triple therapy) were low and within the range observed following dual therapy (FF/VI and UMEC/VI) and monotherapy (FF, UMEC, and VI) (7, 8).

Discussion

Our results show that once-daily FF/UMEC/VI offered clinically meaningful and statistically significant improvements at Week 24 in lung function and health-related quality of life compared with BUD/FOR. The improvements in health-related quality of life were reflected in the consistent reduction in total symptoms, measured using the E-RS: COPD. At each 4-weekly time point, FF/UMEC/VI demonstrated greater symptom reduction than BUD/FOR. Clinically meaningful and statistically significant reductions in exacerbation rates for patients with COPD were also observed with

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FF/UMEC/VI compared with BUD/FOR, at Week 24. Importantly, the benefits of FF/UMEC/VI on lung function, health-related quality of life, and exacerbation rate were sustained over 52 weeks in the EXT population. The magnitude of the between-treatment difference in SGRQ Total score between treatment groups at Week 52 failed to achieve statistical significance, possibly due to the smaller size of this subgroup. The lung function findings reported here are in keeping with the results of shorter studies of triple therapy using FF/VI and UMEC in two separate inhalers (4, 9).

The safety profile of FF/UMEC/VI, including the systemic exposure, was in line with the known profiles of the component drugs, and findings from the 52-week EXT population suggest that there are no cumulative adverse effects from once-daily FF/UMEC/VI. While the incidence of pneumonia was higher with FF/UMEC/VI than with BUD/FOR in the ITT population up to 24 weeks, it was similar between the two groups in the smaller EXT population at 52 weeks. The incidence of pneumonia with FF/UMEC/VI observed here is consistent with reports from other 24-week studies of FF/VI for COPD, which reported incidences of up to 2% (10, 11), and studies of BUD/FOR for COPD (12, 13). The incidence of pneumonia is also similar to that observed in another study of ICS/LABA/LAMA therapy for COPD, in which pneumonia occurred in 3% of patients in both the triple therapy and the ICS/LABA comparator arms (14) and is less than the incidence reported in 52-week studies of FF/VI (15) and BUD/FOR (16). No excess risk of pneumonia with FF or VI either alone or in combination, compared with placebo, was found in the SUMMIT study (although SUMMIT included patients with moderate airflow limitation and only 39% had a history of exacerbations) (17).

Although this study was focused on non-exacerbation outcomes and the

proportion of patients with exacerbations in the overall population was low, there were clear efficacy benefits in favor of FF/UMEC/VI on these outcome measures in both the ITT and EXT populations.

FULFIL was designed to be as inclusive as possible, allowing patients with COPD who also had significant cardiovascular disease to be enrolled. Furthermore, patients remained on their usual standard medications during the run-in and were not artificially required to withdraw medications. This meant the study population may more closely reflect the real-world population of patients with COPD and increases the generalizability of the study findings. FULFIL was also designed to minimize data loss, by enabling data collection to continue following treatment discontinuation. All SAE reports were independently adjudicated, and a chest radiograph was required for all patients with suspected pneumonia or a moderate/severe exacerbation, which improved the characterization of safety findings.

This study compared an ICS/LABA/LAMA (FF/UMEC/VI) combination with an ICS/LABA (BUD/FOR) using different dosing regimens (once daily vs. twice daily) in different inhalers. The double-dummy study design aimed to mitigate some of these differences, so the results reported are a direct comparison of the products rather than the addition of a LAMA to ICS/LABA. However, there is evidence supporting the value of incremental LAMA therapy (4, 9, 14, 18). Two randomized, 3-month studies showed clinically relevant improvements in lung function with UMEC plus FF/VI, compared with placebo plus FF/VI, in patients with moderate-to-very severe COPD (9). The TRILOGY study (14) showed that triple therapy compared with ICS/LABA had a modest benefit with a reduction in exacerbations and an improvement in health-related quality of life; however, this appeared to wane as the study continued. A *post-hoc* analysis of four trials that assessed UMEC or placebo plus ICS/LABA

