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Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations

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Summary
Background: Umeclidinium (UMEC; long-acting muscarinic antagonist [LAMA])/vilanterol (VI; long-acting beta$_2$-agonist [LABA]) and fluticasone propionate/salmeterol (FP/SAL) (inhaled corticosteroid/LABA) are approved maintenance therapies for chronic obstructive pulmonary disease (COPD). Two studies compared efficacy and safety of UMEC/VI with FP/SAL in patients with moderate-to-severe COPD with no exacerbations in the previous year.
Methods: In these 12-week, multicenter, double-blind, parallel-group, double-dummy trials, randomized (1:1) patients received once-daily UMEC/VI 62.5/25 mcg or twice-daily FP/SAL 250/50 mcg (DB2114930 n = 353 and 353; DB2114951 n = 349 and 348, respectively; intent-to-treat). Endpoints included 0–24 h weighted mean (wm) forced expiratory volume in 1 s (FEV_1) (Day 84; primary), trough FEV_1 (Day 85; secondary), other lung function endpoints,

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dyspnea, quality of life (QoL) and safety.
Results: UMEC/VI demonstrated statistically significant, clinically meaningful improvements in lung function measures versus FP/SAL. For 0–24 h wmFEV$_1$ (Day 84), improvements with UMEC/VI versus FP/SAL were 74 mL (95% confidence interval [CI]: 38–110; DB2114930) and 101 mL (63–139; DB2114951) (both $p < 0.001$). Trough FEV$_1$ improvements were 82 mL (45–119) and 98 mL (59–137) (both $p < 0.001$) for UMEC/VI versus FP/SAL, respectively. Both treatments demonstrated similar, clinically meaningful improvements from baseline in dyspnea (Transition Dyspnea Index focal score >1 unit) and QoL (St George's Respiratory Questionnaire Total score >4-unit decrease) in both studies with no statistical differences between treatments. Adverse event rates were similar: 26 and 30% UMEC/VI; 27 and 31% FP/SAL.
Conclusions: Once-daily UMEC/VI 62.5/25 mcg over 12 weeks resulted in statistically significant, clinically meaningful improvements in lung function versus twice-daily FP/SAL 250/50 mcg in patients with moderate-to-severe COPD with infrequent exacerbations. Both treatments improved dyspnea and QoL.
Clinical trial registration: DB2114930/NCT01817764; DB2114951/NCT01879410.

Introduction

Inhaled corticosteroid (ICS)/long-acting beta$_2$ agonist (LABA) combinations and long-acting muscarinic antagonist (LAMA)/LABA combinations are two treatments for patients with chronic obstructive pulmonary disease (COPD) which have both been shown to improve airflow obstruction [1]. Additionally, ICS/LABA combinations have also been shown to reduce exacerbations in patients with a history of exacerbations [2]. As long-term ICS use may be associated with adverse events (AEs) [3,4], the ICS benefits versus risks should be considered when treating particular groups of patients with COPD. Guidelines recommend treatment with ICS/LABA for patients with COPD with severe airflow impairment and/or frequent exacerbations, i.e. patients with GOLD C (non-symptomatic) and D (symptomatic) COPD [1]. However, patients with GOLD B disease who have a lower risk of exacerbation are often prescribed ICS/LABAs [5]. LAMA/LABA combinations are currently recommended as a treatment option for patients with GOLD B disease as well as those with GOLD C and D disease [1]. However, few studies have compared the treatment benefits of ICS/LABAs and LAMA/LABAs in patients with COPD with symptomatic, moderate-to-severe COPD with an infrequent exacerbation history (GOLD B and a subset of GOLD D).

Umeclidinium (UMEC, a LAMA) combined with vilanterol (VI, a LABA) is approved in several countries, including the USA and EU, as a once-daily (62.5/25 mcg) maintenance COPD treatment [6,7]. In patients with COPD, lung function was statistically significantly improved with UMEC/VI versus placebo [8,9] and versus monotherapy treatments [8–10]. UMEC/VI and monotherapy treatments were also well tolerated [8–11]. The ICS/LABA combination fluticasone propionate/salmeterol (FP/SAL) at a dose of 250/50 mcg is approved in the USA, but not Europe, as a twice-daily maintenance COPD medication [12]. Statistically significant improvements in lung function and reductions in exacerbations have been demonstrated with FP/SAL versus placebo and monotherapy in moderate-to-severe COPD [13–15].

Three studies have compared UMEC/VI with FP/SAL; one with 500/50 mcg FP/SAL [16] and two with 250/50 mcg FP/SAL described herein. The primary objectives of these studies were to investigate whether the once-daily LAMA/LABA combination UMEC/VI 62.5/25 mcg would show greater improvements in lung function, dyspnea and quality of life (QoL) than twice-daily FP/SAL 250/50 mcg over 12 weeks in patients with symptomatic moderate-to-severe COPD with a history of infrequent COPD exacerbations.

Materials and methods

Patients

All patients provided written informed consent. These studies were approved by local ethics committees (Appendix A, Table A.1) and conducted in accordance with the Declaration of Helsinki [17] and Good Clinical Practice guidelines [18]. For both studies, key inclusion criteria were patients with symptomatic (dyspnea score ≥2, modified Medical Research Council [mMRC] Dyspnea Scale), moderate-to-severe COPD (forced expiratory volume in 1 s [FEV$_1$] ≥30% and ≤70%) without a documented history of an exacerbation (COPD symptoms requiring treatment with either oral corticosteroids, antibiotics and/or hospitalization) in the year before screening. See Appendix B for further details.

