ORIGINAL RESEARCH

Efficacy and Safety of Umeclidinium/Vilanterol in Current and Former Smokers with COPD: A Prespecified Analysis of The EMAX Trial

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ABSTRACT

Introduction: Smoking may reduce the efficacy of inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD), but its impact on bronchodilator efficacy is unclear. This analysis of the EMAX trial explored efficacy and safety of dual- versus mono-bronchodilator therapy in current or former smokers with COPD.

Methods: The 24-week EMAX trial evaluated lung function, symptoms, health status, exacerbations, clinically important deterioration, and safety with umeclidinium/vilanterol, umeclidinium, and salmeterol in symptomatic patients at low exacerbation risk who were not receiving ICS. Current and former smoker subgroups were defined by smoking status at screening.

Results: The analysis included 1203 (50%) current smokers and 1221 (50%) former smokers. Both subgroups demonstrated greater improvements from baseline in trough FEV_1 at week 24 (primary endpoint) with umeclidinium/vilanterol versus umeclidinium (least squares [LS] mean difference, mL [95% CI]; current: 84 [50, 117]; former: 49 [18, 80]) and salmeterol (current: 165 [132, 198]; former: 117

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[86, 148]) and larger reductions in rescue medication inhalations/day over 24 weeks versus umeclidinium (LS mean difference [95% CI]; current: -0.42 [-0.63, -0.20]; former: -0.25 -0.44, -0.05]) and salmeterol (current: -0.28 [-0.49, -0.06]; former: -0.29 [-0.49, -0.09]). Umeclidinium/vilanterol increased the odds (odds ratio [95% CI]) of clinically significant improvement at week 24 in Transition Dyspnea Index versus umeclidinium (current: 1.54 [1.16, 2.06]; former: 1.32 [0.99, 1.75]) and salmeterol (current: 1.37 (1.03, 1.82); former: 1.60 [1.20, 2.13]) and Evaluating Respiratory Symptoms–COPD versus umeclidinium (current: 1.54 [1.13, 2.09]; former: 1.50 [1.11, 2.04]) and salmeterol (current: 1.53 [1.13, 2.08]; former: 1.53 [1.12, 2.08]). All treatments were well tolerated in both subgroups.

Conclusions: In current and former smokers, umeclidinium/vilanterol provided greater improvements in lung function and symptoms versus umeclidinium and salmeterol, supporting consideration of dual-bronchodilator therapy in symptomatic patients with COPD regardless of their smoking status.

PLAIN LANGUAGE SUMMARY

Patients with chronic obstructive pulmonary disease (COPD) often require daily medication to control their COPD. Many patients with COPD are smokers, and smoking is one of the most common causes of COPD. This means that it is important to find out whether COPD medications are effective in both smokers and nonsmokers. We analyzed data from a clinical trial (EMAX) that investigated the use of a combination of two bronchodilators, which are inhaled medications that help to open the airways. We compared umeclidinium/vilanterol, a dual-bronchodilator combination, with a single bronchodilator (either umeclidinium or salmeterol) over 6 months. We found that both current and former smokers who were treated with umeclidinium/vilanterol had larger improvements in lung function than those receiving umeclidinium or salmeterol. Current or former smokers who were treated with umeclidinium/vilanterol used their reliever inhaler less than those treated with umeclidinium or salmeterol. Patients treated with umeclidinium/vilanterol were generally less likely to experience disease worsening compared with umeclidinium or salmeterol if they were former smokers, or compared with salmeterol if they were current smokers. Our findings suggest that umeclidinium/vilanterol may be more effective than a single bronchodilator for daily treatment of patients with COPD who are current or former smokers. Physicians should consider prescribing a combination of two bronchodilators to patients who have symptoms, whether or not they currently smoke, as well as encouraging smoking cessation for all patients.

Key Summary Points

Why carry out this study?

Clinical trials have demonstrated significantly greater improvements in lung function, symptoms, and health-related quality of life with long-acting muscarinic antagonist/long-acting β₂-agonist (LAMA/LABA) dual therapies compared with LAMA or LABA monotherapies; however, few studies have explored the efficacy of these treatments in current and former smokers with chronic obstructive pulmonary disease (COPD).

