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Magnitude of umeclidinium/vilanterol lung function effect depends on monotherapy responses: Results from two randomised controlled trials

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ABSTRACT

Purpose: Dual therapy with bronchodilators of different pharmacological classes may produce greater lung function improvements than either drug alone. However, the relationship between a patient's response to monotherapy and response to dual bronchodilator therapy is currently unknown. We aimed to investigate whether dual therapy with umeclidinium/vilanterol provides additional benefit over umeclidinium or vilanterol monotherapy in patients with chronic obstructive pulmonary disease (COPD) identified as responsive (increase from baseline in forced expiratory volume in 1s [FEV_1] of ≥12% and ≥200 mL, Day 1) or non-responsive to monotherapy.

Methods: In two randomised, double-blind, three-way complete-block, cross-over studies (DB2116132 n = 207; DB2116133 n = 182; intent-to-treat), all patients (moderate-to-very severe COPD) were randomised to 1 of 6 sequences and received once-daily umeclidinium 62.5mcg, vilanterol 25mcg, and umeclidinium/vilanterol 62.5/25mcg (one treatment/14-day period; 10–14-day washout). Key endpoints were 0–6 h weighted mean FEV_1 (Day 14) and trough FEV_1 (Day 15). Adverse events, vital signs and COPD exacerbations were assessed. Pooled data are presented.

Results: Umeclidinium/vilanterol significantly ($p \leq 0.001$, unless stated otherwise) increased 0–6 h weighted mean FEV_1 versus umeclidinium in umeclidinium-responders (+114 mL), versus vilanterol in vilanterol-responders (+92 mL) and versus umeclidinium (+70 mL) and vilanterol (+62 mL) in non-responders. Improvements in trough FEV_1 occurred with umeclidinium/vilanterol versus umeclidinium in umeclidinium-responders (+77 mL), versus vilanterol in vilanterol-responders (+86 mL), and versus umeclidinium (+42 mL [$p = 0.020$]) and vilanterol (+58 mL) in non-responders. All treatments were well tolerated.

Conclusions: Once-daily umeclidinium/vilanterol significantly improved lung function in patients with COPD, with quantitatively greater improvements in patients identified as responders to umeclidinium and vilanterol monotherapy than non-responders.

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; ITT, intent-to-treat; LS, least squares; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; MCID, minimally clinically important difference; NA, not analysed; SD, standard deviation; SE, standard error; UMEC, umeclidinium; VI, vilanterol; wm, weighted mean.

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1. Introduction

The long-acting muscarinic antagonist (LAMA) umeclidinium (UMEC) is approved both as a monobronchodilator and in combination with the long-acting beta$_2$-agonist (LABA) vilanterol (VI) for maintenance treatment of chronic obstructive pulmonary disease (COPD) in the US, EU and several other countries [1–4]. The scientific concept underlying dual bronchodilator treatment is that using two bronchodilators with different mechanisms of action will lead to additive clinical benefits [5]. Parallel group studies in patients with COPD have demonstrated that UMEC/VI significantly improved lung function versus placebo [6,7] and versus each monotherapy component [6–8].

The therapeutic response to all bronchodilators varies between patients [5]. An important point of interest for using LAMA/LABA combinations, including UMEC/VI, in clinical practice is identifying patient subgroups likely to gain the most benefit from dual therapy. The absolute magnitude of clinical benefit with a dual combination may be related to the individual response to the component monotherapies. Similarly, the additional benefit of adding a second bronchodilator to monotherapy may be related to individual responsiveness to monotherapy. We have therefore investigated the relationships between monobronchodilator therapy and dual therapy responses within the same patient.

We conducted two, three-way, complete block cross-over studies, comparing the improvement in lung function with once-daily UMEC/VI 62.5/25mcg with that of its monotherapy components, in subgroups of patients with COPD, based on response to monotherapy with UMEC 62.5mcg and VI 25mcg. The aim of these studies was to investigate whether individual lung function responses to long-acting bronchodilator monotherapy predict the response to dual bronchodilator treatment, in terms of the absolute effect size and the additive benefit achieved. Preliminary results from the individual studies have been previously presented at the European Respiratory Society Annual Congress in Munich in 2014 [9].

2. Methods

2.1. Study design and patients

Both studies were phase IIIb, multicentre, randomised, double-blind, three-way, complete block, cross-over trials (GSK study/ www.clinicaltrials.gov numbers: DB2116132/NCT02014480; DB2116133/NCT01716520). DB2116132 was conducted in Slovakia and Ukraine (23 centres; 5 February 2013 to 11 June 2013). DB2116133 was conducted in Germany and Estonia (21 centres; 19 October 2012 to 6 March 2013).

Eligible patients had moderate-to-very-severe COPD [10] with a pre- and post-salbutamol forced expiratory volume in 1s (FEV_1)/ forced vital capacity (FVC) ratio <0.70 and $FEV_1 \leq 70\%$ predicted normal. Other key inclusion criteria were: age ≥40 years; current or former (stopped smoking for ≥6 months) cigarette smokers with a history of ≥10 smoking pack-years. Key exclusion criteria were: asthma/other known respiratory disorders; hospitalisation for COPD or pneumonia within 12 weeks of screening.

Studies were approved by local ethics committees and conducted in accordance with the Declaration of Helsinki [11] and Good Clinical Practice guidelines [12]. Written informed consent was obtained from all patients.

2.2. Randomisation and treatment

Patients were randomised equally to 1 of 6 treatment sequences dispensed using a Registration and Medication Ordering System (GSK, Brentford, UK).