Study design, randomization and treatment

Both studies (Fig. 1; see Appendix B for study visit details) were multicenter, randomized, double-blind, double-dummy, parallel-group trials (GSK/www.clinicaltrials.gov numbers: DB2114930/NCT01817764, DB2114951/NCT01879410). DB2114930 was conducted between 26 March 2013 and 26 October 2013 in 63 centers in seven countries (Argentina, Chile, Greece, Peru, Romania, Ukraine, USA). DB2114951 was conducted in 71 centers in seven countries (Chile, Mexico, Norway, Romania, Russian

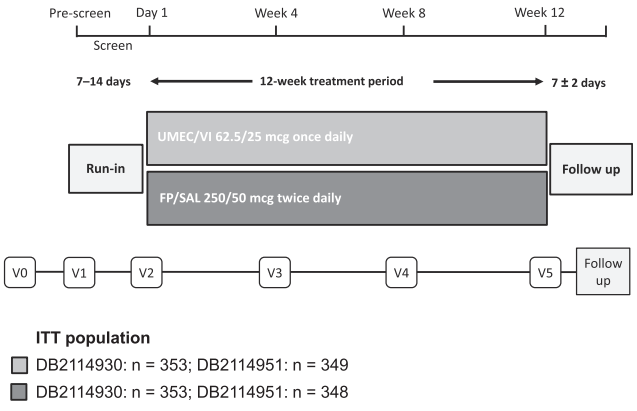

Figure 1 Study design. FP/SAL, fluticasone propionate/salmeterol; ITT, intent-to-treat; UMEC, umeclidinium; V, clinic visit; VI, vilanterol.

Federation, South Africa, USA) between 13 June 2013 and 9 January 2014.

A central randomization schedule was generated using a validated computer system (RandAll; GSK, Brentford, UK). A registration and medication ordering system (GSK, Brentford, UK) was used to randomize patients 1:1 to either UMEC/VI or FP/SAL. Study personnel and patients were blinded to study medication.

Discontinuation requirements of previous medication are shown in Table B.1. Randomized patients received either once-daily UMEC/VI 62.5/25 mcg (delivered doses 55/22 mcg, morning) via the ELLIPTA®[1] dry powder inhaler (DPI) and twice-daily placebo (DISKUS®[2]) or twice-daily FP/SAL 250/50 mcg via the DISKUS and once-daily placebo (ELLIPTA DPI) for 12 weeks. Inhaler dose counters were reviewed at each visit to assess compliance.

Outcome assessments

Endpoints were nearly identical for both studies (Appendix B); inspiratory capacity (IC) was only evaluated in DB2114930.

Efficacy (lung function) assessments

Primary and secondary endpoints were 0–24 h weighted mean (wm) FEV_1 (Day 84) and trough FEV_1 (Day 85), respectively. Other lung function endpoints included: 0–24 h serial FEV_1 (Day 84); peak FEV_1 over 0–6 h post-dose (Days 1 and 84); trough FEV_1 (Days 28, 56 and 84); time to onset (FEV_1 $\geq$100 mL increase above baseline during 0–6 h post-dose, Day 1); proportion of patients achieving an increase from baseline in: a) trough FEV_1 $\geq$100 mL (Day 85), b) FEV_1 $\geq$12% and $\geq$200 mL during 0–6 h post-dose (Day 1) and c) FEV_1 $\geq$100 mL at 5 and 15 min and 1, 3 and 6 h post-dose (Day 1; post-hoc analyses); 0–24 h wm forced vital capacity (FVC) at Day 84; trough FVC (Day 85); 0–6 wm FVC (Days 1 and 84); IC (Day 84; DB2114930 only).

[1] ELLIPTA® is a trademark of the GSK group of companies.
[2] DISKUS® is a trademark of the GSK group of companies.

Health outcomes and symptomatic endpoints

Dyspnea and QoL were assessed using the Transition Dyspnea Index (TDI) (Days 28, 56 and 84; interviewer-administered form) and the St George's Respiratory Questionnaire (SGRQ) for patients with COPD (baseline, Days 28 and 84), respectively. Rescue medication use was recorded. The EuroQol-5D (EQ-5D) questionnaire and the COPD Assessment Test (CAT) were used to assess health outcomes and COPD-related health status, respectively, at randomization/baseline and Day 84.

Safety evaluations

Safety and tolerability included monitoring AEs (coded using the Medical Dictionary for Regulatory Activities), COPD exacerbations (an acute worsening of COPD symptoms requiring use of antibiotics, systemic corticosteroids, and/or emergency treatment or hospitalization) and vital signs throughout both studies.

Statistical analyses

Accounting for 0–24 h $wmFEV_1$ variability and predicted drop-out rate, in each study 355 randomized patients/group would provide 284 evaluable patients/group to detect a 60 mL treatment difference in 0–24 h $wmFEV_1$ with 90% power (Appendix B).

An analysis of covariance model (covariates: baseline FEV_1, smoking status and treatment) was used to analyze 0–24 h $wmFEV_1$ (Day 84). Trough FEV_1 (Day 85) was analyzed using a mixed model for repeated measures analysis (covariates: baseline FEV_1, smoking status, day, treatment, day by baseline interaction and day by treatment interaction, where day is nominal). See Appendix B for further analyses.

All analyses were conducted for all randomized patients who took at least one dose of study medication (intent-to-treat [ITT] population). A step-down, closed-testing procedure was used to account for multiplicity across primary and secondary endpoints (Appendix B).

Results

Study populations

Of 921 patients enrolled, 867 were screened, 707 were randomized (Fig. 2a) and 634 completed DB2114930 (UMEC/VI: 319; FP/SAL: 315). For DB2114951, of 966 patients enrolled, 910 were screened, 700 were randomized (Fig. 2b) and 638 completed the study (UMEC/VI: 326; FP/SAL: 312). Fig. 2 summarizes withdrawal reasons.

Within each study, patient demographics and characteristics were well balanced between groups (Table 1), though no formal statistical comparisons were performed. Overall, 50% of patients had moderate COPD (GOLD stage II) and 50% had severe COPD (GOLD stage III), while mean % predicted FEV_1 was ~50% and mean SGRQ score was ~47. COPD medication pre-enrollment is summarized in Appendix B.