This prespecified analysis of the randomized, double-blind EMAX trial explored the efficacy and safety of umeclidinium/vilanterol (UMEC/VI) compared with UMEC or salmeterol (SAL) in current and former smokers.

What was learned during this study?

Improvements in lung function and reductions in rescue medication use were seen in both current and former smokers receiving UMEC/VI compared with those treated with UMEC or SAL.

These findings suggest that dual-bronchodilator therapy may be an appropriate treatment option for patients with symptomatic COPD irrespective of their smoking status.

INTRODUCTION

In patients with chronic obstructive pulmonary disease (COPD), poorly controlled symptoms are associated with worse health-related quality of life, increased risk of COPD exacerbations, and a poor disease prognosis [1–3]. Smoking is one of the most prominent risk factors for COPD, and the prevalence of COPD is higher in current and former smokers than in nonsmokers [4]. Among patients with COPD, current smokers have a greater rate of decline in lung function than former smokers [5, 6], and smoking also has an impact on COPD symptoms and health status [7, 8]. Smoking cessation can reduce long-term mortality risk [9] and is therefore an important element of COPD management, along with pharmacological maintenance therapy for many patients [4, 10]. However, it remains unclear how the efficacy of maintenance treatment for COPD is affected by patients' smoking behavior.

Long-acting bronchodilators are recommended for most patients requiring maintenance therapy for COPD [4, 10]. Many patients remain symptomatic during treatment with one long-acting bronchodilator [11], suggesting a need for additional therapy. Analyses of clinical trial data have demonstrated greater improvements in lung function, symptoms, and health status with long-acting muscarinic antagonist/long-acting β₂-agonist (LAMA/LABA) dual therapy compared with LAMA or LABA monotherapy [12–15]. The efficacy of inhaled corticosteroid (ICS) treatment in patients with COPD appears to be impaired by smoking, but the effect of smoking on the efficacy of bronchodilators is less well understood. A post hoc analysis of the 12-month SUMMIT trial showed blunted improvement in lung function with ICS and ICS/LABA versus placebo, as well as a smaller reduction in exacerbation rates with ICS/LABA versus placebo, among current smokers compared with former smokers [16]. A systematic review of seven clinical trials (including SUMMIT) also found that current smokers gained less benefit from ICS-containing therapy than former smokers [17]. In contrast, the SUMMIT analysis showed similar benefits of the LABA vilanterol versus placebo between current and former smokers [16]. The LAMAs tiotropium and glycopyrronium have also demonstrated improvements in lung function and health-related quality of life compared with placebo in both current and former smokers [18, 19]. Similarly, in a post hoc analysis of the FLIGHT studies, improvements in lung function, symptoms, and health status observed with the LAMA/LABA indacaterol/

glycopyrronium compared with its constituent monotherapies and placebo after 12 weeks of treatment were similar between current and former smokers [20]. Taken together this evidence suggests that, in contrast with ICS-containing therapy, the efficacy of bronchodilator therapy is less affected by patients' smoking status.

The aim of this prespecified analysis of the EMAX trial was to evaluate the efficacy and safety of umeclidinium/vilanterol in current and former smokers with COPD. We hypothesized that both current smokers and former smokers would achieve greater improvements in lung function, symptoms, and health status with umeclidinium/vilanterol (UMEC/VI) compared with UMEC and salmeterol (SAL). In addition, we explored whether the magnitude of improvements from baseline with UMEC/VI, UMEC, or SAL was similar in current and former smokers.

METHODS

Study Design and Ethical Approval

EMAX was a multicenter, double-blind, double-dummy, three-arm parallel-group trial, in which patients were randomized 1:1:1 to 24 weeks of once-daily UMEC/VI (62.5/25 µg) via the ELLIPTA inhaler, once-daily UMEC (62.5 µg) via ELLIPTA, or twice-daily SAL (50 µg) via the DISKUS inhaler. The trial began in June 2017 and was completed in June 2018. Full details of the trial methodology have been published previously [21].

