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ORIGINAL RESEARCH

Once-Daily Triple Therapy in Patients with Advanced COPD: Healthcare Resource Utilization Data and Associated Costs from the FULFIL Trial

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease is associated with a high healthcare resource and cost burden. Healthcare resource utilization was analyzed in patients with symptomatic chronic obstructive pulmonary disease at risk of exacerbations in the FULFIL study. Patients received either once-daily, single inhaler triple therapy (fluticasone furoate/umeclidinium/vilanterol) 100 μg/62.5 μg/25 μg or twice-daily dual inhaled corticosteroid/long-acting beta agonist therapy (budesonide/formoterol) 400 μg/12 μg.

Methods: FULFIL was a phase III, randomized, double-blind, double-dummy, multicenter study. Unscheduled contacts with healthcare providers were recorded by patients in a daily electronic diary; the costs of healthcare resource utilization were calculated post hoc using UK reference costs.

Results: Over 24 weeks, slightly fewer patients who received fluticasone furoate/umeclidinium/vilanterol (169/911; 18.6%) required

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contacts with healthcare providers compared with budesonide/formoterol (180/899; 20.0%). Over 52 weeks in an extension population, fewer patients who received fluticasone furoate/umeclidinium/vilanterol required unscheduled contacts with healthcare providers compared with budesonide/formoterol (25.2% vs. 32.7%). Non-drug costs per treated patient per year were lower in the fluticasone furoate/umeclidinium/vilanterol group than the budesonide/formoterol group over 24 and 52 weeks (£653.80 vs. £763.32 and £749.22 vs. £988.03, respectively), with the total annualized cost over 24 weeks being slightly greater for fluticasone furoate/umeclidinium/vilanterol than budesonide/formoterol (£1,289.35 vs. £1,267.45).

Conclusions: This healthcare resource utilization evidence suggests that, in a clinical trial setting over a 24- or 52-week timeframe, non-drug costs associated with management of a single inhaler fluticasone furoate/umeclidinium/vilanterol are lower compared with twice-daily budesonide/formoterol.

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Keywords: Budesonide/formoterol; COPD burden; Cost analyses; Fluticasone furoate/umeclidinium/vilanterol; Randomized controlled trials; Single inhaler triple therapy; Trial-based healthcare resource utilization

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is associated with high healthcare resource and cost burdens, which are predicted to increase because of the continued exposure to COPD risk factors and the aging population [1, 2]. Furthermore, healthcare costs, particularly hospitalization costs, increase with COPD severity [2].

The Global Initiative for Chronic Obstructive Lung Disease strategy document recommends the use of one or more long-acting muscarinic antagonists (LAMAs) or long-acting beta agonists (LABAs) in addition to an inhaled corticosteroid (ICS) [triple pharmacologic therapy (ICS/LAMA/LABA)] for patients with symptomatic COPD who are at risk of exacerbations [2]. In addition, while patients with COPD may initially receive ICS/LABA dual therapy, many need to 'step-up' to a triple-therapy regimen to achieve symptom control [3]. A number of studies have shown that using triple therapy (ICS/LAMA/LABA) can reduce hospitalization rates, compared with dual therapy or monotherapy [4–7].

FULFIL (Lung FUnction and quality of LiFe assessment in COPD with closed trIpLe therapy) was the first study to compare once-daily single inhaler triple ICS/LAMA/LABA therapy with twice-daily dual ICS/LABA therapy in patients with symptomatic COPD [8]. Previously reported findings from FULFIL demonstrated clinically and statistically significant improvements in lung function and health-related quality of life and a reduced exacerbation rate with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) compared with budesonide/formoterol (BUD/FOR) [8]. The incidence of previous exacerbations has been shown to be a predictor of exacerbation risk [9–11], and this increased risk is also associated with increased disease impact and symptom burden, demonstrated by raised COPD Assessment Test scores and Medical Research Council dyspnea scores [9–11]. Of note is the fact that dyspnea is the most frequently reported symptom experienced by patients with COPD, and thus a driving factor in healthcare resource utilization (HCRU) [2]. As FF/UMEC/VI was previously reported to be associated with reduced symptoms and exacerbation rates compared with BUD/FOR, FF/UMEC/VI may reduce overall healthcare costs [8]. Furthermore, initial use of triple therapy in patients with exacerbation history or who are highly symptomatic, rather than dual ICS/LABA, may be more efficient at reducing long-term use of healthcare resources and costs compared with using a 'step-up' approach from ICS/LABA, as the improved symptom control may result in fewer required contacts with healthcare providers. Therefore, as part of the FULFIL study, HCRU and associated cost data were evaluated. In FULFIL, the number of contacts with healthcare providers, drug utilization, and healthcare (non-drug) resource use were collected and summarized for the FF/UMEC/VI

and BUD/FOR treatment groups. Here, we report the cost data calculated post hoc, to evaluate the impact of a single inhaler triple therapy on HCRU and costs.