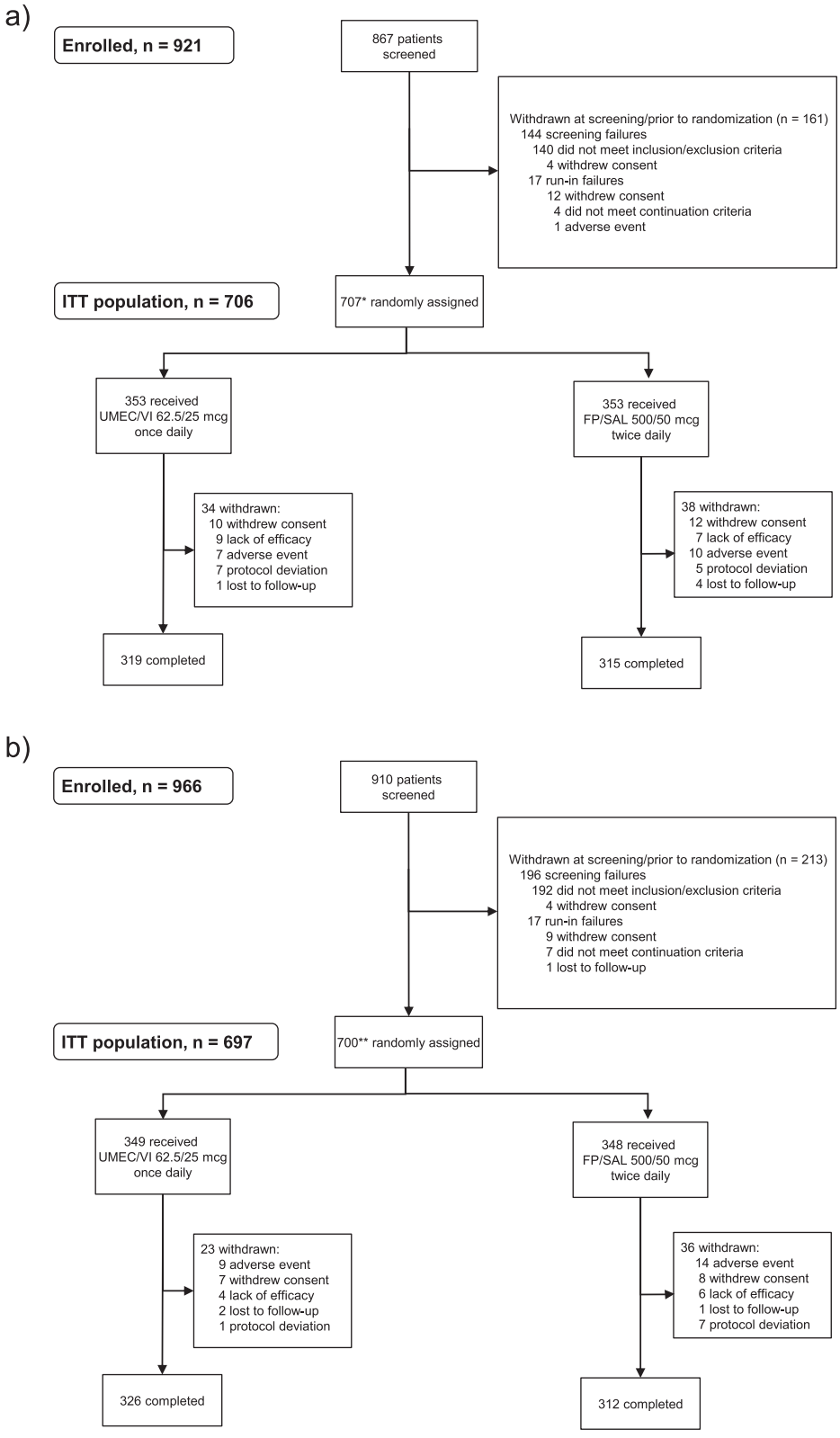

Figure 2 Flow diagram for disposition of patients (CONSORT). a) DB2114930. b) DB2114951. FP/SAL, fluticasone propionate/salmeterol; ITT, intent-to-treat; UMEC, umeclidinium; VI, vilanterol. *One patient was randomized to UMEC/VI but withdrew consent prior to the administration of study medication. **Three patients were randomized in error; two of these patients were run-in failures and the third patient was a screen failure; none of these patients received study treatment.

Table 1 Patient demographics and lung function at baseline (ITT population).