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(including the two studies described previously) showed that triple therapy improved lung function and health-related quality of life, and reduced the risk of exacerbations compared with ICS/LABA (4). Of note, in FULFIL, the benefits of FF/UMEC/VI over BUD/FOR seem substantially greater and more persistent than those seen in the comparison of beclomethasone dipropionate/formoterol/glycopyrronium bromide with beclomethasone dipropionate/formoterol (14). This could be due to the advantages of once-daily versus twice-daily dosing, the differences in the individual components, or a combination of the two. Further study is needed to clarify the drivers of these differences.

Results from the FULFIL study demonstrated the clinical value of triple therapy using FF/UMEC/VI, compared with dual BUD/FOR therapy, for symptomatic patients with advanced COPD who are at risk of exacerbations. Once-daily single inhaler triple therapy provides a straightforward dosing option for patients with COPD and this reduction in polypharmacy using multiple inhalers may reduce the likelihood of inhaler use errors, although all inhaler types may be associated with errors in use (19–21). Single inhaler triple therapy offers clinically important benefits in lung function, health-related quality of life, and reduction in risk of exacerbation, which were also observed over 52 weeks.

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Figure Legends

Figure 1. Mean change from baseline in trough FEV_1 over (*A*) 24 weeks (ITT population) and (*B*) 52 weeks (EXT population). The bars indicate 95% confidence intervals. BUD = budesonide; CI = confidence interval; EXT = extension; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FOR = formoterol; ITT = intent-to-treat; LS = least squares; UMEC = umeclidinium; VI = vilanterol.

Figure 2. Mean change from baseline in 4-weekly E-RS total score (ITT population). The bars indicate 95% confidence intervals. BUD = budesonide; CI = confidence interval; E-RS = Evaluating Respiratory Symptoms; FF = fluticasone furoate; FOR = formoterol; ITT = intent-to-treat; LS = least squares; UMEC = umeclidinium; VI = vilanterol.

Tables and Figures

Table 1. Patient Characteristics at Baseline (ITT and EXT Populations)*

Characteristic	ITT Population (24 Weeks)		
	FF/UMEC/VI 100/62.5/25 µg (n = 911)	**BUD/FOR 400/12 µg (n = 899)**	**Total (N = 1,810)**
Age, yr	64.2 (8.56)	63.7 (8.71)	63.9 (8.64)
Female, n (%)	233 (26)	236 (26)	469 (26)
Current smokers, n (%)	400 (44)	394 (44)	794 (44)
Smoking pack-years	39.5 (21.87)	39.2 (22.15)	39.4 (22.00)
Cardiovascular risk factors†, n (%)	599 (66)	602 (67)	1,201 (66)
Moderate/severe COPD exacerbation in previous 12 months, n (%)			
0	313 (34)	317 (35)	630 (35)
1	252 (28)	253 (28)	505 (28)
≥ 2	346 (38)	329 (37)	675 (37)
History of pneumonia, n (%)	87 (10)	99 (11)	186 (10)
FEV_1 absolute, mL	1349 (0.46)	1339 (0.48)	1344 (0.47)
FEV_1 predicted, %	45.5 (12.97)	45.1 (13.64)	45.3 (13.30)
SGRQ Total score	51.8 (16.29)	50.8 (16.73)	–
E-RS: COPD	13.20 (5.828)	12.97 (5.928)	–
	EXT Population (52 Weeks)		
	FF/UMEC/VI 100/62.5/25 µg	**BUD/FOR 400/12 µg**	**Total**