The EMAX trial was conducted in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments, and received appropriate ethical approval (Supplementary Table S1). Patients provided written informed consent at the pre-screening or screening visit.

Patients

Eligible patients were at least 40 years of age and were current/former smokers with a COPD diagnosis, pre- and post-albuterol forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio < 0.7, post-albuterol FEV_1 of at least 30% to at most 80% predicted (Global Initiative for Chronic Obstructive Lung Disease [GOLD] grade 2/3), COPD Assessment Test (CAT) score $\geq$ 10, and at most one moderate and no severe exacerbations in the previous year. Prior to screening and during the 4-week run-in period, treatment with at most one maintenance bronchodilator monotherapy (LAMA or LABA) was permitted. Patients had no ICS or ICS/LABA treatment for at least 6 weeks prior to run-in, and no LAMA/LABA combination therapy for at least 2 weeks prior to run-in. After the run-in period, patients received study treatment for 24 weeks.

In this analysis, patients were categorized into two subgroups based on their smoking status at screening (current smoker or former smoker). The EMAX trial did not include any patients who had never smoked.

Endpoints

Outcomes evaluated in the EMAX trial included spirometry, patient-reported outcomes (PROs), exacerbations, clinically important deteriorations (CID), and safety. For this analysis, spirometry outcomes were change from baseline in trough FEV_1, FVC, and inspiratory capacity (IC). PROs were self-administered computerized Transition Dyspnea Index (SAC-TDI) focal score, Evaluating Respiratory Symptoms–COPD (E-RS) total score, rescue medication use (inhalations/day and the proportion of rescue-free days), global assessment of disease severity (GADS), St George's Respiratory Questionnaire (SGRQ) total score, and CAT total score. Response rates were also evaluated for SAC-TDI score (at least a 1-unit improvement from baseline) [22], E-RS score (at least a 2-point reduction from baseline) [23], SGRQ score (at least a 4-point reduction from baseline) [24], and CAT score (at least a 2-point reduction from baseline) [25]. Risk of a first CID was assessed in individual patients according to three composite definitions: 1. a first moderate or severe exacerbation, and/or a trough FEV_1 decrease from baseline of at least 100 mL, and/or a

deterioration in SGRQ (at least 4 units from baseline); 2. as per the first definition with a CAT deterioration (at least 2 units from baseline) replacing SGRQ deterioration; 3. a first moderate or severe exacerbation, and/or a SGRQ deterioration, and/or a CAT deterioration, and/or a SAC-TDI deterioration (at least a 1-unit decrease from baseline). Safety outcomes included the incidence of adverse events (AEs) and serious AEs (SAEs).

Statistical Analysis

The EMAX trial was powered to detect differences in trough FEV_1 and SAC-TDI at week 24 in the intent-to-treat (ITT) population. The trial was not powered to detect differences between treatments in the smaller smoking status subgroups, so no formal statistical comparison was performed between subgroups. Accordingly, treatment differences with 95% confidence intervals (CI) are reported without reference to statistical significance between subgroups; however, P values are shown in the figures and tables.

Full details of the statistical analyses have been reported previously [21]. Mixed model repeated measures (MMRM) analyses were performed for change from baseline in spirometry outcomes and PROs, and least squares (LS) mean and LS mean change from baseline are reported with estimated treatment differences and 95% CIs. Generalized linear mixed model analyses were used to evaluate response rates, and corresponding odds ratios (OR) are reported with 95% CIs. A Cox proportional hazards model was used to generate hazard ratios (HR) and 95% CIs for time to first CID.

RESULTS

Study Population

The EMAX ITT population included 2425 patients, of whom 1203 (50%) were current smokers (UMEC/VI: 394; UMEC: 396; SAL: 413) and 1221 (50%) were former smokers (UMEC/VI: 418; UMEC: 407; SAL: 396).