	DB2114930			DB2114951		
	UMEC/VI 62.5/25 mcg (N = 353)	FP/SAL 250/50 mcg (N = 353)	Total (N = 706)	UMEC/VI 62.5/25 mcg (N = 349)	FP/SAL 250/50 mcg (N = 348)	Total (N = 697)
Age, mean ± SD, years	62.5 ± 9.05	63.0 ± 8.91	62.8 ± 8.97	63.2 ± 8.57	64.0 ± 8.53	63.6 ± 8.55
Sex: male, *n* (%)	253 (72)	244 (69)	497 (70)	264 (76)	264 (76)	528 (76)
BMI, mean ± SD (range), kg/m^2[a]	27.55 ± 4.908 (16.9–45.3)	27.30 ± 5.560 (16.2–53.1)	27.42 ± 5.242 (16.2–53.1)	27.40 ± 6.139 (15.6–62.3)	26.74 ± 5.559 (15.9–49.4)	27.07 ± 5.861 (15.6–62.3)
Race, *n* (%)						
White	341 (97)	343 (97)	684 (97)	317 (91)	326 (94)	643 (92)
African American/African heritage	4 (1)	3 (<1)	7 (<1)	18 (5)	13 (4)	31 (4)
American Indian or Alaska native	5 (1)	5 (1)	10 (1)	7 (2)	2 (<1)	9 (1)
Asian	3 (<1)	2 (<1)	5 (<1)	4 (1)	2 (<1)	6 (<1)
American Indian or Alaska native & White	0	0	0	3 (<1)	5 (1)	8 (1)
Smoking history and status						
Current smoker, *n* (%)	159 (45)	145 (41)	304 (43)	179 (51)	184 (53)	363 (52)
Years smoked, mean ± SD (range)	36.5 ± 11.85 (10–66)	37.0 ± 11.36 (10–65)	36.7 ± 11.60 (10–66)	39.1 ± 10.58 (10–67)	39.6 ± 10.61 (10–66)	39.4 ± 10.59 (10–67)
No. cigarettes/day, mean ± SD (range)	23.6 ± 10.69 (4–65)	22.5 ± 10.75 (6–80)	23.1 ± 10.73 (4–80)	22.7 ± 10.41 (5–70)	22.4 ± 10.44 (5–100)	22.5 ± 10.42 (5–100)
Smoking pack years, mean ± SD (range)	43.2 ± 25.27 (10–162)	41.7 ± 24.35 (10–159)	42.5 ± 24.80 (10–162)	43.8 ± 22.19 (10–135)	44.5 ± 26.13 (10–285)	44.1 ± 24.22 (10–285)
COPD history						
Duration of COPD, n (%), years						
<1	11 (3)	19 (5)	30 (4)	23 (7)	20 (6)	43 (6)
≥1–<5	114 (32)	123 (35)	237 (34)	133 (38)	127 (36)	260 (37)
≥5–<10	124 (35)	122 (35)	246 (35)	100 (29)	103 (30)	203 (29)
≥10	104 (29)	89 (25)	193 (27)	93 (27)	98 (28)	191 (27)
COPD type, n (%)[b]						
Chronic bronchitis	264 (75)	271 (77)	535 (76)	250 (72)	248 (72)	498 (72)
Emphysema	210 (59)	208 (59)	418 (59)	213 (61)	228 (66)	441 (64)
Screening lung function, mean (SD)						
Pre-albuterol FEV_1, L[c]	1.311 (0.4077)	1.333 (0.4539)	1.322 (0.4312)	1.338 (0.4412)	1.332 (0.4651)	1.335 (0.4530)
Post-albuterol FEV_1, L[d]	1.443 (0.4212)	1.459 (0.4661)	1.451 (0.4440)	1.492 (0.4463)	1.485 (0.4747)	1.488 (0.4603)
Pre-albuterol FEV_1/FVC, (%FEV_1)[c]	47.5 (10.61)	46.8 (10.78)	47.2 (10.69)	47.3 (10.73)	47.0 (10.72)	47.2 (10.71)
Post-albuterol FEV_1/FVC, (%FEV_1)[d]	48.6 (10.71)	48.3 (10.82)	48.5 (10.76)	48.3 (10.75)	48.0 (10.55)	48.2 (10.65)
Post-albuterol percent predicted FEV_1, %[d]	49.2 (10.82)	49.6 (10.88)	49.4 (10.85)	49.4 (10.81)	49.5 (10.87)	49.5 (10.83)
Percent reversibility to albuterol, %[c,d]	11.5 (12.61)	11.1 (13.45)	11.3 (13.03)	13.2 (14.08)	13.4 (13.59)	13.3 (13.83)
Reversibility to albuterol, mL[c,d]	132.5 (139.39)	126.7 (148.52)	129.6 (143.96)	152.9 (152.43)	152.8 (164.79)	152.9 (158.62)

GOLD stage (percent predicted FEV_1) and reversibility, n (%)[d]						
Stage I (≥80%)	0	0	0	0	0	0
Stage II (≥50% to < 80%)	170 (48)	177 (50)	347 (49)	173 (50)	173 (50)	346 (50)
Stage III (≥30% to < 50%)	182 (52)	175 (50)	357 (51)	176 (50)	175 (50)	351 (50)
Stage IV (<30%)	0	0	0	0	0	0
Reversible to albuterol[c]	92 (26)	97 (28)	189 (27)	120 (34)	119 (34)	239 (34)
mMRC dyspnea scale, median (range)	2.0 (2–4)	2.0 (2–4)	2.0 (2–4)	2.0 (2–4)	2.0 (2–4)	2.0 (2–4)
BDI focal score, mean (SD)[e]	6.1 (2.13)	6.1 (1.91)	–	6.2 (2.00)	6.0 (2.08)	–
Health-related QoL/health outcomes, mean (SD)						
SGRQ Total score[f]	46.17 (17.039)	45.79 (17.340)	–	47.22 (17.511)	48.36 (17.625)	–
EQ-5D utility score[g]	0.70 (0.228)	0.68 (0.243)	–	0.70 (0.229)	0.70 (0.225)	–
CAT score	17.67 (7.016)	17.80 (7.130)	–	17.88 (7.562)	18.97 (7.507)	–

BDI, Baseline Dyspnea Index; BMI, body mass index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQol-5D; FEV_1, forced expiratory volume in 1 s; FP/SAL, fluticasone propionate/salmeterol; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; ITT, intent-to-treat; mMRC, modified Medical Research Council; No., number; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire for COPD patients; UMEC, umeclidinium; VI, vilanterol.

[a] $n = 346$ (UMEC/VI), 347 (FP/SAL) and 693 (Total) in DB2114951.

[b] Patients could select chronic bronchitis, emphysema or both.

[c] $n = 348$ (UMEC/VI) and 696 (Total) in DB2114951.

[d] $n = 352$ (UMEC/VI and FP/SAL) and 704 (Total) in DB2114930.

[e] $n = 346$ (UMEC/VI and FP/SAL) in DB2114930, and 345 (UMEC/VI) and 343 (FP/SAL) in DB2114951.

[f] $n = 347$ (UMEC/VI) and 351 (FP/SAL) in DB2114930, and 344 (UMEC/VI) and 343 (FP/SAL) in DB2114951.

[g] $n = 352$ (UMEC/VI) in DB2114930.

Table 2 Results from the analyses of the primary, secondary and selected other endpoints (ITT population).