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	(n = 210)	(n = 220)	(N = 430)
Age, yr	63.7 (7.76)	63.3 (8.43)	63.5 (8.10)
Female, n (%)	53 (25)	58 (26)	111 (26)
Current smokers, n (%)	95 (45)	97 (44)	192 (45)
Smoking pack-years	39.8 (19.92)	39.6 (23.12)	39.7 (21.59)
Cardiovascular risk factors†, n (%)	144 (69)	152 (69)	296 (69)
Moderate/severe COPD exacerbation in previous 12 months, n (%)			
0	62 (30)	72 (33)	134 (31)
1	77 (37)	79 (36)	156 (36)
≥ 2	71 (34)	69 (31)	140 (33)
History of pneumonia, n (%)	18 (9)	20 (9)	38 (9)
FEV_1 absolute, mL	1425 (0.50)	1368 (0.51)	1396 (0.51)
FEV_1 predicted, %	47.1 (13.30)	45.4 (14.85)	46.2 (14.13)
SGRQ Total score	53.0 (16.14)	50.8 (15.49)	–
E-RS: COPD	13.54 (5.439)	13.00 (5.576)	–

Definition of abbreviations: BUD = budesonide; COPD = chronic obstructive pulmonary disease; E-RS: COPD = Evaluating Respiratory Symptoms in COPD; EXT = extension; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FOR = formoterol; ITT = intent-to-treat; SD = standard deviation; SGRQ = St George's Respiratory Questionnaire; UMEC = umeclidinium; VI = vilanterol.

*Data are mean (SD) unless otherwise stated.

†Cardiovascular risk factors included, but were not limited to, hypertension, hypercholesterolemia, coronary heart disease, and diabetes mellitus.

Table 2. Trough FEV_1 and SGRQ Responses (ITT and EXT Populations)

	ITT Population (24 Weeks)	
	FF/UMEC/VI 100/62.5/25 µg (n = 911)	**BUD/FOR 400/12 µg (n = 899)**
Trough FEV_1, mL		
LS mean at Week 24	1,418	1,247
95% CI	1,401,1,434	1,230,1,263
LS mean change from baseline	142	-29
95% CI	126,158	-46,-13
FF/UMEC/VI vs. BUD/FOR difference (95% CI)	171 (148,194)	
***P*-value**	<0.001	
Proportion of trough FEV_1 responders*, n	907	892
Responders, % (n)	50 (453)	21 (184)
FF/UMEC/VI vs. BUD/FOR OR (95% CI)	4.03 (3.27,4.97)	
***P*-value**	<0.001	
Change from baseline in SGRQ Total score, n	846	791

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LS mean at Week 24	44.7	46.9
95% CI	43.8,45.5	46.0,47.8
LS mean change	-6.6	-4.3
95% CI	-7.4,-5.7	-5.2,-3.4
FF/UMEC/VI vs. BUD/FOR		
difference (95% CI)	-2.2 (-3.5,-1.0)	
***P*-value**	<0.001	
Proportion of responders[†],		
n	904	893
Responders, n (%)	448 (50)	368 (41)
FF/UMEC/VI vs. BUD/FOR		
OR (95% CI)	1.41 (1.16,1.70)	
***P*-value**	<0.001	

	EXT Population (52 Weeks)	
	FF/UMEC/VI 100/62.5/25 µg (n = 210)	**BUD/FOR 400/12 µg (n = 220)**
Trough FEV_1, mL		
LS mean at Week 52	1,429	1,250
95% CI	1,395,1,462	1,216,1,284
LS mean change from baseline	126	-53

95% CI	92,159	-87,-20
FF/UMEC/VI vs. BUD/FOR		
difference (95% CI)	179 (131,226)	
***P*-value**	<0.001	
Proportion of trough FEV_1 responders*, n		
Responders, % (n)	46 (96)	16 (34)
FF/UMEC/VI vs. BUD/FOR		
OR (95% CI)	4.79 (3.02,7.61)	
***P*-value**	<0.001	
Change from baseline in SGRQ Total score, n	182	174
LS mean at Week 52	47.3	50.0
95% CI	45.3,49.3	48.0,52.0
LS mean change	-4.6	-1.9
95% CI	-6.5,-2.6	-3.9,0.1
FF/UMEC/VI vs. BUD/FOR		
difference (95% CI)	-2.7 (-5.5,0.2)	
***P*-value**	0.065	
Proportion of responders†, n	209	219
Responders, n (%)	91 (44)	73 (33)

