Comparative Efficacy of Umeclidinium/Vilanterol, Umeclidinium, and Salmeterol in Symptomatic Patients With Chronic Obstructive Pulmonary Disease Free of Inhaled Corticosteroids: The EMAX Trial

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Background

- Long-acting muscarinic antagonist/long-acting β_2-agonist (LAMA/LABA) combination therapy may be considered as initial therapy in symptomatic patients with chronic obstructive pulmonary disease (COPD) with low exacerbation risk who experience severe breathlessness, or as stepwise additions from monotherapy in patients who remain symptomatic or experience exacerbations.[1]
- LAMA/LABAs provide incremental improvements in symptoms versus monotherapy. However, the magnitude of this benefit remains uncertain because between-class comparator trials have consistently included patients using concurrent inhaled corticosteroids (ICS),[2-6] which may confound efficacy comparisons between therapies.[7,8]
- Consequently, trials of dual- versus mono-bronchodilator therapy in ICS-free low-risk patients are needed.
- The Early MAXimization of bronchodilation for improving COPD stability (EMAX) trial was thus designed to compare umeclidinium/vilanterol (UMEC/VI), UMEC, and salmeterol (SAL) in symptomatic ICS-free patients at low exacerbation risk.

Methods

Study design

- This 24-week, double-blind, parallel-group study randomized patients 1:1:1 to UMEC/VI 62.5/25 mcg once daily via ELLIPTA inhaler, UMEC 62.5 mcg once daily via ELLIPTA inhaler or SAL 50 mcg twice daily via DISKUS inhaler.
- Eligible patients were ≥40 years of age, ICS and LAMA/LABA free, current/former smokers (≥10 pack-years smoking history), with a COPD diagnosis,[9] and had a pre- and post-albuterol forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio of <0.7, a post-albuterol FEV_1 ≥30%–≤80% predicted, a history of ≤1 moderate exacerbation (and no severe exacerbations) in the previous year, and a COPD Assessment Test (CAT) score ≥10.

Endpoints

- This study was powered to detect an 80 mL difference in trough FEV_1 with UMEC/VI versus UMEC (primary endpoint) and a 0.5 unit difference in Self-administered Computerized Transition Dyspnea Index (SAC-TDI) at 24 weeks.
- Additional spirometry assessments included trough FEV_1, FVC, and inspiratory capacity (IC) over 24 weeks.
- Patient-reported symptoms were evaluated over 24 weeks using Evaluating Respiratory Symptoms-COPD (E-RS) score, rescue albuterol use, and Subject Global Rating of Change in COPD Severity (SGRSI). Health status was assessed using St George's Respiratory Questionnaire (SGRQ) and CAT scores.
- Risk of a first moderate/severe exacerbation was assessed over 24 weeks.
- Adverse events (AEs) were also captured.

Statistical analysis

- Pairwise statistical comparisons between UMEC/VI and both monotherapies were calculated for least squares (LS) mean change from baseline and proportion of responders.

Results

Patients

- The intent-to-treat (ITT) population included 2425 patients (UMEC/VI: 812; UMEC: 804; SAL: 809). In total, 375 (15%) patients withdrew from the study (UMEC/VI: 95 [12%]; UMEC: 154 [19%]; SAL: 126 [16%]). Demographics and baseline characteristics were similar between treatment arms (**Table 1**).

Lung function

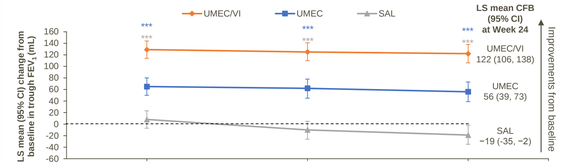
- Change from baseline in trough FEV_1 at Week 24 was significantly greater for UMEC/VI versus UMEC and versus SAL (**Figure 1**).
- UMEC/VI also demonstrated greater LS mean (95% confidence interval [CI]) improvements at Week 24 versus UMEC and SAL in trough FVC (vs UMEC: 79 mL [42, 116], *P*<0.001; vs SAL: 189 mL [152, 225], *P*<0.001) and IC (vs UMEC: 41 mL [4, 77], *P*=0.028; vs SAL: 116 mL [80, 152], *P*<0.001).