Endpoint	DB2114930		DB2114951	
	UMEC/VI 62.5/25 mcg ($N = 353$)	FP/SAL 250/50 mcg ($N = 353$)	UMEC/VI 62.5/25 mcg ($N = 349$)	FP/SAL 250/50 mcg ($N = 348$)
Primary endpoint				
0–24 h wmFEV$_1$ on Day 84, L				
N	315	310	322	311
LS mean (SE)	1.494 (0.0130)	1.420 (0.0131)	1.533 (0.0137)	1.432 (0.0139)
LS mean (SE) change from baseline	0.165 (0.0130)	0.091 (0.0131)	0.213 (0.0137)	0.112 (0.0139)
Treatment difference (95% CI)	0.074 (0.038–0.110)		0.101 (0.063–0.139)	
	$p < 0.001$		$p < 0.001$	
Secondary endpoint				
Trough FEV$_1$ on Day 85, L				
n[a]	341	339	335	336
n[b]	317	312	323	311
LS mean (SE)	1.488 (0.0133)	1.406 (0.0134)	1.499 (0.0138)	1.401 (0.0140)
LS mean (SE) change from baseline	0.154 (0.0133)	0.072 (0.0134)	0.185 (0.0138)	0.087 (0.0140)
Treatment difference (95% CI)	0.082 (0.045–0.119)		0.098 (0.059–0.137)	
	$p < 0.001$		$p < 0.001$	
Other endpoints (selected)				
Peak FEV$_1$ 0–6 h, L				
Day 1				
n[a]	353	351	346	348
n[b]	353	351	346	347
LS mean (SE)	1.586 (0.0086)	1.521 (0.0087)	1.601 (0.0089)	1.544 (0.0089)
LS mean (SE) change from baseline	0.258 (0.0086)	0.193 (0.0087)	0.286 (0.0089)	0.230 (0.0089)
Treatment difference (95% CI)	0.064 (0.040–0.089)		0.056 (0.032–0.081)	
	$p < 0.001$		$p < 0.001$	
Day 84				
n[a]	353	351	346	348
n[b]	320	314	325	312
LS mean (SE)	1.642 (0.0141)	1.536 (0.0142)	1.685 (0.0146)	1.563 (0.0148)
LS mean (SE) change from baseline	0.314 (0.0141)	0.208 (0.0142)	0.371 (0.0146)	0.248 (0.0148)
Treatment difference (95% CI)	0.107 (0.067–0.146)		0.122 (0.081–0.163)	
	$p < 0.001$		$p < 0.001$	
Time to onset on Day 1 (increase in 0–6 h post-dose FEV$_1$ ≥ 100 mL above baseline)				
N	353	351	346	347
Median time to onset, min	18	63	16	58
Hazard ratio (95% CI)	1.4 (1.2–1.6)		1.6 (1.3–1.9)	
	$p < 0.001$		$p < 0.001$	
Proportion of patients achieving an increase in FEV$_1$ ≥ 100 mL above baseline at 5 min post-dose on Day 1 (post-hoc analysis)				
N	344	344	339	345
Increase, *n* (%)	123 (36)	86 (25)	160 (47)	107 (31)
No increase, *n* (%)	221 (64)	258 (75)	179 (53)	238 (69)
Odds ratio (95% CI)	1.66 (1.20–2.31)		1.98 (1.45–2.72)	
	$p = 0.003$		$p < 0.001$	
Proportion of patients achieving an increase in 0–6 h post-dose FEV$_1$ ≥ 12% and ≥200 mL above baseline on Day 1				
N	353	351	347	347
Increase, *n* (%)	198 (56)	129 (37)	216 (62)	173 (50)
No increase, *n* (%)	155 (44)	222 (63)	131 (38)	174 (50)
Odds ratio (95% CI)	2.18 (1.61–2.95)		1.66 (1.23–2.24)	
	$p < 0.001$		$p = 0.001$	
Proportion of patients achieving an increase in trough FEV$_1$ ≥ 100 mL above baseline on Day 85				
N	318	312	324	311
Increase, *n* (%)	189 (59)	130 (42)	207 (64)	141 (45)
No increase, *n* (%)	129 (41)	182 (58)	117 (36)	170 (55)
	2.04 (1.48–2.81)		2.18 (1.58–3.00)	
	$p < 0.001$		$p < 0.001$	

Table 2 (*continued*)

Endpoint	DB2114930		DB2114951	
	UMEC/VI 62.5/25 mcg ($N = 353$)	FP/SAL 250/50 mcg ($N = 353$)	UMEC/VI 62.5/25 mcg ($N = 349$)	FP/SAL 250/50 mcg ($N = 348$)
Trough IC on Day 84, L				
N	320	316	–	–
LS mean (SE)	2.248 (0.0188)	2.149 (0.0190)	–	–
LS mean (SE) change from baseline	0.126 (0.0188)	0.027 (0.0190)	–	–
Treatment difference (95% CI)	0.099 (0.046–0.151) $p < 0.001$		–	

Analysis of the primary endpoint was performed using ANCOVA with covariates of baseline FEV_1, smoking status and treatment. Analysis of secondary endpoint was by MMRM analysis including covariates of baseline FEV_1, smoking status, day, treatment, day by baseline and day by treatment interactions, where day is nominal.

CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FP/SAL, fluticasone propionate/salmeterol; IC, inspiratory capacity; ITT, intent-to-treat; LS, least squares; MRMM, mixed-effect model repeated measure model; SE, standard error; UMEC, umeclidinium; VI, vilanterol; wm, weighted mean.

[a] Number of patients with analyzable data for 1 or more time points.

[b] Number of patients with analyzable data at the current time point.

Mean (standard deviation [SD]) treatment compliance was 98.5% (4.9%) and 104.1% (120.1%) for UMEC/VI and 98.1% (7.1%) and 105.9% (150.3%) for FP/SAL in DB2114930 and DB2114951, respectively.

Efficacy

Primary and secondary endpoints

In both studies, UMEC/VI demonstrated statistically significant and clinically meaningful improvements in least squares (LS) mean change from baseline in 0–24 h $wmFEV_1$ (primary endpoint) versus FP/SAL on Day 84 (Table 2; $p < 0.001$). This finding is supported by the statistically significant improvement in LS mean change from baseline in FEV_1 at all time points for UMEC/VI versus FP/SAL (Fig. 3; except at 18 h in DB2114930). UMEC/VI gave clinically meaningful and statistically significant ($p < 0.001$) improvements in LS mean change from baseline in trough FEV_1 on Day 85 (secondary endpoint) versus FP/SAL (Table 2, Fig. 4). Similar improvements were seen on Days 28, 56 and 84 (Fig. 4) in both studies.