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FF/UMEC/VI vs. BUD/FOR	
OR (95% CI)	1.50 (1.01,2.24)
***P*-value**	0.046

Definition of abbreviations: BUD = budesonide; CI = confidence interval; EXT = extension; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FOR = formoterol; ITT = intent-to-treat; LS = least squares; OR = odds ratio; SGRQ = St George's Respiratory Questionnaire; UMEC = umeclidinium; VI = vilanterol.

*Response was defined as a trough FEV_1 of ≥ 100 mL above baseline.

†Response was defined as an SGRQ Total score change of ≥ 4 units below baseline.

Table 3. Annual Exacerbation Rates (ITT and EXT Populations)

	Up to 24 Weeks		Up to 52 Weeks	
Annual Rate of COPD Exacerbations	**FF/UMEC/VI 100/62.5/25 µg (n = 911)**	**BUD/FOR 400/12 µg (n = 899)**	**FF/UMEC/VI 100/62.5/25 µg (n = 210)**	**BUD/FOR 400/12 µg (n = 220)**
Population, n	907	892	210	219
Moderate and severe exacerbations				
Mean rate	0.22	0.34	0.20	0.36
Ratio (95% CI); *P*-value	0.65 (0.49,0.86); 0.002		0.56 (0.37,0.85); 0.006	
Reduction in rate, % (95% CI)	35 (14,51)		44 (15,63)	
Mild, moderate, and severe exacerbations				
Mean rate	0.25	0.39	0.22	0.40
Ratio (95% CI); *P*-value	0.65 (0.50,0.84); <0.001		0.55 (0.37,0.81); 0.003	
Reduction in rate, % (95% CI)	35 (16,50)		45 (19,63)	

Definition of abbreviations: BUD = budesonide; CI = confidence interval; COPD = chronic obstructive pulmonary disease; EXT = extension; FF = fluticasone furoate; FOR = formoterol; ITT = intent-to-treat; UMEC = umeclidinium; VI = vilanterol.

Ratios and *P*-values are calculated for FF/UMEC/VI vs. BUD/FOR.

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Table 4. Adverse Events and Adverse Events of Special Interest (ITT and EXT Populations)

Adverse Events Occurring in ≥ 2% of Patients in Either Population, n (%)	ITT Population (24 Weeks)		EXT Population (52 Weeks)	
	FF/UMEC/VI 100/62.5/25 µg (n = 911)	BUD/FOR 400/12 µg (n = 899)	FF/UMEC/VI 100/62.5/25 µg (n = 210)	BUD/FOR 400/12 µg (n = 220)
Nasopharyngitis	64 (7)	43 (5)	23 (11)	22 (10)
Headache	44 (5)	53 (6)	17 (8)	22 (10)
URTI	20 (2)	19 (2)	6 (3)	10 (5)
COPD	15 (2)	23 (3)	5 (2)	22 (10)
Back pain	19 (2)	18 (2)	4 (2)	5 (2)
Arthralgia	17 (2)	13 (1)	5 (2)	6 (3)
Pneumonia	19 (2)	7 (< 1)	4 (2)	4 (2)
Pharyngitis	15 (2)	9 (1)	5 (2)	1 (< 1)
Oropharyngeal pain	9 (< 1)	10 (1)	6 (3)	1 (< 1)
Dizziness	–	–	1 (< 1)	6 (3)
Blood pressure increased	4 (< 1)	8 (< 1)	0	4 (2)
Dyspnea	–	–	0	4 (2)
Vertigo	–	–	0	4 (2)
Adverse Events of Special Interest				
Cardiovascular effects	39 (4.3)	47 (5.2)	18 (8.6)	22 (10.0)
Pneumonia	20 (2.2)	7 (0.8)	4 (1.9)	4 (1.8)
Local steroid effects*	19 (2.1)	24 (2.7)	8 (3.8)	7 (3.2)