Table 1 shows baseline demographics and clinical characteristics of current and former smokers. On average, current smokers were slightly younger than former smokers, and a higher percentage were female. A greater proportion of current smokers than former smokers received no maintenance therapy in the 30 days prior to screening. Current smokers had a greater symptom burden as shown by higher baseline E-RS, CAT, and SGRQ scores and rescue medication use at baseline. A slightly smaller proportion of current smokers than former smokers experienced a moderate exacerbation in the prior year. Within each subgroup, baseline characteristics were well balanced between treatment groups (Supplementary Table 2).

Lung Function Outcomes

Across all treatments and both subgroups, only UMEC/VI in current smokers provided mean improvements in trough FEV_1 that consistently exceeded the minimum clinically important difference of 100 mL across all time points (Fig. 1). At week 24, mean (95% CI) change from baseline in trough FEV_1 was higher with UMEC/VI versus UMEC by 84 (50, 117) mL in current smokers and 49 (18, 80) mL in former smokers; the corresponding treatment differences for UMEC/VI versus SAL were 165 (132, 198) mL in current smokers and 117 (86, 148) mL in former smokers (Table 2). Mean changes from baseline in trough FVC and trough IC at week 24 and all earlier time points were also numerically greater with UMEC/VI than UMEC and SAL in current and former smokers (Table 2; Supplementary Fig. S1).

Symptom Severity and Health Status Outcomes

In both current and former smokers, larger mean SAC-TDI focal score and improvements from baseline in E-RS total score were observed with UMEC/VI compared with UMEC or SAL at all time points (Table 2; Figs. 2, 3). There were also greater odds of a clinically significant improvement for both outcomes at week 24 with UMEC/VI compared with UMEC or SAL

Table 1 Patient demographics and baseline characteristics

Characteristic	ITT ($N = 2425$)	Current smokers ($N = 1203$)	Former smokers ($N = 1221$)
Age, years, mean (SD)	64.6 (8.5)	61.7 (7.7)	67.5 (8.2)
Female, n (%)	988 (41)	561 (47)	427 (35)
Smoking pack-years, mean (SD)	48.4 (26.5)	48.0 (25.5)	48.8 (27.5)
No prior maintenance medication (from 30 days prior to screening), n (%)	849 (35)	493 (41)	255 (21)
Patients with a moderate COPD exacerbation in prior year[a], n (%)	393 (16)	164 (14)	228 (19)
Duration of COPD, years, mean (SD)	8.8 (6.9)	7.7 (6.3)	8.8 (6.8)
Post-salbutamol FEV_1, mL, mean (SD)	1595 (511)	1647 (515)	1545 (502)
Post-salbutamol % predicted FEV_1, mean (SD)	55.4 (12.7)	56.0 (12.5)	54.9 (12.9)
Post-salbutamol FEV_1/FVC, mean (SD)	0.52 (0.10)	0.52 (0.10)	0.51 (0.10)
% reversibility to salbutamol, mean (SD)	10.5 (13.1)	10.8 (12.5)	10.1 (13.7)
GOLD spirometric grade[b], n (%)			
2 (% predicted FEV_1 50% to < 80%)	1569 (65)	796 (66)	773 (63)
3 (% predicted FEV_1 30% to < 50%)	851 (35)	403 (33)	447 (37)
FEV_1, mL, mean (SD)	1491 (517)	1545 (515)	1437 (514)
BDI score, mean (SD)	7.0 (1.9)	7.0 (2.0)	7.0 (1.8)
E-RS total score, mean (SD)	10.6 (5.7)	11.5 (5.8)	9.7 (5.6)
SGRQ score, mean (SD)	44.7 (16.2)	46.6 (16.8)	42.8 (15.2)
CAT score, mean (SD)	19.2 (6.1)	20.2 (6.4)	18.2 (5.7)
Rescue salbutamol, puffs/day, mean (SD)	2.2 (2.5)	2.5 (2.7)	1.9 (2.2)

BDI Baseline Dyspnoea Index, *CAT* COPD Assessment Test, *COPD* chronic obstructive pulmonary disease, *E-RS* Evaluating Respiratory Symptoms–COPD, *FEV₁* forced expiratory volume in 1 s, *FVC* forced vital capacity, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *ITT* intent to treat, *SAL* salmeterol, *SD* standard deviation, *SGRQ* St George's Respiratory Questionnaire, *UMEC* umeclidinium