Table 1. Patient demographics and clinical characteristics

Characteristic	UMEC/VI (N=812)	UMEC (N=804)	SAL (N=809)	Total (N=2425)
Age, years, mean (SD)	64.6 (8.4)	64.9 (8.5)	64.4 (8.5)	64.6 (8.5)
Female, n (%)	319 (39)	327 (41)	342 (42)	988 (41)
Current smoker at screening, n (%)	394 (49)	396 (49)	413 (51)	1203 (50)
Smoking pack-years, mean (SD)	49.4 (27.7)	47.6 (25.9)	48.1 (25.8)	48.4 (26.5)
Post-albuterol FEV_1, mL, mean (SD)	1577 (506)	1609 (503)	1600 (523)	1595 (511)
Post-albuterol % predicted FEV_1, mean (SD)	54.9 (12.8)	55.9 (12.6)	55.6 (12.8)	55.4 (12.7)
Post-albuterol FEV_1/FVC, mean (SD)	0.51 (0.10)	0.52 (0.10)	0.52 (0.10)	0.52 (0.10)
% reversibility to albuterol, mean (SD)	10.4 (12.8)	10.2 (13.3)	10.7 (13.3)	10.5 (13.1)
One moderate COPD exacerbation history in prior year*, n (%)	123 (15)	124 (15)	146 (18)	393 (16)
GOLD grade†, n (%)				
2	518 (64)	529 (66)	522 (65)	1569 (65)
3	294 (36)	271 (34)	286 (35)	851 (35)
COPD duration, years, mean (SD)	8.8 (6.9)	7.8 (6.0)	8.3 (6.7)	8.3 (6.6)
Baseline FEV_1, mL, mean (SD)	1474 (513)	1503 (505)	1495 (533)	1491 (517)
BDI score, mean (SD)	7.0 (1.8)	7.0 (1.9)	7.1 (1.8)	7.01 (1.9)
Baseline CAT score, mean (SD)	19.0 (6.0)	19.3 (6.0)	19.2 (5.9)	19.2 (6.0)
Baseline rescue albuterol, puffs/day, mean (SD)	2.18 (2.55)	2.13 (2.35)	2.17 (2.48)	2.16 (2.46)

*Number of exacerbations requiring oral or systemic corticosteroids and/or antibiotics in 12 months prior to screening (patients with >1 moderate exacerbation or with a severe exacerbation [requiring hospitalization] were excluded).
†An additional 4 patients (<1%) with GOLD grade 1 were randomized (UMEC n=3; SAL n=1).
BDI, baseline dyspnea index; GOLD, Global initiative for chronic Obstructive Lung Disease; SD, standard deviation

Figure 1. LS mean change from baseline in spirometry endpoints at Week 24



	Difference (95% CI)		
UMEC/VI vs UMEC	64 mL (44, 85)	64 mL (41, 86)	66 mL (43, 89)
UMEC/VI vs SAL	121 mL (100, 142)	136 mL (114, 158)	141 mL (118, 164)

***P<0.001. Week 4 UMEC/VI: n=764; UMEC: n=719; SAL: n=732. Week 12 UMEC/VI: n=730; UMEC: n=672; SAL: n=689. Week 24 UMEC/VI: n=691; UMEC: n=621; SAL: n=654. CFB, change from baseline

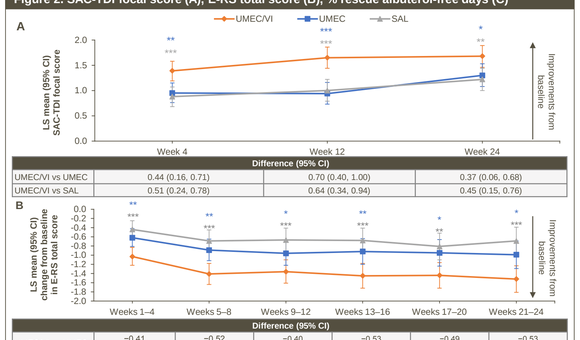
Patient-reported symptoms

- At all time points, UMEC/VI demonstrated significantly greater improvements from baseline in SAC-TDI, E-RS score, and percentage of rescue albuterol-free days versus both monotherapies (**Figure 2**).
- LS mean (95% CI) in SAC-TDI at Week 24 was 1.68 (1.46, 1.89) for UMEC/VI, 1.30 (1.08, 1.53) for UMEC, and 1.22 (1.00, 1.44) for SAL.
- The proportion of SAC-TDI responders at Week 24, E-RS responders at Weeks 21–24, and ordered odds for an improved response using SGRSI at Week 24 all significantly favored UMEC/VI versus UMEC and SAL (**Figure 3**).