Anticholinergic syndrome*	16 (1.8)	17 (1.9)	4 (1.9)	12 (5.5)
Hypersensitivity	10 (1.1)	10 (1.1)	3 (1.4)	1 (0.5)
Hyperglycemia/ diabetes**	5 (0.5)	4 (0.4)	0	4 (1.8)
Decreased bone mineral density	4 (0.4)	6 (0.7)	1 (0.5)	1 (0.5)
LRTI (excluding pneumonia)	3 (0.3)	4 (0.4)	1 (0.5)	0
Ocular effects*	1 (0.1)	4 (0.4)	–	–
Urinary retention	1 (0.1)	0	–	–
Asthma/ bronchospasm	0	1 (0.1)	–	–

Definition of abbreviations: BUD = budesonide; COPD = chronic obstructive pulmonary disease; EXT = extension; FF = fluticasone furoate; FOR = formoterol; ITT = intent-to-treat; LRTI = lower respiratory tract infection; UMEC = umeclidinium; URTI = upper respiratory tract infection; VI = vilanterol. *These terms are derived from the Standardized Medical Dictionary for Regulatory Activities (MedDRA). **New-onset diabetes.

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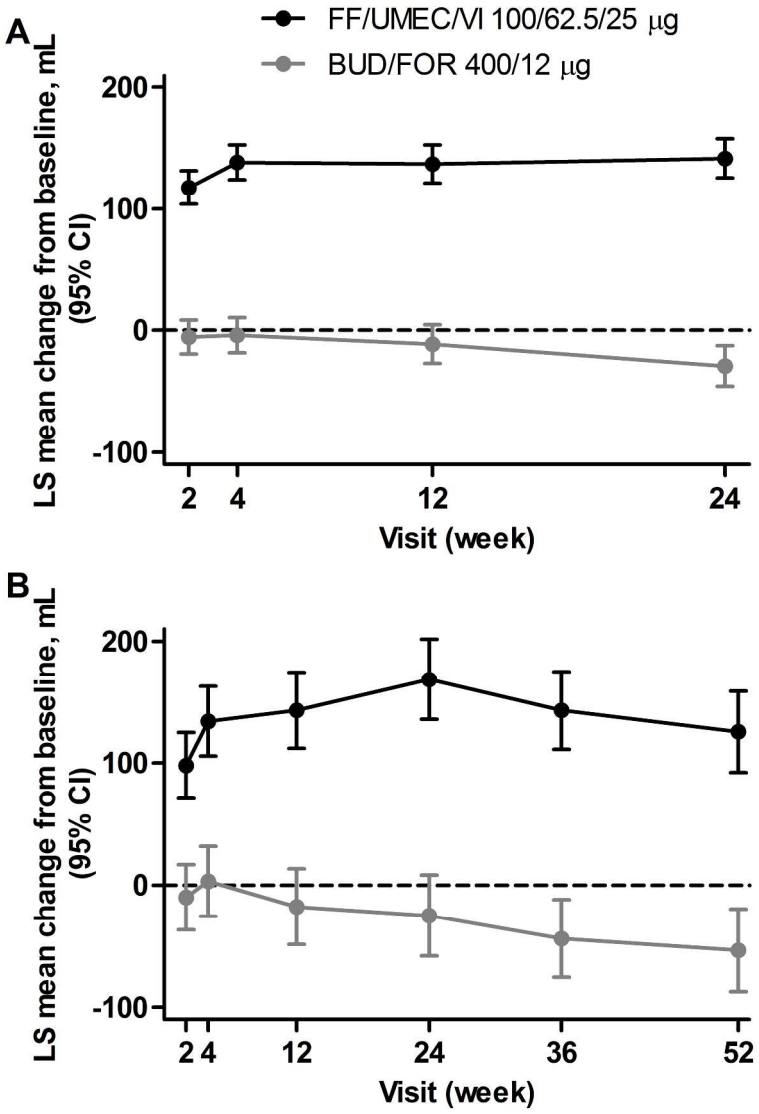