METHODS

Study Design

This study comprised an analysis of HCRU collected from patients enrolled in both treatment groups in the FULFIL trial with the application of associated United Kingdom (UK) cost data. FULFIL was a phase III, randomized, double-blind, double-dummy, parallel-group, multicenter study (see Fig. S1 in the online data supplement) [8]. The co-primary outcomes of FULFIL were to evaluate the effects of FF/UMEC/VI on forced expiratory volume in 1 s (FEV_1) and St George's Respiratory Questionnaire total score compared with BUD/FOR after 24 weeks of treatment [8].

Patients

FULFIL enrolled 1810 male and female patients with symptomatic COPD who were at risk of exacerbations and aged ≥40 years with: FEV_1 <50% and COPD Assessment Test ≥10, or with FEV_1 ≥50–<80% and COPD Assessment Test ≥10 with either ≥2 moderate or ≥1 severe exacerbation in the past year [8]. All patients included in this study met the Global Initiative for Chronic Obstructive Lung Disease 2011–2016 criteria for advanced higher risk disease at study initiation. Full inclusion and exclusion criteria are provided in the online data supplement. Patients from 159 sites in 15 countries (Bulgaria, China, Czech Republic, Estonia, Germany, Greece, Hungary, Italy, Republic of Korea, Mexico, Poland, Romania, Russian Federation, Slovakia, and Ukraine) were randomized to receive 24 weeks of once-daily FF/UMEC/VI (100 μg/62.5 μg/25 μg; $n = 911$) using a single ELLIPTA® inhaler or twice-daily BUD/FOR (400 μg/12 μg; $n = 899$) using the Turbohaler® (intent-to-treat [ITT] population) [8]. A subset of patients received blinded study treatment for up to 52 weeks [extension (EXT) population; $n = 430$] [8]. Demographic and disease characteristics were recorded at baseline. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients included in the study. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Evaluation of HCRU

Patients recorded unscheduled contacts with healthcare providers between study visits using a paper diary. The following types of unscheduled contacts with healthcare providers were recorded: home visits (day or night), office/practice visits, urgent care/outpatient visits, emergency department visits, and hospitalizations. Visits/contacts were reviewed at each study visit and were classified by study sites as due to 'COPD exacerbation', 'worsening of COPD', or 'health issue unrelated to COPD'. Collection of these data ceased upon study treatment discontinuation.

The costs of contacts with healthcare providers were calculated post hoc by multiplying the number of events with the average per event cost, which was taken from the 2015–16 UK National Health Service Reference Costs and Personal Social Services Research Unit Costs of Health and Social Care 2011 (inflated to 2016) and 2015 (Table 1) [12–14]. The drug costs used in the analysis are outlined in Table 2, and these were taken from the Monthly Index of Medical Specialties [15]. The cost of FF/UMEC/VI was assumed to be equal to the added cost of Incruse® ELLIPTA® and Relvar® ELLIPTA®.

Descriptive Analyses

The total number of visits for each type of contact with healthcare providers and the number of days spent on general ward or in intensive care (hospitalizations) were summarized. Using a micro-costing approach, non-drug costs were

Table 1 Healthcare costs [12–14]

Visit type	Unit cost	References
Home visits (day)[a]	£129.88	Personal Social Service Research Unit—Unit Costs of Health and Social Care 2011, inflated to 2016
Home visits (night)[a]	£129.88	Personal Social Service Research Unit—Unit Costs of Health and Social Care 2011, inflated to 2016
Office/practice visits[a]	£36.00	Personal Social Service Research Unit—Unit Costs of Health and Social Care 2015
Urgent care/ outpatient visits[a]	£145.54	NHS reference costs 2015–16
Emergency room visits[a]	£195.81	NHS reference costs 2015–16
General ward[b]	£425.81	NHS reference costs 2015–16
Intensive care[b]	£1307.26	NHS reference costs 2015–16

[a] Cost per visit
[b] Cost per day

calculated by multiplying resource-use data collected from FULFIL by standard UK unit costs as described above. Drug costs, adjusted for exposure time (including deaths), were included. Subsequent treatment costs and HCRU costs were also applied for patients who discontinued treatment (calculated for remaining time frame, after adjustment for exposure days). For subsequent treatment costs, type of subsequent treatment after study drug discontinuation and percentage of patients receiving each subsequent treatment were assumed based on data seen in the FULFIL trial. HCRU costs for patients who discontinued treatment were based on average of daily non-drug costs across both arms during the trial period. The cost of rescue medication was added based on mean number of occasions of rescue use per day (Ventolin Accuhaler; Table 2).