Health-related quality of life

- At Week 24, SGRQ response rates significantly favored UMEC/VI versus SAL but not versus UMEC (**Figure 3**).
- Response rates for CAT at Week 24 were significantly greater with UMEC/VI versus both monotherapies (**Figure 3**).

Figure 2. SAC-TDI focal score (A), E-RS total score (B), % rescue albuterol-free days (C)

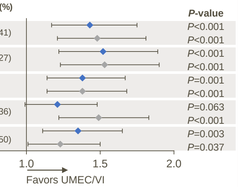


Difference (95% CI)						
UMEC/VI vs UMEC	0.44 (0.16, 0.71)		0.70 (0.40, 1.00)		0.37 (0.06, 0.68)	
UMEC/VI vs SAL	0.51 (0.24, 0.78)		0.64 (0.34, 0.94)		0.45 (0.15, 0.76)	
Difference (95% CI)						
UMEC/VI vs UMEC	−0.41 (−0.69, −0.13)	−0.52 (−0.86, −0.19)	−0.40 (−0.76, −0.04)	−0.53 (−0.92, −0.14)	−0.49 (−0.90, −0.09)	−0.53 (−0.95, −0.11)
UMEC/VI vs SAL	−0.58 (−0.86, −0.31)	−0.72 (−1.05, −0.39)	−0.69 (−1.05, −0.32)	−0.77 (−1.15, −0.38)	−0.63 (−1.04, −0.23)	−0.83 (−1.25, −0.42)
Difference (95% CI)						
UMEC/VI vs UMEC	5.48 (2.62, 8.33)	6.18 (3.03, 9.33)	5.16 (1.88, 8.44)	5.67 (2.28, 9.06)	7.11 (3.68, 10.55)	5.44 (1.91, 8.97)
UMEC/VI vs SAL	4.17 (1.32, 7.02)	4.80 (1.66, 7.94)	5.20 (1.93, 8.47)	5.05 (1.66, 8.43)	5.53 (2.11, 8.95)	3.53 (0.01, 7.04)

*P<0.05, **P<0.01, ***P<0.001. **(A)** Week 4 UMEC/VI: n=788; UMEC: n=753; SAL: n=764. Week 12 UMEC/VI: n=751; UMEC: n=699; SAL: n=714. Week 24 UMEC/VI: n=704; UMEC: n=636; SAL: n=673. **(B)** Weeks 1–4 UMEC/VI: n=792; UMEC: n=769; SAL: n=789. Weeks 5–8 UMEC/VI: n=769; UMEC: n=737; SAL: n=751. Weeks 9–12 UMEC/VI: n=755; UMEC: n=718; SAL: n=726. Weeks 13–16 UMEC/VI: n=729; UMEC: n=678; SAL: n=700. Weeks 17–20 UMEC/VI: n=712; UMEC: n=655; SAL: n=683. Weeks 21–24 UMEC/VI: n=677; UMEC: n=621; SAL: n=653. **(C)** Weeks 1–4 UMEC/VI: n=810; UMEC: n=799; SAL: n=805. Weeks 5–8 UMEC/VI: n=789; UMEC: n=759; SAL: n=770. Weeks 9–12 UMEC/VI: n=775; UMEC: n=737; SAL: n=748. Weeks 13–16 UMEC/VI: n=752; UMEC: n=702; SAL: n=723. Weeks 17–20 UMEC/VI: n=734; UMEC: n=683; SAL: n=701. Weeks 21–24 UMEC/VI: n=718; UMEC: n=665; SAL: n=688.