In descriptive summaries, raw mean change from baseline for both endpoints was greater with UMEC/VI than with FP/SAL regardless of GOLD subgroup. For UMEC/VI, the mean change was slightly greater in patients with GOLD II versus GOLD III COPD (Table B.2) in both studies for both endpoints, and for FP/SAL in DB2114930. In DB2114951, with FP/SAL the mean change was slightly lower in patients with GOLD II versus GOLD III COPD for both endpoints (Table B.2).

Other lung function endpoints

Statistically significant improvements in LS mean change from baseline in peak FEV_1 0–6 h occurred with UMEC/VI versus FP/SAL on Days 1 ($p < 0.001$) and 84 ($p < 0.001$) in both studies (Table 2).

Median time to onset on Day 1 was significantly ($p < 0.001$ both studies) shorter with UMEC/VI versus FP/SAL (Table 2). For both studies, the proportion of patients achieving an increase in FEV_1 ≥100 mL above baseline was significantly greater with UMEC/VI versus FP/SAL at 5 min (Table 2), 15 min, 1, 3 and 6 h post-dose (Table B.3).

Patients receiving UMEC/VI had statistically significantly greater odds than those treated with FP/SAL of achieving an increase in FEV_1 ≥12% and ≥200 mL above baseline during 0–6 h post-dose on Day 1 versus not achieving this increase ($p < 0.001$ DB2114930; $p = 0.001$ DB2114951), and of achieving an increase in trough FEV_1 ≥100 mL above baseline on Day 85 versus not achieving this increase ($p < 0.001$ both studies; Table 2).

In both studies, UMEC/VI demonstrated statistically significant improvements in FVC endpoints versus FP/SAL (Table B.4). In DB2114930, UMEC/VI statistically significantly improved the LS mean change from baseline in trough IC on Day 84 versus FP/SAL ($p < 0.001$; Table 2).

Health outcomes and symptomatic endpoints

In both studies, UMEC/VI and FP/SAL treatment resulted in clinically meaningful TDI focal scores (>1 unit) and improvements in mean SGRQ total scores (≥4 unit decrease from baseline) at all time points (Table B.5), except for FP/SAL on Day 28 in DB2114951. No statistically significant treatment differences were seen between UMEC/VI and FP/SAL in either endpoint at any time point (Table B.5), except on Day 28 in DB2114951 where the difference in SGRQ total score was −1.95 ($p = 0.026$) favoring UMEC/VI.

The LS mean change from baseline in the mean number of puffs of rescue medication/day over 12 weeks was statistically significantly reduced with UMEC/VI versus FP/SAL in DB2114951 and similar between treatment groups in DB2114930 (Table B.6). The change from baseline in percentage of rescue-free days over 12 weeks was similar between groups within each study (Table B.6).

No treatment differences were seen in the mean change from baseline on Day 84 in the EQ-5D utility score or in CAT scores within each study (Table B.7).

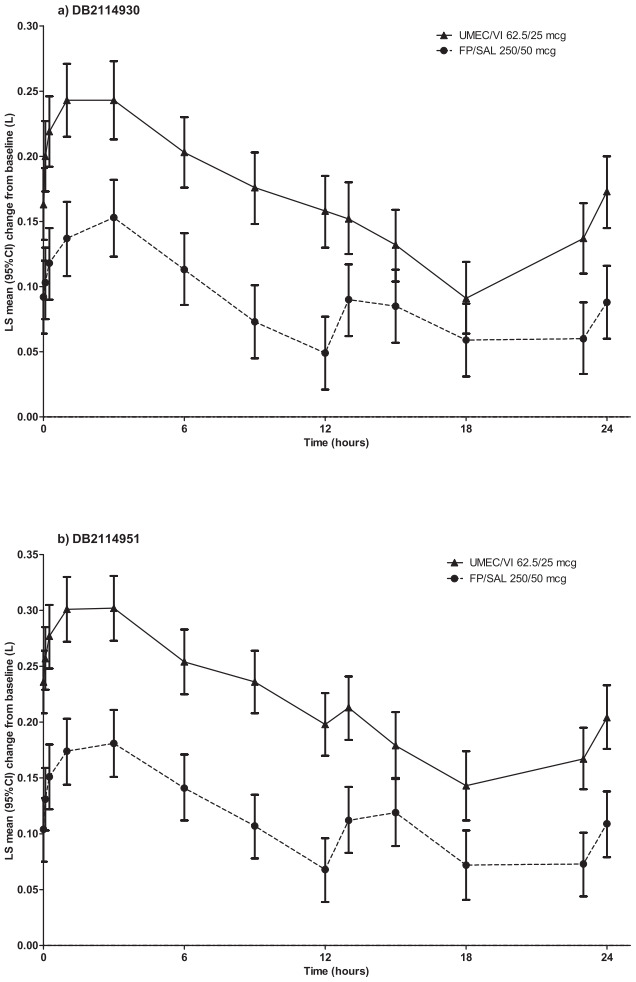

Figure 3 LS mean (95% CI) change from baseline in FEV_1 (L) over 0—24 h on Day 84 (ITT population). CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FP/SAL, fluticasone propionate/salmeterol; ITT, intent-to-treat; LS, least squares; UMEC, umeclidinium; VI, vilanterol.