RESULTS

Baseline characteristics were similar between treatment groups in the ITT and EXT populations, and between the ITT and EXT populations (see Table S1 in the online data supplement), as reported previously [8].

HCRU and Costs in the ITT Population

Over 24 weeks, slightly fewer patients who received FF/UMEC/VI (169/911; 18.6%) required unscheduled contacts with healthcare providers than those who received BUD/FOR (180/899; 20.0%) (Table 3). The proportion of patients who required unscheduled contacts with a healthcare provider for COPD exacerbations was lower in the group who received FF/UMEC/VI (8.2% of patients) compared with the group who received BUD/FOR (11.0% of patients) (Table 3). Office/practice visits were the most frequent type of unscheduled contact patients had with healthcare providers (FF/UMEC/VI group, 70.0% of patients; BUD/FOR group, 71.2% of patients). The total number of urgent care/outpatient visits was greater in the FF/UMEC/VI group compared with the BUD/FOR group (23.0% of patients vs. 17.5% of patients). Slightly fewer patients in the FF/UMEC/VI group were hospitalized compared with the BUD/FOR group (4.3% of patients vs. 5.5% of patients).

Total non-drug costs (while on study treatment) were lower in the group who received FF/UMEC/VI than BUD/FOR in the ITT population (£266,095.84 vs. £297,160.93) (Table 4). Based on these non-drug HCRU (costs per healthcare visit), annualized non-drug costs per patient were lower for FF/UMEC/VI than BUD/FOR (£653.80 vs. £763.32) (Table 4). The total annualized cost (non-drug and drug costs) was slightly greater for FF/UMEC/VI than BUD/FOR (£1289.35 vs. £1267.45).

Table 2 Drug costs (monthly index of medical specialties [MIMS] June 2017) [15]

	Dose strength	Package volume number	Cost per package (£)	Cost per dose (£)	Daily dose	Cost per day (£)
Umeclidinium (INCRUSE® ELLIPTA®)	62.5 μg	30	27.50	0.92	1	0.92
Fluticasone furoate/vilanterol (Relvar® ELLIPTA®)	100 μg/25 μg	30	22.00	0.73	1	0.73
Budesonide/formoterol fumarate (Symbicort®)	400 μg/12 μg	60	38.00	0.63	2	1.27
Ventolin Accuhaler[a]	200 μg per inhalation	60	3.60	0.06		
Tiotropium (Spiriva®)[b]	18 μg	30	34.87	1.16	1	1.16
Fluticasone propionate/salmeterol (Seretide® Accuhaler®)[b]	500 μg/50 μg	60	40.92	0.68	2	1.36
Umeclidinium bromide/vilanterol (Anoro® ELLIPTA®)[b]	62.5 μg/25 μg	30	32.50	1.08	1	1.08
Indacaterol maleate/glycopyrronium bromide (Ultibro® Breezhaler®)[b]	110 μg/50 μg	30	32.50	1.08	1	1.08

[a] Rescue medication
[b] Subsequent therapy after initial study drug discontinuation

HCRU and Costs in the EXT Population

In the 430 patients who completed 52 weeks' treatment, a smaller proportion of patients who received FF/UMEC/VI required unscheduled contacts with healthcare providers compared with BUD/FOR (25.2% of patients vs. 32.7% of patients) (Table 3). Fewer patients in the FF/UMEC/VI group had unscheduled contacts with healthcare providers due to COPD exacerbations compared with the BUD/FOR group (11.9% of patients vs. 20.9% of patients) (Table 3). Office/practice visits were the most frequent unscheduled type of contacts with healthcare providers, and patients in the FF/UMEC/VI group visited less frequently than patients in the BUD/FOR group (78.9% of patients vs. 87.4% of patients). The number of urgent care/outpatient visits was lower in the FF/UMEC/VI group compared with the BUD/FOR group (7.4% of patients vs. 9.0% of patients). Fewer patients in the FF/UMEC/VI group were hospitalized compared with the BUD/FOR group (9.5% of patients vs. 13.6% of patients).

Based on non-drug HCRU (costs per healthcare visit), annualized non-drug costs per patient were lower for FF/UMEC/VI than BUD/FOR (£749.22 vs. £988.03) (Table 4). The total annualized cost (non-drug and drug costs) for the EXT population was lower for the FF/UMEC/VI group than the BUD/FOR group (£1376.95 vs. £1470.18) (Table 4).

