Comparative Efficacy and Safety of Umeclidinium/Vilanterol, Umeclidinium, and Salmeterol in Symptomatic Maintenance-Naïve and Maintenance-Treated Chronic Obstructive Pulmonary Disease: A Pre-specified Secondary Analysis of the EMAX Trial

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Background

- Long-acting muscarinic antagonist (LAMA) or long-acting β_2-agonist (LABA) monotherapy is recommended as first-line maintenance therapy in symptomatic patients with chronic obstructive pulmonary disease (COPD) at low exacerbation risk.[1]
- LAMA/LABA combinations are recommended as first-line maintenance for patients with severe breathlessness or as a step-up option.[1] These recommendations have been formulated without prospective data on bronchodilator efficacy in maintenance-naïve (MN) patients.
- This was a pre-specified subgroup analysis of LAMA/LABA versus LAMA and LABA monotherapy in the Early MAXimization of bronchodilation for improving COPD stability (EMAX) trial. Prospective lung function and symptom outcomes were compared between umeclidinium/vilanterol (UMEC/VI), UMEC, and salmeterol (SAL) in both maintenance-treated (MT) and MN patients to investigate whether early intensification of bronchodilation is effective and well tolerated in these patients.
- Analyses in the intent-to-treat (ITT) population demonstrated early and sustained improvements in lung function and symptom outcomes with UMEC/VI versus both UMEC and SAL.[2] The risk of a first moderate/severe exacerbation was also reduced with UMEC/VI versus SAL in the ITT population.[2]

Methods

- This 24-week, multicenter, double-blind, double-dummy, 3-arm parallel-group trial randomized patients 1:1:1 to once-daily UMEC/VI 62.5/25 mcg, once-daily UMEC 62.5 mcg, or twice-daily SAL 50 mcg.
- Patients were current or former smokers, ≥40 years of age who were inhaled corticosteroid-free for ≥10 weeks prior to randomization, with a post-albuterol forced expiratory volume in one second (FEV_1) ≥30%–≤80%, FEV_1/forced vital capacity (FVC) ratio <0.7, COPD Assessment Test (CAT) score ≥10, and ≤1 moderate exacerbation in the last year.
- In the ≥30-day period prior to screening, MT patients had one maintenance medication, a LAMA or a LABA bronchodilator, while MN patients received no COPD maintenance medications apart from short-acting bronchodilators as rescue therapy. Randomization was stratified by use of maintenance bronchodilator at baseline (yes/no).
- Lung function endpoints were trough FEV_1, trough FVC, and trough inspiratory capacity (IC).
- Symptom outcomes were self-administered computerized Transition Dyspnea Index (TDI) score, daily Evaluating Respiratory Symptoms (E-RS) total score, inhalations/day of rescue medication use and percentage of rescue medication-free days.
- Risk of a first moderate/severe exacerbation was also evaluated.

Results

Study population

- In total, 1676 (69%) MT patients and 749 (31%) MN patients were randomized and received at least one dose of study medication.
- Compared with the MT subgroup, the MN subgroup had a higher proportion of current smokers (66% vs 42%) were more symptomatic with a mean CAT score of 20.9 (vs 18.4), and a higher mean daily use of albuterol (2.8 vs 1.9 inhalations). Fewer MN patients compared with MT patients had a moderate exacerbation in the previous year (10% vs 19%) (**Table 1**).

Lung function outcomes

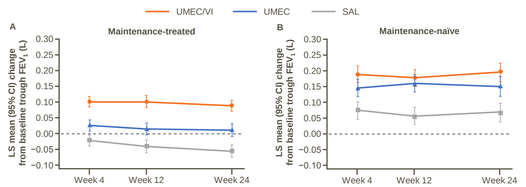
- Significantly greater improvements in FEV_1 with UMEC/VI versus UMEC and SAL were observed at Week 4 and sustained at Week 24 in both the MT and MN subgroups (**Figures 1 and 2**).
- At Week 24, the odds (95% confidence intervals [CI]) of a clinically important response on trough FEV_1 (≥100 mL change from baseline) were significantly higher in patients with UMEC/VI versus UMEC (2.22 [1.71, 2.89]) and SAL (3.79 [2.85, 5.05]) in the MT subgroup, and versus SAL (2.38 [1.64, 3.44]) in the MN subgroup (post hoc analysis, $P<0.001$).
- In the MT subgroup, mean increase from baseline in trough FVC and IC at Week 24 was significantly greater with UMEC/VI versus UMEC and SAL ($P<0.05$). In the MN subgroup, change from baseline in trough FVC and IC at Week 24 were significantly greater with UMEC/VI versus SAL. For UMEC/VI versus UMEC the difference in trough FVC was statistically significant; however, the increase in trough IC was not (**Figure 2**).