Patients received each of three treatments in a random order: UMEC 62.5mcg (delivered dose 55mcg; GSK, London, UK), VI

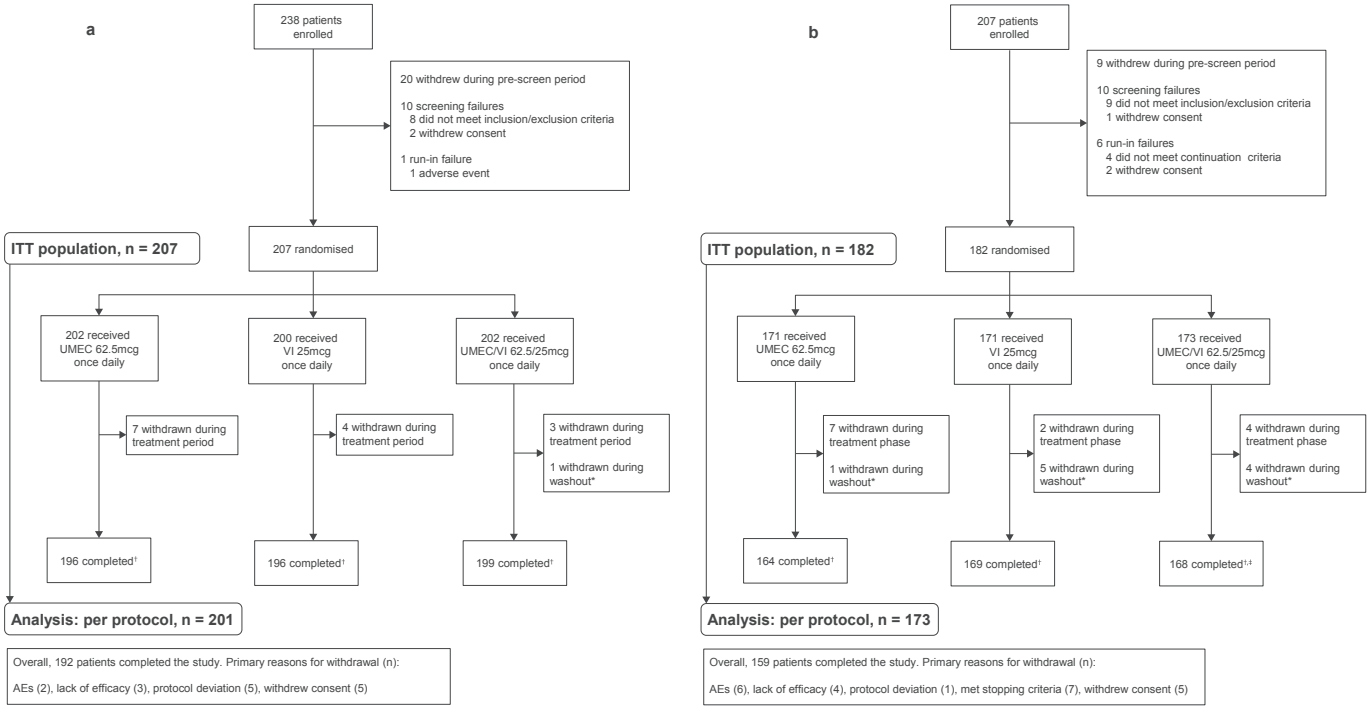

Fig. 1. Flow diagram for disposition of patients (CONSORT) for a) DB2116132 and b) DB2116133. *Patients withdrawing during washout are counted under the last treatment taken; a patient was considered to have completed the treatment period if they had a Day 15 visit in that period; zone patient did not attend Day 15 of that treatment period but continued in the study; therefore, they were not counted as a completer for that period.

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

	DB2116132 (n = 207)	DB2116133 (n = 182)	Pooled (n = 389)
Age, mean ± SD, years	60.5 ± 7.99	63.2 ± 8.19	61.8 ± 8.18
Male, n (%)	169 (82)	127 (70)	296 (76)
BMI, mean ± SD (range), kg/m^2	27.18 ± 4.596 (17.6–43.0)	27.53 ± 4.953 (16.4–45.0)	27.34 ± 4.763 (16.4–45.0)
White race, n (%)	207 (100)	182 (100)	389 (100)
Smoking history and status			
Current smoker, n (%)	115 (56)	100 (55)	215 (55)
Years smoked, mean ± SD (range)	33.0 ± 10.44 (10–60)	37.6 ± 9.54 (13–62)	35.2 ± 10.28 (10–62)
No. of cigarettes/day, mean ± SD (range)	18.7 ± 4.43 (6–40)	21.9 ± 10.61 (5–80)	20.2 ± 8.09 (5–80)
Smoking pack years, mean ± SD (range)	30.8 ± 12.21 (10–80)	41.3 ± 23.78 (10–172)	35.7 ± 19.25 (10–172)
COPD history			
Duration of COPD, n (%), years			
<1	1 (<1)	4 (2)	NA
≥1–<5	59 (29)	64 (35)	NA
≥5–<10	70 (34)	56 (31)	NA
≥10	77 (37)	58 (32)	NA
COPD type, n (%)[a]			
Chronic bronchitis	163 (79)	152 (84)	NA
Emphysema	123 (59)	80 (44)	NA
COPD exacerbation history 12 months prior to screening, n (%)			
Required oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation)			
0	119 (57)	156 (86)	275 (71)
1	66 (32)	22 (12)	88 (23)
2	19 (9)	4 (2)	23 (6)
>2	3 (1)	0	3 (<1)
Required hospitalisation			
0	128 (62)	179 (98)	307 (79)
1	56 (27)	3 (2)	59 (15)
2	23 (11)	0	23 (6)
Screening lung function, mean (SD)			
Pre-bronchodilator FEV_1, L	1.354 (0.4732)	1.297 (0.4054)	1.328 (0.4431)
Post-salbutamol FEV_1, L	1.454 (0.4936)	1.466 (0.4249)	1.460 (0.4622)
Post-ipratropium FEV_1, L	1.522 (0.5104)[d]	1.554 (0.4487)	1.537 (0.4820)[e]
Post-salbutamol percent predicted FEV_1, %	45.1 (13.14)	47.8 (11.19)	46.4 (12.32)
Percent reversibility to salbutamol, %	8.2 (11.73)	14.4 (13.32)	11.1 (12.86)
Reversibility to salbutamol, mL	99.0 (141.41)	169.6 (140.09)	132 (144.98)
Percent reversibility to salbutamol and ipratropium, %	14.0 (15.25)[d]	21.5 (16.53)	17.5 (16.28)[e]
Reversibility to salbutamol and ipratropium, mL	168.0 (183.57)[d]	256.9 (179.17)	209.8 (186.65)[e]
GOLD stage (percent predicted FEV_1), n (%)			
Stage I (≥80%)	0	0	0
Stage II (≥50% to <80%)	83 (40)	80 (44)	163 (42)
Stage III (≥30% to <50%)	95 (46)	91 (50)	186 (48)
Stage IV (<30%)	29 (14)	11 (6)	40 (10)
Reversibility, n (%)			
Reversible to salbutamol[b]	32 (15)	71 (39)	103 (26)
Reversible to salbutamol and ipratropium[c]	73 (36)[d]	105 (58)	178 (46)[e]
Current medical condition in ≥20% of patients, n (%)			
Any condition	162 (78)	153 (84)	NA
Cardiovascular risk factors	105 (51)	111 (61)	NA
Hypertension	98 (47)	99 (54)	NA
Hyperlipidaemia	17 (8)	44 (24)	NA
Cardiac disorders	74 (36)	22 (12)	NA
Musculoskeletal disorders	36 (17)	45 (25)	NA