DISCUSSION

Analysis of UK costs associated with FULFIL HCRU data suggests that the use of single inhaler triple therapy (FF/UMEC/VI) in patients with symptomatic COPD who are at risk of exacerbations is cost effective compared with ICS/LABA (BUD/FOR). Findings from the FULFIL study demonstrate that FF/UMEC/VI for

Table 3 Unscheduled healthcare resource utilization in the ITT and EXT populations

Unscheduled healthcare resource utilization	ITT population		EXT population	
	FF/UMEC/VI ($n = 911$)	BUD/FOR ($n = 899$)	FF/UMEC/VI ($n = 210$)	BUD/FOR ($n = 220$)
Patient-years	407.0	389.3	196.9	194.6
Average (mean) exposure days	163.2	158.2	342.5	323.1
Unscheduled contact, *n* (%)				
Yes	169 (18.6)	180 (20.0)	53 (25.2)	72 (32.7)
No	742 (81.4)	719 (80.0)	157 (74.8)	148 (67.3)
Total number (% total visits)[a]				
Home visits (day)	11 (2.7)	26 (6.8)	7 (7.4)	0 (0)
Home visits (night)	0 (0)	3 (0.8)	0 (0)	0 (0)
Office/practice visits	289 (70.0)	272 (71.2)	75 (78.9)	97 (87.4)
Urgent care/outpatient visits	95 (23.0)	67 (17.5)	7 (7.4)	10 (9.0)
Emergency room visits	18 (4.4)	14 (3.7)	6 (6.3)	4 (3.6)
Total number of days[b]				
General ward	452 ($n = 34$, 3.7%)	431 ($n = 38$, 4.2%)	253 ($n = 16$, 7.6%)	303 ($n = 25$, 11.4%)
Intensive care	34 ($n = 5$, 0.5%)	67 ($n = 11$, 1.2%)	26 ($n = 4$, 1.9%)	44 ($n = 5$, 2.3%)
Contact type[c], *n* (%)				
COPD exacerbation	75 (8.2)	99 (11.0)	25 (11.9)	46 (20.9)
Worsening of COPD	28 (3.1)	27 (3.0)	2 (<1)	10 (4.5)
Health issue unrelated to COPD	95 (10.4)	90 (10.0)	31 (14.8)	27 (12.3)

BUD/FOR budesonide/formoterol, *COPD* chronic obstructive pulmonary disease, *EXT* extension, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *ITT* intent-to-treat

[a] Total number of contacts across all patients

[b] Total number of days across all patients

[c] Patients can be counted only once within each sub-category, but can be counted in more than one sub-category

COPD is associated with clinically meaningful improvements in lung function and health-related quality of life, and reduced exacerbations, compared with BUD/FOR [8]. FULFIL also demonstrated that the incidence of pneumonia was higher in the FF/UMEC/VI group than the BUD/FOR group in the ITT population over 24 weeks (2.2% and 0.8%, respectively), but was similar between the two groups in the EXT population at 52 weeks (1.9% and 1.8%, respectively) [8]. The HCRU evidence described here suggests that the longer-term use (as shown over 52 weeks) of FF/UMEC/VI reduces the economic and healthcare resource burdens of COPD compared with BUD/FOR, in a clinical trial setting. However, it should also be noted that these findings are based on the smaller EXT patient population, and that the smaller sample size may also have influenced the observed outcomes. The proportion of patients requiring

Table 4 Per-patient and total costs in the ITT and EXT populations

Costs (£)	ITT population		EXT population	
	FF/UMEC/VI ($n = 911$)	BUD/FOR ($n = 899$)	FF/UMEC/VI ($n = 210$)	BUD/FOR ($n = 220$)
Total population non-drug costs (while on study drug)	266,095.84	297,160.93	147,521.27	192,270.26
Total population drug costs (while on study drug)	245,314.08	180,147.61	118,676.25	90,037.20
Non-drug costs per treated patient (PP)-year per timeframe[a]	653.80	763.32	749.22	988.03
Non-drug costs (while on study drug), PP	292.09	330.55	702.48	873.96
Non-drug costs after treatment discontinuation, PP[b]	9.32	19.02	41.74	79.40
Total drug costs (initial study drug treatment[c], subsequent therapy and rescue medication), PP per timeframe	293.67	235.41	632.73	516.83
Study drug costs (initial[c]), PP	269.28	200.39	565.13	409.26
Cost of rescue medication[d], PP	16.13	18.14	30.58	37.13
Subsequent treatment costs after discontinuation from study drug, PP[e]	8.27	16.88	37.03	70.44
Total cost per patient per time frame[a]	595.08	584.98	1376.95	1470.18
Total cost per patient per year	1289.35	1267.45	1376.95	1470.18