Table 1. Demographics and baseline characteristics

	ITT (N=2425)	Maintenance-treated (N=1676)	Maintenance-naïve (N=749)
Age, years, mean (SD)	64.6 (8.5)	65.4 (8.4)	63.0 (8.3)
Female, n (%)	988 (41)	645 (38)	343 (46)
Current smoker, n (%)	1203 (50)	710 (42)	493 (66)
Smoking pack-years, mean (SD)	48.4 (26.5)	47.7 (27.0)	49.9 (25.2)
Duration of COPD, years, mean (SD)	8.3 (6.6)	8.3 (6.5)	8.3 (6.8)
Moderate COPD exacerbation in past 12 months*, n (%)	393 (16)	316 (19)	77 (10)
Post-albuterol percent predicted FEV_1, mean (SD)	55.4 (12.7)	54.7 (12.9)	57.0 (12.3)
Post-albuterol FEV_1/FVC, mean (SD)	0.52 (0.10)	0.51 (0.10)	0.54 (0.10)
Percent reversibility to albuterol, mean (SD)	10.5 (13.1)	9.4 (13.1)	12.8 (12.8)
GOLD grade†, n (%)			
2	1569 (65)	1043 (62)	526 (70)
3	851 (35)	629 (38)	222 (30)
BDI focal score, mean (SD)	7.0 (1.9)	7.0 (1.8)	7.1 (2.0)
Baseline CAT score, mean (SD)	19.2 (6.1)	18.4 (5.5)	20.9 (6.5)
Baseline rescue medication use, mean puffs per day (SD)	2.2 (2.5)	1.9 (2.1)	2.8 (3.0)

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

Figure 1. LS mean change from baseline in trough FEV_1 over 24 weeks in (A) MT and (B) MN subgroups



UMEC/VI treatment difference, mL (95 CI)			
UMEC	75 (50, 100)	86 (59, 114)	77 (50, 104)
SAL	122 (98, 147)	141 (114, 168)	145 (118, 172)

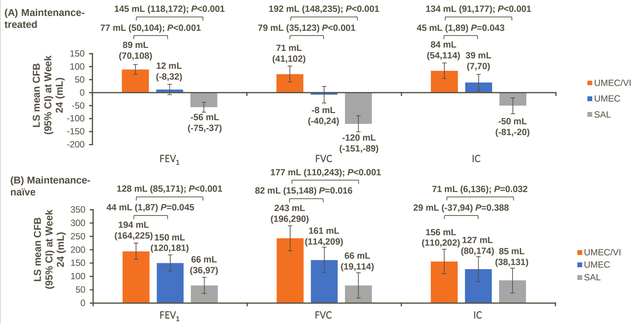
UMEC/VI treatment difference, mL (95 CI)			
UMEC	44 (5, 83)	16 (-23, 54)	44 (1, 87)
SAL	116 (77, 155)	120 (82, 159)	128 (85, 171)

Analysis performed using mixed model repeated measures with covariates of baseline FEV_1, geographical region, visit, treatment, visit by baseline and visit by treatment interactions, where visit is nominal. LS, least squares