Figure 1

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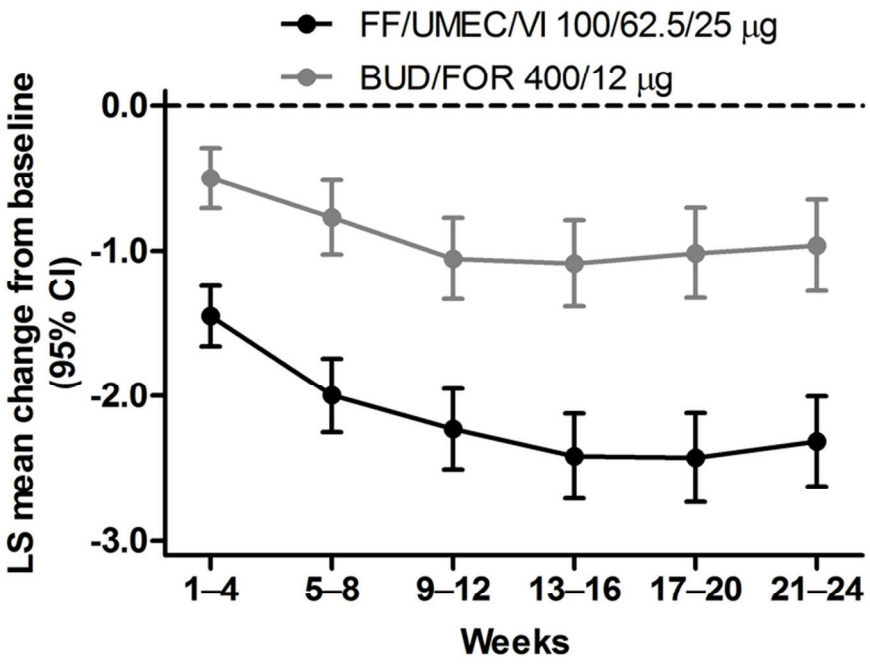

Figure 2

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FULFIL Trial: Once-Daily Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease

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Online Data Supplement

Methods

Patients

Patients were enrolled from approximately 200 study centers globally. Additional criteria for excluding patients from the FULFIL study were: chronic obstructive pulmonary disease (COPD) caused by α_1-antitrypsin deficiency, other significant respiratory disorders, lung resection within 12 months of screening, or other clinically significant diseases. Patients who had pneumonia or severe COPD exacerbations were excluded if the events had not resolved within 14 days of screening. Patients with a respiratory tract infection that had not resolved within 7 days of screening, an abnormal chest X-ray, or an abnormal and clinically significant 12-lead electrocardiogram (ECG) finding were also excluded.

Patients were randomized using the interactive voice recognition system (Registration and Medication Ordering System [RAMOS]), stratified by smoking status.

Efficacy Assessments

COPD exacerbations were defined as: mild (self-managed by the patient by increasing rescue medication use); moderate (required treatment with oral/systemic corticosteroids and/or antibiotics, without hospitalization); or severe (required in-patient hospitalization).

Daily symptoms were recorded in electronic diaries (eDiaries). The eDiary alerted the patient to contact their investigator if they had worsening symptoms over three consecutive days, and the patients were instructed to contact their investigator if they received this alert. Investigators also received an alert. Data were automatically

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downloaded from the eDiary and transferred to a portal that could be accessed by the investigators. An interaction between the patient and the investigator was required to allow a physician to determine whether changes in symptoms were simply normal variation in the disease, or necessitated further therapy. Thus, the diagnosis of an exacerbation required clinical judgment combined with reported symptoms, mimicking clinical practice.