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1s; GOLD, Global initiative for chronic Obstructive Lung Disease; ITT, intent-to-treat; NA, not analysed; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

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

[b] Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of salbutamol. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.

[c] Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of both salbutamol and ipratropium. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.

[d] n = 205.

[e] n = 387.

25mcg (delivered dose 22mcg; GSK, London, UK) and UMEC/VI 62.5/25mcg (delivered dose 55/22mcg; GSK, London, UK). These once-daily treatments were administered via the ELLIPTA®[1] dry powder inhaler for 14 days with a 10–14-day washout between each treatment. Baseline spirometry was defined as the mean value obtained from the −30 min and −5 min assessments on Day 1. Serial spirometry assessments were conducted on Day 1 and Day 14. Measurements were obtained 15 min, 30 min, 1 h, 3 h and 6 h after morning dosing. Trough spirometry was obtained at clinic

[1] ELLIPTA® is a trademark of the GlaxoSmithKline group of companies.

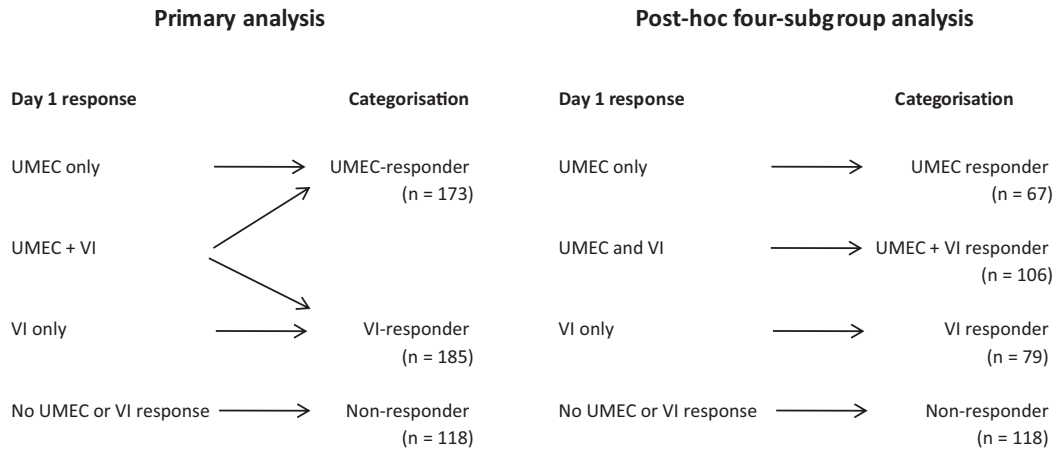

Fig. 2. Treatment comparisons investigated in primary analysis and in post-hoc four-subgroup analysis. UMEC, umeclidinium; VI, vilanterol.

visits on Day 2, Day 14 and Day 15 of each treatment period, with measurements taken 23 and 24 h after the previous morning dosing (see Supplementary Methods for further details of randomisation and treatment).

2.3. Outcome measures

The primary endpoint was weighted mean (wm) FEV_1 over 0–6 h post-dose on Day 14 of each treatment period, and the key secondary endpoint was trough FEV_1 on Day 15. Data from studies DB2116132 and DB2116133 were pooled for these analyses. Other secondary endpoints were: proportion of patients responsive to UMEC/VI, UMEC, or VI on Day 1 (FEV_1 increase from baseline of $\geq$12% and $\geq$200 mL at any time 0–6 h post-dose), and proportion of patients who had a larger change from baseline in 0–6 h $wmFEV_1$ on Day 14 with UMEC/VI versus each monotherapy. Additional endpoints are described in the Supplementary Methods. Safety assessments included adverse events (AEs), vital signs and COPD exacerbations. Twelve-lead electrocardiograms (ECGs) and clinical laboratory tests (haematology and clinical chemistry) were