BUD/FOR budesonide/formoterol, *EXT* extension, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *ITT* intent-to-treat

[a] 24 weeks (ITT) or 52 weeks (EXT) for the relevant population

[b] Calculated for remaining time frame (after adjustment for exposure days); based on average on daily non-drug costs across both arms during trial period

[c] Initial study drug costs refer to costs of drug patients were assigned to during randomization of FULFIL; as opposed to subsequent therapy, which refers to drugs post-discontinuation

[d] Based on mean number of occasions of rescue medication use per day

[e] Calculated for remaining time frame (after adjustment for exposure days); type of subsequent treatment after study drug discontinuation and % of patients receiving each subsequent treatment were assumed based on data seen in the FULFIL trial

unscheduled healthcare visits and the number of contacts needed for COPD exacerbations were lower with FF/UMEC/VI than BUD/FOR, over 24 and 52 weeks in the ITT and EXT populations, respectively. Therefore, improvements in lung function and health-related quality of life, and reduced exacerbation rates observed with FF/UMEC/VI were achieved without an overall cost increase over 52 weeks. These findings from the primary analysis and the reduction from baseline in COPD Assessment Test score observed with FF/UMEC/VI, together with reduced St George's Respiratory Questionnaire scores, may have contributed to improved patient health status and thus reduced HCRU and costs seen in this analysis.

Population-based studies of COPD treatment patterns demonstrate that open triple therapy (the use of ICS/LAMA/LABA delivered by multiple inhalers) is already widely used in the management of COPD [3, 16]. In the US-based COPDGene observational cohort, among patients with COPD who were receiving treatment, 34% of patients were taking an open triple regimen [16]. Results from a study based on the UK Clinical Practice Research Database revealed that over a 2-year period of time, 35% of patients with COPD who were initially

prescribed a LAMA and 39% who were initially prescribed an ICS/LABA stepped up to an open triple therapy regimen [3]. Triple therapy has previously been shown to be associated with reduced exacerbation rate, and all-cause and cardiovascular mortality in UK clinical practice [17, 18]. As triple therapy is recommended and often used in the management of COPD, the results from FULFIL are likely to be applicable to daily practice, particularly in clinical settings with substantial use of ICS/LABA dual therapy, and these HCRU findings provide support for this approach.

The study design of FULFIL (inclusivity, continuation of patients' usual COPD medications throughout the run-in period) [8] means the findings are likely to be representative of the overall COPD population in real-world clinical practice.

Although different inhalers were used in each treatment group, the double-blind, double-dummy design ensured that between-group differences were not influenced by patient preference. However, FULFIL only evaluated the effects of FF/UMEC/VI compared with ICS/LABA, not dual bronchodilator therapy; this comparison is currently being evaluated in the InforMing the PAthway of COPD Treatment (IMPACT) study, which will provide additional data on the clinical efficacy and safety of FF/UMEC/VI [19]. It should be noted that study-based analyses often underestimate HCRU as some unscheduled HCRU may fall within planned study visits. Further studies that provide robust cost effectiveness analyses of FF/UMEC/VI compared with ICS/LABA over longer periods of time than 52 weeks would also be valuable, including those that include a societal perspective as well as a healthcare system perspective.

In conclusion, over 24 weeks (ITT) in the FULFIL study, treatment with FF/UMEC/VI was associated with a reduction in the total number of contacts with healthcare providers compared with BUD/FOR among patients with COPD, particularly those required due to disease exacerbations. This reduction was also seen in the EXT population over 52 weeks. In both the ITT and EXT populations, non-drug healthcare costs were lower among patients with COPD in the FF/UMEC/VI group compared with the BUD/FOR group. Total costs were higher for FF/UMEC/VI than BUD/FOR over 24 weeks but lower for FF/UMEC/VI than BUD/FOR over 52 weeks, suggesting either an influence of the reduced patient population or a long-term cost advantage of single inhaler triple ICS/LABA/LAMA therapy compared with ICS/LABA combination therapy in a clinical trial setting. Although the cost findings reported here are UK-specific, country-specific unit costs can be applied to the HCRU data in order to make the findings relevant to other countries. Results from the HCRU analysis of FULFIL in combination with the efficacy results suggest that the use of FF/UMEC/VI in patients with COPD who are symptomatic and/or at risk of exacerbations can improve lung function and health-related quality of life, and reduce exacerbations. These benefits are achieved without increasing costs over a 52-week period, which may contribute to reducing economic and healthcare resource burdens.

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