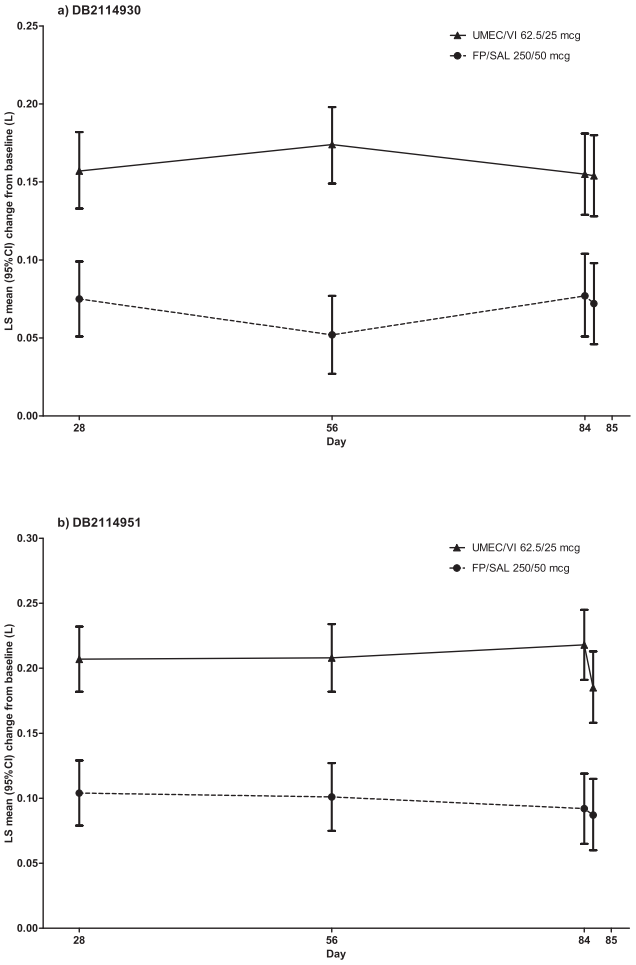

Figure 4 LS mean (95% CI) change from baseline in trough FEV_1 (L) at Days 28, 56, 84 and 85 (ITT population). CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FP/SAL, fluticasone propionate/salmeterol; ITT, intent-to-treat; LS, least squares; UMEC, umeclidinium; VI, vilanterol.

Safety assessments

In both studies, UMEC/VI and FP/SAL were well tolerated, with no marked differences in AE profiles between these treatments (Table 3). The most common AEs in both groups were headache and nasopharyngitis in both studies. The number of patients with cardiac AEs (UMEC/VI $n = 4$; FP/SAL $n = 7$ [DB2114930]; UMEC/VI $n = 10$; FP/SAL $n = 7$ [DB2114951]), or pneumonia (UMEC/VI $n = 1$; FP/SAL $n = 4$ [DB2114930]; UMEC/VI $n = 2$; FP/SAL $n = 4$ [DB2114951]) was very low in both studies. Other safety findings are summarized in Appendix B.

Discussion

This manuscript reports for the first time comparative efficacy data for UMEC/VI versus FP/SAL in patients with COPD. In these two large-scale studies, once-daily UMEC/VI (62.5/25 mcg) resulted in consistent, statistically significant and clinically meaningful improvements in FEV_1 and FVC measures at various time points over 12 weeks versus twice-daily FP/SAL (250/50 mcg) in patients with symptomatic moderate-to-severe COPD and infrequent exacerbations. Clinically meaningful improvements in dyspnea and QoL occurred with both treatments. Both combinations were well tolerated.

GOLD-recommended COPD treatments are currently based on four patient categories [1]. However, GOLD groups are heterogeneous [19], which challenges current COPD classifications [20]. Defining the most appropriate management for individual patients is of clinical interest. We explored the potential role of a non-ICS containing bronchodilator combination in patients with moderate-to-severe COPD with dyspnea symptoms at baseline and without a history of exacerbations by comparing the efficacy and safety of UMEC/VI with FP/SAL. In both studies, ≈50% of patients met full GOLD B criteria and ≈50% met GOLD D criteria for lung function and symptoms [1].

Compared with FP/SAL, UMEC/VI demonstrated statistically and clinically meaningful improvements in lung function endpoints in the overall populations. Based on descriptive summaries, $wmFEV_1$ and trough FEV_1

Table 3 Summary of incidence of on-treatment AEs, SAEs, AEs of special interest, most frequent AEs and COPD exacerbation (ITT population).

	DB2114930		DB2114951	
	UMEC/VI 62.5/25 mcg ($N = 353$)	FP/SAL 250/50 mcg ($N = 353$)	UMEC/VI 62.5/25 mcg ($N = 349$)	FP/SAL 250/50 mcg ($N = 348$)
AEs, *n* (%)				
Any	93 (26)	96 (27)	104 (30)	108 (31)
Drug-related	6 (2)	7 (2)	6 (2)	20 (6)
Leading to permanent discontinuation or withdrawal	7 (2)	10 (3)	9 (3)	14 (4)
Serious AEs, *n* (%)				
Any	6 (2)	10 (3)	11 (3)	13 (4)
Drug-related	1 (<1)	0	0	1 (<1)
Fatal	0	1 (<1)	2 (<1)	3 (<1)
AEs of special interest, *n* (%)				
Cardiac arrhythmias	2 (<1)	2 (<1)	4 (1)	5 (1)
Cardiac failure	0	1 (<1)	4 (1)	2 (<1)
Cardiac ischemia	1 (<1)	3 (<1)	2 (<1)	2 (<1)
Stroke	1 (<1)	2 (<1)	0	0
Pneumonia	1 (<1)	4 (1)	2 (<1)	4 (1)
LRTI (excluding pneumonia)	0	3 (<1)	3 (<1)	2 (<1)
AEs occurring in ≥3% patients in any treatment group, *n* (%)				
Headache	23 (7)	17 (5)	24 (7)	23 (7)
Nasopharyngitis	16 (5)	8 (2)	14 (4)	6 (2)
COPD exacerbations, *n* (%)	12 (3)	11 (3)	9 (3)	11 (3)

AE, adverse event; COPD, chronic obstructive pulmonary disease; FP/SAL, fluticasone propionate/salmeterol; ITT, intent-to-treat; LRTI, lower respiratory tract infection; UMEC, umeclidinium; VI, vilanterol.

improvements with UMEC/VI were greater than with FP/SAL in GOLD II and III subgroups. These findings confirm the preliminary results reported for a similar study comparing once-daily UMEC/VI (62.5/25 mcg) with twice-daily FP/SAL at 500/50 mcg [16]. All three studies demonstrated that patients with symptomatic COPD without a history of exacerbations may achieve greater lung function benefits with UMEC/VI versus FP/SAL.