[a] Number of patients with exacerbations requiring oral or systemic corticosteroids and/or antibiotics (moderate) in 12 months prior to screening (patients with more than one moderate exacerbation or with a severe exacerbation [requiring hospitalization] were excluded)

[b] An additional 4 (< 1%) current smokers with GOLD grade 1 were randomized (UMEC $n = 3$; SAL $n = 1$)

(percentage of responders; SAC-TDI: UMEC/VI, 49–51% vs UMEC and SAL, 39–42%; E-RS: UMEC/VI, 35–37% vs UMEC and SAL, 26–29%; Fig. 4). Patients receiving UMEC/VI demonstrated larger reductions in mean rescue medication inhalations/day over 24 weeks versus UMEC and SAL in both smoking subgroups (Table 2; Figs. 5, 6). Improvements in the percentage of rescue-free days across all time points were seen with UMEC/VI compared with UMEC and SAL in current smokers, but this effect was less clear in former smokers (Table 2; Figs. 5, 6).
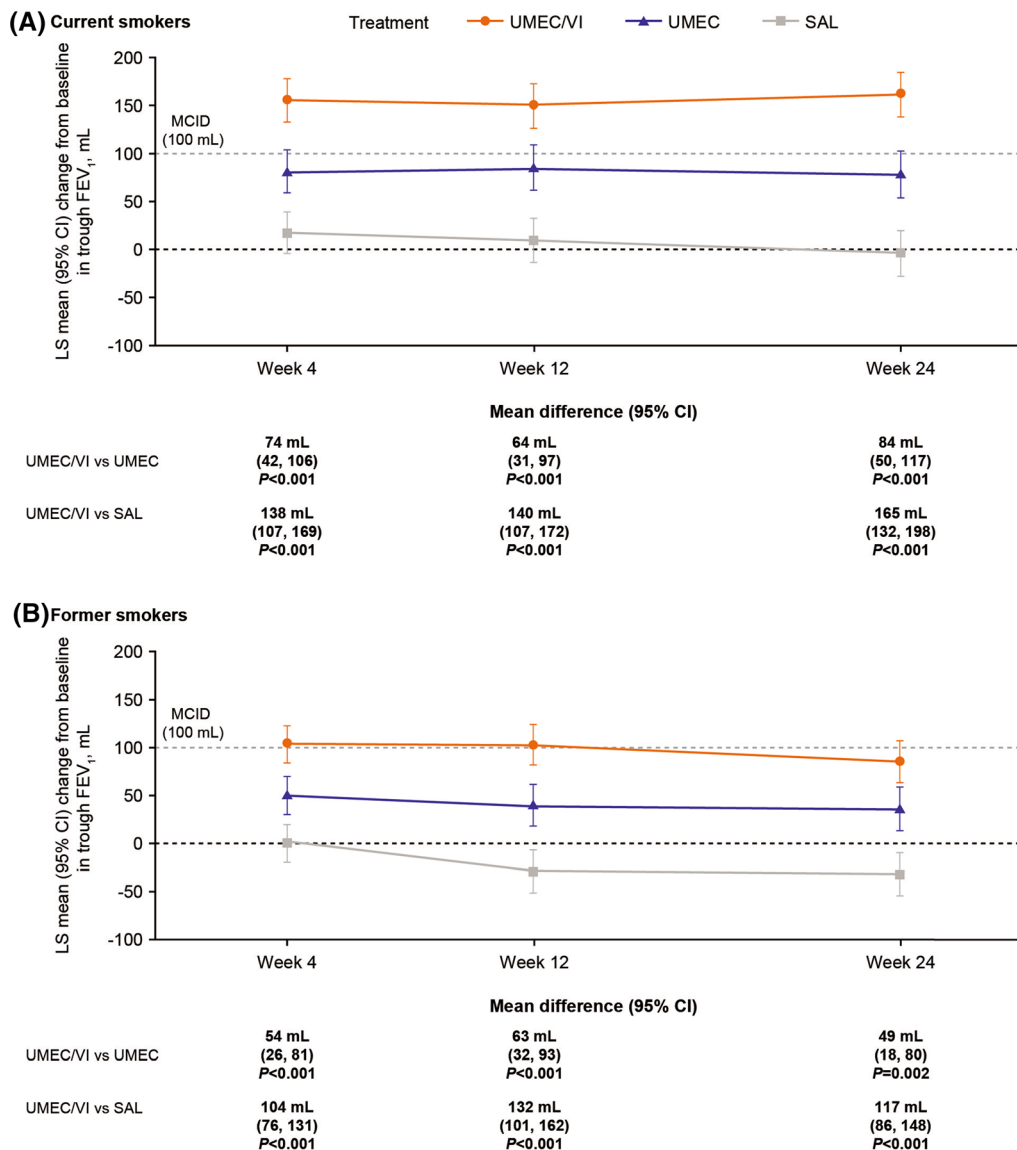
Fig. 1 Change from baseline in trough FEV_1 at weeks 4, 12, and 24 in **A** current smokers and **B** former smokers. *CI* confidence interval, FEV_1 forced expiratory volume in 1 s, *LS* least squares, *MCID* minimum clinically important difference, *SAL* salmeterol, *UMEC* umeclidinium, *VI* vilanterol