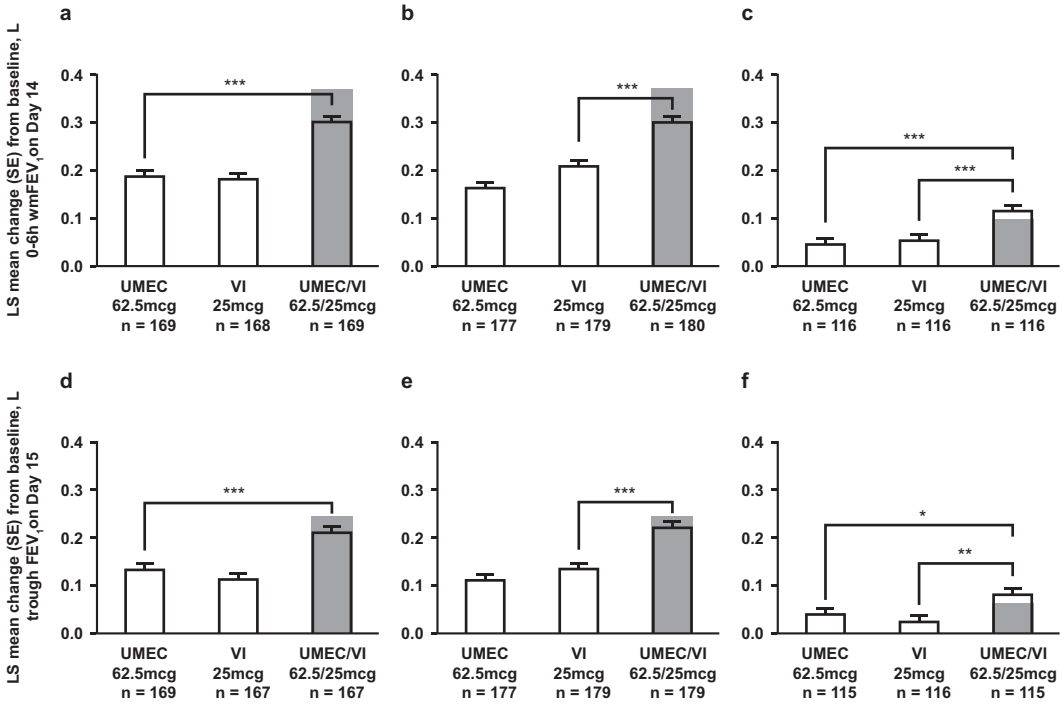

Fig. 3. Primary analysis of 0–6 h $wmFEV_1$ on Day 14 (panels a–c) and trough FEV_1 on Day 15 (panels d–f) according to whether patients were UMEC-responders[a] (panel a and d), VI-responders[b] (panel b and e) or non-responders to UMEC and VI (panel c and f) on Day 1 (pooled data, ITT population). Grey bars represent the expected fully additive effect of both monotherapies (calculated by combining the LS mean change from baseline observed for the UMEC and VI monotherapies). An additive effect is defined as more than either monotherapy effect but less than the combined total effect of both monotherapies, a fully additive effect is defined as equal to the combined effect of both monotherapies. [a]UMEC-responder: responder to UMEC monotherapy or responder to both UMEC monotherapy and VI monotherapy; [b]VI-responder: responder to VI monotherapy or responder to both VI monotherapy and UMEC monotherapy. *$p = 0.020$ for UMEC/VI versus UMEC in non-responders to UMEC and VI (panel f) **$p = 0.001$ for UMEC/VI versus VI in non-responders to UMEC and VI (panel f) ***$p < 0.001$ for: UMEC/VI versus UMEC in UMEC responders (panels a and d); UMEC/VI versus VI in VI responders (panels b and e); UMEC/VI versus UMEC and versus VI in non-responders to UMEC and VI (panel c) FEV_1, forced expiratory volume in 1s; ITT, intent-to-treat; LS, least squares; SE, standard error; UMEC, umeclidinium; VI, vilanterol; wm, weighted mean.

evaluated in DB2116133 only.

2.4. Statistical analyses

Patients were classified as responders or non-responders according to bronchodilator response on Day 1; a responder had an FEV_1 increase from baseline of ≥12% and ≥200 mL at any time 0–6 h post-dose on Day 1. Patients without data were classified as 'missing'. For 0–6 h $wmFEV_1$ (Day 14) and trough FEV_1 (Day 15), patients who were responders to UMEC only and patients who were responders to both UMEC and VI were considered UMEC-responders. Similarly, patients who were responders to VI only and those who were responders to both UMEC and VI were considered VI-responders.

In addition, a post-hoc four-subgroup analysis of both primary and secondary endpoints was conducted in responders to UMEC only, responders to VI only, responders to both UMEC and VI, and non-responders No adjustments for multiplicity were performed in these analyses of pooled data. See Supplementary Methods for other statistical methods and sample size calculations.

3. Results

In DB2116132, of 238 enrolled patients, 207 were in the intent-to-treat (ITT) population and 192 (93%) completed the study (Fig. 1a). In DB2116133, 207 patients were enrolled, the ITT population consisted of 182 patients and 159 (87%) completed the study (Fig. 1b). Fig. 1 summarises withdrawal reasons.

Patient demographics and baseline characteristics were generally consistent between studies (Table 1). Lung function was similar in both studies, with most patients having moderate-to-severe COPD; although 14% (DB2116132) and 6% (DB2116133) of patients had very severe COPD (FEV_1% predicted <30%). More patients were found to be reversible as defined by FEV_1>12% and 200 mL post-salbutamol and post-salbutamol/ipratropium, respectively, in the DB2116133 study (39% and 58%) than the DB2116132 study (15% and 36%). More patients in DB2116132 experienced COPD exacerbations in the year prior to screening versus DB2116133. Baseline reversibility to short-acting bronchodilators was lower in DB2116132 versus DB2116133. COPD medication is summarised online (Table A1). Treatment compliance in all groups was very high (Supplementary Results).

3.1. Summary of treatment response (Day 1)

In the primary analysis, 173 patients were UMEC-responders, 185 were VI-responders and 118 were non-responders; 19 patients had missing data (either missing both monotherapy treatments or was a non-responder to one monotherapy and missing the other treatment) (Fig. 2). In the additional post-hoc four-subgroup analysis, there were 67 responders to UMEC only, 79 responders to VI only, 106 responders to both UMEC and VI, and 118 non-responders (Fig. 2). Proportions of patients in each response category were generally similar between studies (Supplementary Results).