Figure 3. Proportion of responders for symptom severity and health-related quality of life outcomes

Outcome	UMEC/VI, n/N (%)	UMEC, n/N (%)	SAL, n/N (%)	*P*-value
SAC-TDI*	403/806 (50)	332/799 (42)	330/807 (41)	*P*<0.001
				P<0.001
E-RS†	290/809 (36)	219/800 (27)	217/808 (27)	*P*<0.001
				P<0.001
SGRSI‡	-	-	-	*P*=0.001
				P<0.001
SGRQ§	366/811 (45)	329/802 (41)	291/809 (36)	*P*=0.063
				P<0.001
CAT‖	447/812 (55)	385/804 (48)	406/809 (50)	*P*=0.003
				P=0.037



◆ UMEC/VI vs UMEC ◆ UMEC/VI vs SAL

*SAC-TDI responders were defined as a ≥1-unit improvement from baseline; †E-RS responders were defined as a reduction of ≥2 from baseline; ‡overall assessment of change in COPD severity was rated using a seven-point Likert scale ('Much Better', 'Slightly Better', 'Better', 'No Change', 'Slightly Worse', 'Worse', 'Much Worse'), ordered response ratios were reported as odds of better response category; §SGRQ responders were defined as a ≥4-point reduction from baseline; ‖CAT responders were defined as a ≥2-unit improvement from baseline.
n/N, number of responders/number of patients with analyzable data

Exacerbations

- The risk of a moderate/severe exacerbation to Day 168 was 13%, 16%, and 19% for UMEC/VI, UMEC, and SAL, respectively; UMEC/VI reduced the risk of a moderate/severe exacerbation by 19% (hazard ratio [HR] [95% CI]: 0.81 [0.62, 1.05]; *P*=0.11) versus UMEC and 36% (HR [95% CI]: 0.64 [0.50, 0.83]; *P*<0.001) versus SAL, although significance was only reached versus SAL.

Safety

- Incidences of AEs and non-fatal serious AEs (SAEs) were similar across treatment groups (**Table 2**).
- No SAEs (fatal or non-fatal) were considered drug-related.

Table 2. Safety outcomes

	UMEC/VI (N=812)	UMEC (N=804)	SAL (N=809)
AE, n (%)			
AE	315 (39)	316 (39)	314 (39)
Drug-related AE	29 (4)	37 (5)	27 (3)
AE leading to study withdrawal	32 (4)	36 (4)	26 (3)
SAE, n (%)			
Non-fatal SAE	46 (6)	31 (4)	38 (5)
Fatal SAE*	4 (<1)	4 (<1)	0
Drug-related SAE	0	0	0
Most frequent AEs†, n (%)			
Nasopharyngitis	68 (8)	87 (11)	84 (10)
Upper respiratory tract infection	19 (2)	12 (1)	20 (2)
Influenza	20 (2)	9 (1)	18 (2)
Back pain	10 (1)	13 (2)	15 (2)
Cough	14 (2)	11 (1)	10 (1)
Headache	10 (1)	17 (2)	6 (<1)

*Consistent with previous studies, the incidence of fatal cardiovascular SAEs was <1% in all treatment groups, with three cardiac disorders observed in the UMEC/VI arm and one in the UMEC arm (one acute myocardial infarction in each treatment group); †includes all on-treatment AEs occurring in ≥2% of any treatment group.

Conclusions

- In symptomatic ICS-free patients with low exacerbation risk, UMEC/VI provided consistent improvements from the first month in lung function and a range of COPD symptom measures versus UMEC and SAL.
- The incremental efficacy benefits of UMEC/VI, with no additional safety concerns, demonstrate the potential for early intensification of bronchodilation with LAMA/LABAs in symptomatic low-risk patients, without the requirement for ICS.

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Disclosures

IN, IB, DAL, CC, and PJ are employees of GlaxoSmithKline (GSK) and hold stocks and shares in GSK. MLW was an employee of GSK at the time of the study. LT is a contingent worker on assignment at GSK. FM has received research grants for participating in multicenter trials for AstraZeneca, Boehringer Ingelheim, GSK, Sanofi, and Novartis, and has received unrestricted research grants and personal fees from Boehringer Ingelheim, Grifols, and Novartis. LB has received honoraria for giving a lecture or attending an advisory board for Airsonett, ALK-Abello, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Meda, Novartis, and Teva. EMK has attended advisory boards for Amphastar, Boehringer Ingelheim, Cipla, GSK, Mylan, Novartis, Sunovion, Teva, and Theravance and has received personal fees from Boehringer Ingelheim, Forest, Novartis, Teva, and Theravance. CFV has been an advisor for and/or received personal fees and/or grants from AstraZeneca, Bayer-Schering, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, GSK, Grifols, Menarini, MSD, Mundipharma, Novartis, Pfizer, and Teva. ELLIPTA and DISKUS are owned by or licensed to the GSK group of companies.

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