Safety Assessments

Patients recorded adverse events (AEs) and any medications using a diary worksheet and details were transcribed to the electronic case report form. ECG measurements, vital signs, and hematology and clinical chemistry parameters were recorded. COPD exacerbations were an expected disease-related outcome; thus, they were not recorded as an AE, unless they met the definition of a serious adverse event (SAE). All SAEs reported during the study were adjudicated by an independent clinical endpoint committee. Adverse events of special interest were defined *a priori* to evaluate potential AEs typically associated with the pharmacologic classes of inhaled corticosteroids, long-acting muscarinic antagonist, and long-acting β_2-agonist (Table E1).

Statistical Analyses

Based on the co-primary endpoints and previous experience with the drugs, sample size was calculated to be 688 patients per treatment group, which provided at least 90% power to detect a between-treatment difference of 80 mL for trough forced expiratory volume in 1 second, assuming a standard deviation (SD) of 240 mL, and 2.5 units for St George's Respiratory Questionnaire Total score, assuming an SD of

12 units, at 24 weeks at the 1% significance level. It was estimated that 30% of patients would discontinue treatment without being assessed at Week 24 and therefore 900 randomized patients were required for each treatment group.

Covariates used in the analysis of the co-primary endpoints included treatment group, smoking status, geographical region, visit, baseline value, and baseline-by-visit and treatment group-by-visit interactions.

Least squares (LS) means and LS mean change from baseline with standard errors and 95% confidence intervals were calculated. The number of on-treatment moderate/severe exacerbations and the number of mild/moderate/severe exacerbations were analyzed using a generalized linear model assuming a negative binomial distribution. Average scores for the Evaluating Respiratory Symptoms in COPD over 4-week intervals were analyzed using mixed model repeated measures. Secondary and other efficacy analyses were not adjusted for multiplicity.

Results

Safety Analyses

Drug-related AEs (assessed by the investigator) were reported by 5% of patients in the intent-to-treat population, with no single event occurring in more than 1% of patients in either group. Drug-related SAEs occurred in < 1% of patients and there were no drug-related deaths.

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Table E1. List of Evaluated Adverse Events of Special Interest

AESI Group	AESI Subgroup	Sub-SMQ
Adrenal suppression*		
Anticholinergic syndrome† (SMQ)		
Asthma/bronchospasm (SMQ)		
Cardiovascular effects	Cardiac arrhythmia	Arrhythmia-related investigations, signs and symptoms (SMQ)
		Bradyarrhythmia terms, nonspecific (SMQ)
		Conduction defects (SMQ)
		Disorders of sinus node function (SMQ)
		Cardiac arrhythmia terms, nonspecific (SMQ)
		Supraventricular tachyarrhythmias (SMQ)
		Tachyarrhythmia terms, nonspecific (SMQ)
		Ventricular tachyarrhythmias (SMQ)
	Cardiac failure (SMQ)	

	Ischemic heart disease (SMQ)	
	Hypertension (SMQ)	
	Central nervous system hemorrhages and cerebrovascular conditions (SMQ)	
Ocular effects†	Glaucoma (SMQ)	
	Lens disorder (SMQ)	
Decreased bone mineral density and associated fractures‡		
Effects on potassium*		
Gastrointestinal obstruction (SMQ)		
Hyperglycemia/new onset diabetes mellitus (SMQ)		
Hypersensitivity*		
Local steroid effects*,†		
Pneumonia and LRTI	Pneumonia*	
	LRTI excluding pneumonia*	
Tremor*		
Urinary retention*		

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Definition of abbreviations: AESI = adverse events of special interest; LRTI = lower respiratory tract infection; SMQ = Standardized Medical Dictionary for Regulatory Activities Query.

*Selected Medical Dictionary for Regulatory Activities Preferred Terms.