Change from baseline in mean SGRQ and CAT scores across all time points were not consistently greater with UMEC/VI versus UMEC and SAL in current or former smokers (Supplementary Fig. S2). The odds of a clinically significant improvement in SGRQ score were numerically greater with UMEC/VI versus UMEC and SAL in both current smokers (percentage of responders; UMEC/VI: 45% vs 34–42%) and former smokers (percentage of responders: 45% vs 38–40%) (Fig. 4). Similarly, CAT responder rates were numerically higher for UMEC/VI versus UMEC and SAL in current smokers (percentage of responders; UMEC/VI: 52% vs 46–48%) and former smokers (percentage of responders; 58% vs 48–55%; Fig. 4).

Table 2 Change from baseline in lung function and symptoms outcomes in current and former smokers

	Current smokers			Former smokers		
	UMEC/VI ($n = 394$)	UMEC ($n = 396$)	SAL ($n = 413$)	UMEC/VI ($n = 418$)	UMEC ($n = 407$)	SAL ($n = 396$)
Trough FEV$_1$ at week 24, mL						
LS mean CFB (95% CI)	161 (137, 184)	77 (53, 102)	− 4 (− 28, 19)	85 (63, 106)	36 (13, 58)	− 33 (− 55, − 10)
UMEC/VI vs comparator mean difference (95% CI)	–	84 (50, 117)	165 (132, 198)	–	49 (18, 80)	117 (86, 148)
		$P < 0.001$	$P < 0.001$		$P = 0.002$	$P < 0.001$
Trough FVC at week 24, mL						
LS mean CFB (95% CI)	169 (133, 206)	58 (20, 96)	− 42 (− 79, − 5)	82 (46, 117)	34 (− 3, 71)	− 84 (− 121, − 47)
UMEC/VI vs comparator mean difference (95% CI)	–	111 (58, 164)	211 (160, 263)	–	48 (− 3, 99)	166 (115, 217)
		$P < 0.001$	$P < 0.001$		$P = 0.066$	$P < 0.001$
Trough IC at week 24, mL						
LS mean CFB (95% CI)	141 (104, 178)	98 (59, 136)	23 (− 14, 60)	73 (39, 107)	37 (2, 73)	− 40 (− 76, − 5)
UMEC/VI vs comparator mean difference (95% CI)	–	43 (− 10, 97)	118 (66, 171)	–	35 (− 13, 84)	113 (64, 128)
		$P = 0.112$	$P < 0.001$		$P = 0.155$	$P < 0.001$
SAC-TDI at week 24						
LS mean (95% CI)	1.73 (1.41, 2.05)	1.32 (0.99, 1.65)	1.33 (1.01, 1.64)	1.62 (1.33, 1.90)	1.30 (1.00, 1.60)	1.12 (0.82, 1.42)
UMEC/VI vs comparator mean difference (95% CI)	–	0.41 (− 0.05, 0.87)	0.40 (− 0.05, 0.85)	–	0.32 (− 0.10, 0.73)	0.50 (0.09, 0.91)
		$P = 0.081$	$P = 0.079$		$P = 0.132$	$P = 0.018$