Table 2
Analysis of 0–6 h $wmFEV_1$ on Day 14 in the overall population and stratified by UMEC and VI response on Day 1, Pooled analysis (ITT population).

Status	UMEC 62.5mcg (n = 373)	VI 25mcg (n = 371)	UMEC/VI 62.5/25mcg (n = 375)
Overall population[a]			
n	361	362	366
LS mean change (SE)	0.125 (0.0092)	0.146 (0.0093)	0.234 (0.0092)
UMEC/VI versus monotherapy			
Difference	0.109	0.088	–
(95% CI)	(0.090,0.127)	(0.070,0.107)	–
p-value	<0.001	<0.001	–
Stratified by UMEC and VI response on Day 1[b]			
UMEC-responders[c]			
n	169	168	169
LS mean change (SE)	0.187 (0.0123)	0.181 (0.0124)	0.300 (0.0121)
UMEC/VI versus monotherapy			
Difference	0.114	–	–
(95% CI)	(0.086,0.142)	–	–
p-value	<0.001	–	–
VI-responders[d]			
n	177	179	180
LS mean change (SE)	0.163 (0.0177)	0.208 (0.0116)	0.300 (0.0116)
UMEC/VI versus monotherapy			
Difference	–	0.092	–
(95% CI)	–	(0.066,0.118)	–
p-value	–	<0.001	–
Non-responders			
n	116	116	116
LS mean change (SE)	0.044 (0.0145)	0.052 (0.0144)	0.114 (0.0145)
UMEC/VI versus monotherapy			
Difference	0.070	0.062	–
(95% CI)	(0.038,0.103)	(0.030,0.094)	–
p-value	<0.001	<0.001	–

ANCOVA, analysis of covariance; CI, confidence interval; FEV_1, forced expiratory volume in 1s; ITT, intent-to-treat; LS, least squares; SE, standard error; UMEC, umeclidinium; VI, vilanterol; wm, weighted mean.

[a] Analysis performed using an ANCOVA model with covariates of study, treatment, period, mean baseline, and period baseline.

[b] Analysis performed using an ANCOVA model with covariates of study, treatment, period, mean baseline, period baseline, response type, and treatment by response type interaction.

[c] Responder to UMEC: responder to UMEC monotherapy or responder to both UMEC monotherapy and VI monotherapy.

[d] Responder to VI: responder to VI monotherapy or responder to both VI monotherapy and UMEC monotherapy.

3.2. 0–6 h wmFEV$_1$ on Day 14

In the primary analysis, UMEC/VI significantly increased the least squares (LS) mean change from baseline in wmFEV$_1$ 0–6 h (Day 14) versus each monotherapy in the overall ITT populations, versus UMEC in UMEC-responders (114 mL, $p < 0.001$; Fig. 3a) and versus VI in VI-responders (92 mL, $p < 0.001$; Fig. 3b) (Table 2). In UMEC and VI non-responders, UMEC/VI significantly improved wmFEV$_1$ 0–6 h (Day 14) versus each monotherapy (70 mL versus UMEC, $p < 0.001$; 62 mL versus VI, $p < 0.001$; Fig. 3c) (Table 2). The LS mean change from baseline for UMEC/VI was less than fully additive based on the monocomponent responses in both UMEC-responders (300 mL with UMEC/VI versus 187 mL with UMEC and 181 mL with VI) and VI-responders (300 mL with UMEC/VI versus 163 mL with UMEC and 208 mL with VI; Table 2). Non-responders to both monotherapies showed a LS mean change from baseline in wmFEV$_1$ with UMEC/VI that was numerically lower (114 mL) than that observed in the UMEC responder (300 mL) and VI-responder (300 mL) groups, but more than fully additive based on monotherapy responses (44 mL with UMEC and 52 mL with VI). Results were similar in the individual studies (Table A2).

In the four-subgroup post-hoc analysis, UMEC/VI significantly increased LS mean change from baseline in wmFEV$_1$ 0–6 h (Day 14) versus either monotherapy in all subgroups (Fig. 4a–d). The LS mean change from baseline for wmFEV$_1$ with UMEC/VI was numerically greatest in the responders to both UMEC and VI (372 mL), with lower changes observed in responders to VI only (227 mL), UMEC only (229 mL) and non-responders to both UMEC and VI (114 mL). The LS mean change from baseline for wmFEV$_1$ with UMEC/VI was less than fully additive in responders to both UMEC and VI, fully additive in responders to UMEC only and responders to VI only, and more than fully additive in non-responders (Table A3).

3.3. Trough FEV$_1$ on Day 15

UMEC/VI significantly increased the LS mean change from baseline in trough FEV$_1$ (Day 15) versus each monotherapy in the overall ITT populations, versus UMEC in UMEC-responders (77 mL, $p < 0.001$; Fig. 3d) and versus VI in VI-responders (86 mL, $p < 0.001$; Fig. 3e) (Table 3). In UMEC and VI non-responders, UMEC/VI significantly improved LS mean change from baseline in trough FEV$_1$ (Day 15) versus monotherapy (42 mL versus UMEC, $p = 0.020$; 58 mL versus VI, $p = 0.001$; Fig. 3f) (Table 3). The LS mean change from baseline for UMEC/VI was less than fully additive based on monotherapy responses in both UMEC-responders (209 mL with UMEC/VI versus 132 mL with UMEC and 112 mL with VI) and VI-responders (220 mL with UMEC/VI versus 111 mL with UMEC and 134 mL with VI; Table 3). Non-responders to both monotherapies showed a LS mean change from baseline with UMEC/VI that was numerically lower (81 mL) than that observed with UMEC responder (209 mL) and VI-responder (220 mL) groups, but more than fully additive based on monotherapy responses (39 mL with UMEC and 23 mL with VI). Results were similar in the individual studies (see Supplementary Results; Table A4).