† These terms are derived from the Standardized Medical Dictionary for Regulatory Activities (MedDRA). “Anticholinergic syndrome” is derived from the broad version of the Standardized MedDRA query (SMQ) called “Anticholinergic syndrome (SMQ)”. This includes 50 preferred terms such as agitation, anhidrosis, ataxia, dry mouth, dry eye, and mydriasis. “Ocular effects” is derived from the broad version of “Glaucoma (SMQ)” (74 terms) and the “Lens disorders (SMQ)” (38 terms), including terms such as glaucoma, cataracts, eye pain, intraocular pressure increased, halo vision, vision blurred, and visual acuity reduced. “Local steroid effects” includes a list of 19 preferred terms such as oral candidiasis, mucocutaneous candidiasis, dry throat, and dysphonia.

‡Osteoporosis/osteopenia SMQ plus selected Medical Dictionary for Regulatory Activities Preferred Terms.

Table E2. COPD Medications Taken During Screening by ≥ 5 Patients in Either Treatment Group

	Patients, n (%)		
Medication Combination*	**FF/UMEC/VI 100/62.5/25 µg (n = 911)**	**BUD/FOR 400/12 µg (n = 899)**	**Total N = 1,810**
Full Medication Combination†			
ICS + LABA	268 (29)	259 (29)	527 (29)
ICS + LABA	252 (28)	241 (27)	493 (27)
ICS + LABA + short-acting anticholinergic + short-acting β_2 agonist	9 (< 1)	6 (< 1)	15 (< 1)
ICS + LABA short-acting anticholinergic	3 (< 1)	5 (< 1)	8 (< 1)
ICS + LABA + LAMA	257 (28)	256 (28)	513 (28)
ICS + LABA + LAMA	220 (24)	221 (25)	441 (24)
ICS + LABA + LAMA + short-acting anticholinergic + short-acting β_2 agonist	11 (1)	6 (< 1)	17 (< 1)
ICS + LABA + LAMA + oxygen	5 (< 1)	8 (< 1)	13 (< 1)
ICS + LABA + LAMA + mucolytics	5 (< 1)	6 (< 1)	11 (< 1)
LABA + LAMA	101 (11)	84 (9)	185 (10)
LABA + LAMA	89 (10)	77 (9)	166 (9)
LAMA	79 (9)	79 (9)	158 (9)
LAMA	64 (7)	70 (8)	134 (7)
LAMA + short-acting anticholinergic	8 (< 1)	5 (< 1)	13 (< 1)

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+ short-acting β_2 agonist			
LABA	37 (4)	42 (5)	79 (4)
LABA	27 (3)	30 (3)	57 (3)
LABA + short-acting anticholinergic	6 (< 1)	6 (< 1)	12 (< 1)
ICS + LABA + LAMA + xanthine	33 (4)	44 (5)	77 (4)
ICS + LABA + LAMA + xanthine	18 (2)	31 (3)	49 (3)
ICS + LABA + xanthine	19 (2)	18 (2)	37 (2)
ICS + LABA + xanthine	13 (1)	16 (2)	29 (2)
ICS	15 (2)	12 (1)	27 (1)
ICS	14 (2)	11 (1)	25 (1)
LABA + LAMA + xanthine	10 (1)	12 (1)	22 (1)
LABA + LAMA + xanthine	9 (< 1)	7 (< 1)	16 (< 1)
ICS + LAMA	5 (< 1)	11 (1)	16 (< 1)
ICS + LAMA	3 (< 1)	11 (1)	14 (< 1)
LAMA + xanthine	6 (< 1)	3 (< 1)	9 (< 1)

Definition of abbreviations: BUD = budesonide; COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; FOR = formoterol; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; UMEC = umeclidinium; VI = vilanterol.

*COPD respiratory medication class (RMC) combination based on the individual RMC and any combination of the RMCs: ICS, LABA, LAMA, Xanthine, and PDE4 Inhibitors.

†COPD RMC combination based on all RMCs.

Figure E1. Patient flow in the FULFIL study. BUD = budesonide; FF = fluticasone furoate; FOR = formoterol; ITT = intent-to-treat; UMEC = umeclidinium; VI = vilanterol.