Our findings confirm and extend those of previous studies comparing a LAMA/LABA combination with FP/SAL [21,22]. Lung function was significantly improved with tiotropium (18 mcg once daily)/formoterol (12 mcg twice daily) over 6 weeks versus twice-daily FP/SAL (500/50 mcg) in patients with moderate COPD [21]. Once-daily QVA149 (glycopyrronium/indacaterol) significantly improved lung function versus twice-daily FP/SAL (500/50 mcg) in patients with moderate-to-severe COPD without exacerbations in the prior 12 months in the 26-week ILLUMINATE study [22]. Key differences between our studies and ILLUMINATE were the recruitment of more patients with severe air flow obstruction at baseline (≈50% versus 18%, respectively), and a strict inclusion criterion of an mMRC Dyspnea Scale score ≥2; thus, we evaluated patients with symptomatic moderate-to-severe COPD. Collectively, these studies involving several LAMA/LABA combinations all demonstrate the potential clinical benefits of such a combination versus the commonly used ICS/LABA regimen, FP/SAL, in patients with symptomatic moderate-to-severe COPD with infrequent exacerbations.

In both studies, clinically meaningful improvements in symptomatic endpoints and health outcomes were achieved with both treatments, although there were no statistically significant differences between UMEC/VI and FP/SAL despite the greater lung function improvements in response to UMEC/VI versus FP/SAL. As improved lung function is often associated with beneficial effects on symptomatic and QoL outcomes, the lack of a statistically significant improvement in QoL with UMEC/VI over FP/SAL is surprising. However, substantial improvements in TDI and SGRQ scores were observed for both UMEC/VI and FP/SAL compared with baseline, and other studies with active treatments have also shown lung function improvements with one treatment versus another without treatment differences in SGRQ. For example, in the 26-week ILLUMINATE trial, once-daily QVA statistically significantly improved lung function versus FP/SAL, with statistically significant improvements in TDI that failed to reach the minimal clinically important difference of 1 unit. Additionally, no difference was observed in SGRQ between QVA149 and FP/SAL [22]. The similar effects of FP/SAL and UMEC/VI on these outcomes in our studies might reflect that the current tools (e.g. QoL questionnaires) are not designed to detect differences between two active treatments.

The validity of both studies in comparing lung function changes in response to UMEC/VI versus FP/SAL is confirmed by the changes from baseline in lung function which are consistent with previous studies evaluating UMEC/VI [8–10] and FP/SAL [13–15] in patients with COPD. In our studies, UMEC/VI also decreased air trapping and lung hyperinflation versus FP/SAL, as FVC endpoints and trough IC (only evaluated in DB2114930) were significantly improved. Our findings on IC confirm other reports that LAMA/LABA

combinations [23] improve this endpoint, as does FP/SAL [24,25]. Thus, another potential clinical benefit of UMEC/VI is the reduction of hyperinflation. Overall, there were no new safety concerns with either combination in these studies. The safety findings in both studies were similar to those reported in previous studies of UMEC/VI [8—11] and FP/SAL [13—15].

Both studies had several strengths including: direct comparison of UMEC/VI at the approved clinical regimen with a commonly used ICS-based treatment; recruitment of approximately equal proportions of patients with moderate or severe COPD to each treatment; the use of dyspnea score as an inclusion criterion to ensure patients were symptomatic at baseline; large sample sizes; high treatment compliance; and avoidance of multiple comparisons and multiplicity issues by applying statistical hierarchy methodology. Two potential limitations were the restriction of recruitment to patients with GOLD II and III COPD (potential benefits of UMEC/VI versus FP/SAL are unstudied in mild and very severe COPD), and the short therapy duration.

Conclusions

In patients with symptomatic moderate-to-severe COPD and infrequent COPD exacerbations, once-daily UMEC/VI 62.5/25 mcg demonstrated statistically significant and clinically meaningful improvements in lung function versus twice-daily FP/SAL 250/50 mcg over 12 weeks that were consistent across the two studies. Overall, the incidence of AEs was similar between treatment groups. Our findings suggest that treatment with a steroid-sparing LAMA/LABA combination, such as UMEC/VI, may provide greater benefits in lung function than an ICS/LABA combination, such as FP/SAL. Further studies are required to compare the relative effects of UMEC/VI and FP/SAL on COPD exacerbations.

Conflicts of interest

James F. Donohue has served as consultant to Almirall, AstraZeneca, Boehringer Ingelheim, Elevation Pharmaceuticals, Forest Laboratories, GSK, Mylan, Novartis, Pearl Pharmaceuticals, Pfizer and Sunovion; and has served as a member of Drug Safety Monitoring Boards for the NIH, Novartis, Otsuka, Pearl and Teva. All other authors (Sally Worsley, Chang-Qing Zhu, Liz Hardaker and Alison Church) are employees of and hold stock in GSK.

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Clinical trials

These studies are registered at www.clinicaltrials.gov with identifier numbers NCT01817764 (GSK study number DB2114930) and NCT01879410 (GSK study number DB2114951).

Role of sponsor

The studies were sponsored by GSK. Employees of the sponsor were involved in the conception, design and conduct of the studies, and in data collection and analysis. GSK funded the open-access and data supplement journal charges.

Author contributions

Prof Donohue: contributed to the conception and design of the studies and data interpretation; reviewing drafts of the manuscript including review of the final version.

Ms Worsley: contributed to the data acquisition and data interpretation; reviewing drafts of the manuscript including review of the final version.

Ms Zhu: contributed to the data analysis and data interpretation; reviewing drafts of the manuscript including review of the final version.

Dr Hardaker: contributed to the data interpretation; reviewing drafts of the manuscript including review of the final version.

Dr Church: contributed to the conception and design of the studies and data interpretation; reviewing drafts of the manuscript including review of the final version; ' and is the guarantor of the manuscript, taking responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2015.04.018.

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