In the four-subgroup post-hoc analysis, UMEC/VI significantly increased LS mean change from baseline in trough FEV$_1$ (Day 15) versus either monotherapy in all subgroups (Fig. 4e–h). The LS mean change from baseline for trough FEV$_1$ with UMEC/VI was numerically greatest in the responders to both UMEC and VI (263 mL), with lower changes observed in responders to VI only (177 mL), UMEC only (155 mL) and non-responders to both UMEC

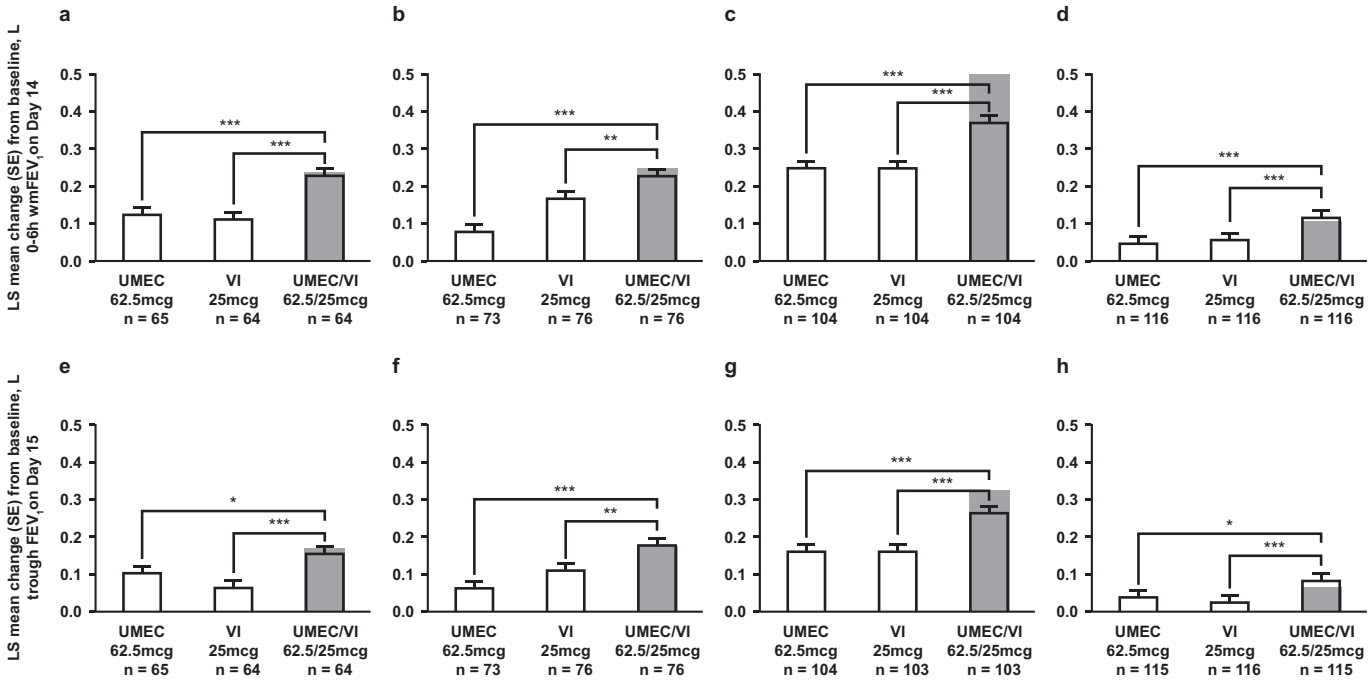

Fig. 4. Four-subgroup post-hoc analysis of 0–6 h wmFEV$_1$ on Day 14 (panels a–d) and trough FEV$_1$ on Day 15 (panels e–h) by whether patients were responders to UMEC only (panels a and e), responders to VI only (panels b and f), responders to UMEC and VI (panels c and g) or non-responders to UMEC and VI (panels d and h) on Day 1 (pooled data, ITT population). Grey bars represent the expected additive effect of both monotherapies (calculated by combining the mean change from baseline observed for the UMEC and VI monotherapies). *$p = 0.036$ for UMEC/VI versus UMEC in responders to UMEC only (panel e) and $p = 0.020$ for UMEC/VI versus UMEC in non-responders (panel h) **$p = 0.003$ for UMEC/VI versus VI in responders to VI only (panel b) and $p = 0.002$ for UMEC/VI versus VI in responders to VI only (panel f) ***$p < 0.001$ for all other comparisons FEV$_1$, forced expiratory volume in 1s; ITT, intent-to-treat; LS, least squares; SE, standard error; UMEC, umeclidinium; VI, vilanterol; wm, weighted mean.

Table 3
Analysis of trough FEV_1 at Day 15 in the overall population and stratified by UMEC and VI response on Day 1, pooled analysis (ITT population).

Status	UMEC 62.5mcg (n = 373)	VI 25mcg (n = 371)	UMEC/VI 62.5/25mcg (n = 375)
Overall population[a]			
n	360	362	365
LS mean change (SE)	0.091 (0.0092)	0.089 (0.0092)	0.168 (0.0091)
UMEC/VI versus monotherapy			
Difference	0.077	0.080	–
(95% CI)	(0.057,0.097)	(0.060,0.100)	–
p-value	<0.001	<0.001	–
Stratified by UMEC and VI response on Day 1[b]			
UMEC-responders[c]			
n	169	167	167
LS mean change (SE)	0.132 (0.0131)	0.112 (0.0132)	0.209 (0.0130)
UMEC/VI versus monotherapy			
Difference	0.077	–	–
(95% CI)	(0.046,0.107)	–	–
p-value	<0.001	–	–
VI-responders[d]			
n	177	179	179
LS mean change (SE)	0.111 (0.0125)	0.134 (0.0124)	0.220 (0.0124)
UMEC/VI versus monotherapy			
Difference	–	0.086	–
(95% CI)	–	(0.057, 0.115)	–
p-value	–	<0.001	–
Non-responders			
n	115	116	115
LS mean change (SE)	0.039 (0.0154)	0.023 (0.0154)	0.081 (0.0154)
UMEC/VI versus monotherapy			
Difference	0.042	0.058	–
(95% CI)	(0.007, 0.078)	(0.023, 0.094)	–
p-value	0.020	0.001	–

ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent-to-treat; LS, least squares; SE, standard error; UMEC, umeclidinium; VI, vilanterol.
[a] Analysis performed using an ANCOVA model with covariates of study, treatment, period, mean baseline, and period baseline.
[b] Analysis performed using an ANCOVA model with covariates of study, treatment, period, mean baseline, period baseline, response type, and treatment by response type interaction.
[c] Responder to UMEC: responder to UMEC monotherapy or responder to both UMEC monotherapy and VI monotherapy.
[d] Responder to VI: responder to VI monotherapy or responder to both VI monotherapy and UMEC monotherapy.

and VI (81 mL). The LS mean change from baseline with UMEC/VI was less than fully additive based on the monotherapy responses in the responders to both UMEC and VI, fully additive in responders to UMEC only and responders to VI only, and more than fully additive in the non-responders (Table A3).

3.4. Other efficacy endpoints

In the pooled analyses, a significantly greater proportion of patients were responsive to UMEC/VI versus UMEC or VI for each response definition (increase from baseline of: ≥12% and ≥200 mL; or ≥130 mL; or ≥100 mL) for $wmFEV_1$ 0–6 h (Day 14) and trough FEV_1 (Day 15) (Table 4). Results of these comparisons for the individual studies were similar to the pooled analyses (Table A5).

The proportion of patients responsive to UMEC/VI, UMEC, or VI on Day 1 (Table A6), and the proportion of patients who had a larger change from baseline in 0–6 h $wmFEV_1$ on Day 14 with UMEC/VI versus each monotherapy (Table A7) are detailed in the Supplementary Results. Serial FEV_1, serial FVC and trough FVC along with rescue medication use (Table A8) and changes from baseline in serial FEV_1 at Day 14 (Fig. A1) are also reported in the Supplementary Results.

3.5. Safety assessments

The overall incidence of AEs in each study was 18% for UMEC/VI, 12% and 16% for UMEC, and 15% and 18% for VI (Table A9). The most common AEs were nasopharyngitis (1% and 4% for UMEC/VI, <1% and 3% for UMEC, and 1% and 6% for VI in each study) and headache (5% and 3% for UMEC/VI, 2% for UMEC, and 5% and 1% for VI). All treatments were well tolerated, with no unexpected findings reported for any treatment. See Supplementary Results for serious AEs, exacerbations, vital sign assessment, ECG and clinical laboratory test results.

4. Discussion

UMEC/VI 62.5/25mcg caused significant lung function improvements in 0–6 h $wmFEV_1$ (Day 14) and trough FEV_1 (Day 15) versus monotherapy in both UMEC and VI responders and non-responders to UMEC and/or VI, but the magnitude of the benefit varied between responder groups. The absolute magnitude of lung function improvement of UMEC/VI was greatest in patients classified as responders to both UMEC and VI on Day 1 (known as dual responders), with the lowest effect seen in non-responders to both monocomponents. Thus, the magnitude of response to a single long-acting bronchodilator therapy can predict the magnitude of benefit achieved from a dual bronchodilator.

The four subgroup post-hoc pooled analyses showed that the benefits of UMEC/VI over monotherapy treatment were more than additive in non-responders to both UMEC and VI, and additive in responders to one monotherapy only. In contrast, the effects of UMEC/VI were less than additive in dual responders. The dose response curve for lung function after bronchodilator use in obstructive lung diseases follows a classical pattern with a steep linear response followed by a plateau as the maximal possible effect is reached [13,14]. Our data suggest that the effects of UMEC and VI in dual responders were near the plateau of this dose response

Table 4
Analysis of proportion of responders (defined as change from baseline of ≥12% and ≥200 mL, or ≥130 mL or ≥100 mL) for 0–6 h wmFEV$_1$ at Day 14 and trough FEV$_1$ at Day 15, pooled analysis (ITT population).

	UMEC 62.5mcg (n = 373)	VI 25mcg (n = 371)	UMEC/VI 62.5/25mcg (n = 375)
0–6 h wmFEV$_1$ at Day 14, change from baseline of ≥12% and ≥200 mL[a]			
Responder	113 (31)	98 (27)	189 (52)
UMEC/VI versus monotherapy			
Odds ratio	2.81	2.80	–
95% CI	2.02, 3.91	2.01, 3.92	–
p-value	<0.001	<0.001	–
0–6 h wmFEV$_1$ at Day 14, change from baseline of ≥130 mL[a]			
Responder	177 (49)	161 (44)	241 (66)
UMEC/VI versus monotherapy			
Odds ratio	2.40	2.31	–
95% CI	1.73, 3.34	1.66, 3.20	–
p-value	<0.001	<0.001	–
0–6 h wmFEV$_1$ at Day 14, change from baseline of ≥100 mL[a]			
Responder	203 (56)	194 (54)	254 (69)
UMEC/VI versus monotherapy			
Odds ratio	2.07	1.81	–
95% CI	1.48, 2.88	1.30, 2.51	–
p-value	<0.001	<0.001	–
Trough FEV$_1$ at Day 15, change from baseline of ≥12% and ≥200 mL[b]			
Responder	98 (27)	65 (18)	144 (39)
UMEC/VI versus monotherapy			
Odds ratio	2.16	2.82	–
95% CI	1.51, 3.09	1.93, 4.13	–
p-value	<0.001	<0.001	–
Trough FEV$_1$ at Day 15, change from baseline of ≥130 mL[b]			
Responder	142 (39)	116 (32)	199 (55)
UMEC/VI versus monotherapy			
Odds ratio	2.21	2.39	–
95% CI	1.59, 3.07	1.71, 3.33	–
p-value	<0.001	<0.001	–
Trough FEV$_1$ at Day 15, change from baseline of ≥100 mL[b]			
Responder	169 (47)	136 (38)	221 (61)
UMEC/VI versus monotherapy			
Odds ratio	2.03	2.43	–
95% CI	1.47, 2.81	1.75, 3.38	–
p-value	<0.001	<0.001	–

Values shown for responders and non-responders are n (%).
CI, confidence interval; FEV$_1$, forced expiratory volume in 1s; ITT, intent-to-treat; UMEC, umeclidinium; VI, vilanterol; wm, weighted mean.
[a] n = 361 (UMEC), 362 (VI), 366 (UMEC/VI).
[b] n = 360 (UMEC), 362 (VI), 365 (UMEC/VI).

curve, therefore, fully additive effects were not achieved.