Symptoms, rescue medication use, and exacerbation risk

- With all treatments, improvements were seen in change from baseline for symptom and rescue medication outcomes at Week 24, with particularly large improvements in the MN subgroup (**Table 2**).
- Statistically significant treatment differences in breathlessness (TDI focal score) were observed with UMEC/VI versus UMEC and SAL in MT patients at Week 24. Increases in TDI focal score were similar in magnitude in the MN subgroup, but did not reach statistical significance (**Table 2**).
- There were significant treatment differences in ER-S total score during Weeks 21–24 with UMEC/VI versus UMEC and SAL in MT patients, but these did not reach statistical significance in MN patients (**Table 2**).
- Statistically significant reductions in the mean rescue medication inhalations/day were observed with UMEC/VI versus UMEC and SAL in the MT and MN subgroups during Weeks 1–24 and significant increases in the percentage of rescue medication-free days were observed with UMEC/VI versus UMEC and SAL in the MN subgroup, but only versus UMEC in the MT subgroup (**Table 2**).
- The risk of a first moderate/severe exacerbation was significantly lower with UMEC/VI versus SAL in the MT and MN subgroups, but did not reach statistical significance for UMEC/VI versus UMEC in either subgroup (**Table 2**).

Figure 2. LS mean change from baseline in trough FEV_1, FVC and IC in (A) MT and (B) MN subgroups



Analysis performed using mixed model repeated measures with covariates of baseline FEV_1, FVC or IC, geographical region, visit, treatment, visit by baseline and visit by treatment interactions, where visit is nominal.
CFB, change from baseline

Table 2. Symptom severity, rescue use and exacerbation outcomes

	Maintenance-treated			Maintenance-naïve		
	UMEC/VI (N=562)	UMEC (N=554)	SAL (N=560)	UMEC/VI (N=250)	UMEC (N=250)	SAL (N=249)
TDI focal score*, Week 24, N LS mean CFB (95% CI) UMEC/VI vs comparator *P*-value	494 1.52 (1.27, 1.77)	439 1.13 (0.87, 1.39) 0.39 (0.03, 0.75) *P*=0.034	467 1.08 (0.83, 1.34) 0.44 (0.08, 0.79) *P*=0.017	210 2.03 (1.62, 2.43)	197 1.65 (1.24, 2.07) 0.37 (-0.21, 0.96) *P*=0.210	206 1.55 (1.14, 1.96) 0.47 (-0.10, 1.05) *P*=0.108
E-RS total score†, Weeks 21–24, N LS mean CFB (95% CI) UMEC/VI vs comparator *P*-value	478 -1.18 (-1.52, -0.84)	432 -0.52 (-0.88, -0.17) -0.66 (-1.15, -0.17) *P*=0.009	453 -0.24 (-0.59, 0.11) -0.94 (-1.43, -0.45) *P*<0.001	199 -2.27 (-2.83, -1.72)	189 -2.02 (-2.58, -1.46) -0.26 (-1.04, 0.53) *P*=0.524	200 -1.79 (-2.25, -1.14) -0.58 (-1.36, 0.20) *P*=0.148
Inhalations/day of rescue albuterol‡, Weeks 1–24, N LS mean CFB (95% CI) UMEC/VI vs comparator *P*-value	560 -0.31 (-0.43, -0.20)	550 -0.03 (-0.15, 0.09) -0.28 (-0.45, -0.12) *P*<0.001	556 -0.06 (-0.18, 0.05) -0.25 (-0.41, -0.08) *P*=0.003	250 -1.26 (-1.46, -1.06)	249 -0.82 (-1.02, -0.62) -0.44 (-0.73, -0.16) *P*=0.002	249 -0.89 (-1.09, -0.69) -0.37 (-0.66, -0.09) *P*=0.010
Percentage of rescue albuterol-free days§, Weeks 1–24, N LS mean CFB (95% CI) UMEC/VI vs comparator *P*-value	560 8.23 (5.77, 10.68)	550 4.45 (1.96, 6.94) 3.78 (0.28, 7.27) *P*=0.034	556 4.97 (2.49, 7.44) 3.26 (-0.23, 6.74) *P*=0.067	250 21.83 (17.80, 25.86)	249 11.25 (7.21, 15.29) 10.59 (4.88, 16.29) *P*<0.001	249 13.57 (9.53, 17.61) 8.26 (2.55, 13.97) *P*=0.005
Moderate/severe exacerbation‖, n (%) UMEC/VI vs comparator HR (95% CI) *P*-value	80 (14)	94 (17) 0.78 (0.58, 1.05) *P*=0.098	111 (20) 0.67 (0.50, 0.89) *P*=0.006	21 (8)	22 (9) 0.92 (0.51, 1.68) *P*=0.791	35 (14) 0.58 (0.34, 1.00) *P*=0.049