For non-responders to both UMEC and VI, the change from baseline of either monotherapy alone (pooled analysis) on 0–6 h wmFEV$_1$ at Day 14 and trough FEV$_1$ at Day 15 were <60 mL and <40 mL, respectively. These effects are well below the published minimally clinically important difference (MCID) for FEV$_1$, which is approximately 100 mL [15]. UMEC/VI treatment in these patients caused increases in FEV$_1$ that were numerically greater than the sum of the monocomponent effects, with 114 mL and 81 mL improvements observed for 0–6 h wmFEV$_1$ and trough FEV$_1$, respectively. These changes with UMEC/VI were around the level of the MCID, while the monotherapy responses were not. While these lung function changes were smaller than the other (responder) subgroups, it is known that the magnitude of change in FEV$_1$ is weakly correlated with clinical outcomes such as exacerbations and health status [16,17], and a small lung function improvement may still improve clinical symptoms. Changes in FEV$_1$ are smaller in patients with more severe disease [18], which may also contribute to this observation. Overall, these results indicate that UMEC/VI therapy may be of benefit to patients in clinical practice who have not previously responded well to long-acting bronchodilator monotherapy.

Our data suggests a more than additive phenomenon of UMEC/VI in patients who are non-responders to monotherapy. The mechanisms behind this observation were not investigated in these studies. However it has been previously shown in isolated human airway muscle that the addition of a beta-agonists decreases the release of acetylcholine from post-ganglionic cholinergic nerve endings by stimulating pre-synaptic beta-receptors on parasympathetic ganglia, resulting in inhibition of cholinergic neurotransmission [19]. Experiments involving rat and guinea pig isolated tracheae indicate that this process may involve the release of inhibitory prostaglandins from airway mucosa [20], thereby amplifying the smooth muscle relaxation induced by muscarinic antagonists. Secondly, direct measurements of patient intrabronchial pressure with a catheter tip micromanometer show that beta-agonists appear to have a greater effect than muscarinic antagonists on peripheral airways whereas inhaled muscarinic antagonists are more likely to act on central airways that are abundantly innervated by parasympathetic nerves [21]. It is therefore possible that the bronchodilator response observed with UMEC/VI is maximised by the different preferential sites of action of beta-agonists and muscarinic antagonists, in addition to their distinct mechanisms of action. Further investigations to understand this observation with UMEC/VI are of clinical interest.

Defining the most appropriate treatment regimen for individual patients is of clinical interest. Previous reports have shown that several LAMA/LABA combinations significantly improve lung function versus monocomponents in patients with COPD [5,7,22–24]. These parallel group studies evaluated efficacy in

overall populations, not in specific patient subgroups. The current study now demonstrates that response to a single dose of long-acting bronchodilator can predict different patterns of response to combination therapy.

Our studies used a well-established design to evaluate short-term efficacy/safety of bronchodilators. Results were qualitatively similar between the studies; although, the magnitude of improvements was variable. UMEC and VI monotherapy and UMEC/VI were well tolerated in both studies, and the AE profiles were consistent with previous 12- or 24-week studies in patients with COPD [6–8,25].

A key strength of these studies is the complete block, crossover design allowing evaluation of within-patient responses to multiple study treatments. Other strengths include: broad inclusion criteria ($FEV_1 \leq 70\%$); large sample sizes; identical designs enabling pooled analyses; use of clinical doses of once-daily UMEC (62.5mcg) and UMEC/VI (62.5/25mcg); and very high compliance with study medication. Potential limitations include: responder status classified on Day 1 using an arbitrary definition of increase from baseline in FEV_1 of $\geq$12% and $\geq$200 mL (this measurement is known to vary between visits [26]); short treatment duration; and the studies not being designed to properly assess endpoints such as symptoms.

In conclusion, these studies demonstrated that the magnitude of improvement in lung function on UMEC/VI versus monotherapy after 14 days varied according to monotherapy response on Day 1. Improvement was greatest amongst patients who responded to UMEC or VI. A second important finding of particular clinical relevance was that non-responders to both UMEC and VI monotherapy achieved a clinically meaningful lung function response when UMEC/VI was administered. In these patients, response to UMEC/VI was more than the additive effect of the monotherapies.

Conflict of interest statement

James F Donohue has chaired speaker training and FDA mock advisory committee preparations for GSK. He has served as a consultant for Almirall, AstraZeneca, Boehringer Ingelheim, Elevation Pharmaceuticals, Forest Laboratories, Mylan, Pfizer and Sunovion; served as a consultant and a member of a Drug Safety Monitoring Board for Novartis and Pearl Pharmaceuticals; and served as a member of a Drug Safety Monitoring Board for Otsuka, Teva and NiH. Dave Saingh has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards and research grants from various pharmaceutical companies including Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, CIPLA, Forest, Genentech, Glenmark, GSK, Johnson & Johnson, Merck, NAPP, Novartis, Pfizer, Roche, Skyepharma, Takeda, Teva, Theravance and Verona. Clare Munzu, Sally Kilbride and Alison Church are employees of and own stock in GSK.

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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.2016.01.001.

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