*TDI analysis performed using MMRM with covariates of BDI focal score, geographical region, visit, treatment, visit by self-administered computerized BDI and visit by treatment interactions, where visit is nominal; †E-RS analysis performed using MMRM with covariates of baseline score, geographical region, 4-weekly period, treatment, 4-weekly period by baseline, and 4-weekly period by treatment interactions; ‡inhalations/day of rescue-free days analysis performed using MMRM with covariates of baseline number of inhalations, geographical region, 4-weekly period, treatment, 4-weekly period by baseline and 4-weekly period by treatment interactions; §percentage of rescue-free days analysis performed using MMRM with covariates of baseline percentage of rescue-free days, geographical region, 4-weekly period, treatment, 4-weekly period by baseline, and 4-weekly period by treatment interactions; ‖exacerbation HR and 95% CI are based on a Cox proportional hazards model with covariates of treatment and geographical region.
HR, hazard ratio; MMRM, Mixed effect model repeat measurement

Safety

- The incidence of on-treatment adverse events (AEs) and serious AEs (SAEs) was similar between the MN and MT subgroups and treatment groups (**Table 3**).
- Fatal SAEs were reported in the MT subgroup, and not in the MN subgroup; however, no fatal or non-fatal SAEs were considered related to the study medication.

Table 3. Adverse events

	Maintenance-treated			Maintenance-naïve		
	UMEC/VI (N=562)	UMEC (N=554)	SAL (N=560)	UMEC/VI (N=250)	UMEC (N=250)	SAL (N=249)
AE, n (%)						
AE	221 (39)	220 (40)	213 (38)	94 (38)	96 (38)	101 (41)
Drug-related AE	20 (4)	25 (5)	15 (3)	9 (4)	12 (5)	12 (5)
AE leading to study withdrawal	21 (4)	26 (5)	17 (3)	11 (4)	10 (4)	9 (4)
SAE, n (%)						
Non-fatal SAE	34 (6)	16 (3)	25 (4)	12 (5)	15 (6)	13 (5)
Fatal SAE*	4 (<1)	4 (<1)	0	0	0	0
Drug-related SAE	0	0	0	0	0	0
AEs occurring in ≥2% of patients on any treatment, n (%)						
Nasopharyngitis	54 (10)	72 (13)	65 (12)	14 (6)	15 (6)	19 (8)
URTI	9 (2)	4 (<1)	11 (2)	10 (4)	8 (3)	9 (4)
Influenza	14 (2)	7 (1)	10 (2)	6 (2)	2 (<1)	8 (3)
Back pain	7 (1)	7 (1)	10 (2)	3 (1)	6 (2)	5 (2)
Cough	11 (2)	6 (1)	7 (1)	3 (1)	5 (2)	3 (1)
Sinusitis	-	-	-	2 (<1)	3 (1)	5 (2)
Oropharyngeal pain	-	-	-	2 (<1)	6 (2)	3 (1)
Headache	8 (1)	12 (2)	4 (<1)	2 (<1)	5 (2)	2 (<1)
Nausea	-	-	-	1 (<1)	7 (3)	3 (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).
URTI, upper respiratory tract infection

Conclusions

- The Global initiative for chronic Obstructive Lung Disease strategy recommends that patients with symptomatic COPD should receive maintenance bronchodilation, yet 31% of patients in this study were MN and therefore undertreated.
- In this pre-specified subgroup analysis of the EMAX trial, UMEC/VI was well tolerated and provided statistically significant, clinically important improvements in lung function versus UMEC and SAL in both MT and MN subgroups.
- These preliminary findings provide the first prospective data of the potential efficacy benefit of LAMA/LABA versus LAMA and LABA monotherapy as initial maintenance therapy.

References

1. Global initiative for chronic Obstructive Lung Disease (GOLD). 2019; 2. Maltais F, et al. *ATS 2019*; Poster P212 (A2446), Session A102, May 19

Disclosures

PJ, IN, IB, DAL, and CC 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. EK 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.

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