Table 2 continued

	Current smokers			Former smokers		
	UMEC/VI (n = 394)	UMEC (n = 396)	SAL (n = 413)	UMEC/VI (n = 418)	UMEC (n = 407)	SAL (n = 396)
E-RS total score at weeks 21–24						
LS mean CFB (95% CI)	− 1.72 (− 2.14, − 1.30)	− 1.25 (− 1.68, − 0.82)	− 1.05 (− 1.47, − 0.64)	− 1.31 (− 1.71, − 0.91)	− 0.74 (− 1.16, − 0.32)	− 0.33 (− 0.75, 0.09)
UMEC/VI vs comparator mean difference (95% CI)	–	− 0.47 (− 1.07, 0.13) P = 0.122	− 0.67 (− 1.26, − 0.08) P = 0.025	–	− 0.57 (− 1.15, 0.01) P = 0.055	− 0.98 (− 1.56, − 0.40) P = 0.001
Rescue medication use over weeks 1–24						
Mean inhalations/day						
LS mean CFB (95% CI)	− 0.81 (− 0.96, − 0.65)	− 0.39 (− 0.54, − 0.24)	− 0.53 (− 0.68, − 0.38)	− 0.41 (− 0.55, − 0.27)	− 0.16 (− 0.30, − 0.02)	− 0.12 (− 0.26, 0.02)
UMEC/VI vs comparator mean difference (95% CI)	–	− 0.42 (− 0.63, − 0.20) P < 0.001	− 0.28 (− 0.49, − 0.06) P = 0.011	–	− 0.25 (− 0.44, − 0.05) P = 0.014	− 0.29 (− 0.49, − 0.09) P = 0.004
% rescue medication-free days						
LS mean CFB (95% CI)	15.5 (12.4, 18.7)	7.5 (4.3, 10.6)	9.0 (5.9, 12.0)	9.3 (6.5, 12.2)	5.8 (2.9, 8.7)	6.5 (3.6, 9.4)
UMEC/VI vs comparator mean difference (95% CI)	–	8.1 (3.6, 12.5) P < 0.001	6.6 (2.2, 11.0) P = 0.003	–	3.5 (− 0.5, 7.6) P = 0.087	2.8 (− 1.2, 6.9) P = 0.172

Table 2 continued

	Current smokers			Former smokers		
	UMEC/VI (*n* = 394)	UMEC (*n* = 396)	SAL (*n* = 413)	UMEC/VI (*n* = 418)	UMEC (*n* = 407)	SAL (*n* = 396)
GADS[a] at week 24						
Proportion of patients reporting improvement from baseline at week 24, *n/N* (%)	224/342 (65)	183/311 (59)	221/346 (64)	249/365 (68)	209/326 (64)	192/328 (59)
UMEC/VI vs comparator ordered odds ratio for improvement in response category (95% CI)	–	1.48 (1.12, 1.95)	1.22 (0.93, 1.60)	–	1.28 (0.98, 1.68)	1.55 (1.18, 2.04)
		P = 0.006	*P* = 0.154		*P* = 0.074	*P* = 0.002

CFB change from baseline, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *E-RS* Evaluating Respiratory Symptoms–COPD, *FEV₁* forced expiratory volume in 1 s, *FVC* forced vital capacity, *IC* inspiratory capacity, *GADS* global assessment of disease severity, *LS* least squares, *SAC-TDI* self-administered computerized Transition Dyspnea Index, *SAL* salmeterol, *SD* standard deviation, *UMEC* umeclidinium, *VI* vilanterol

[a] 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
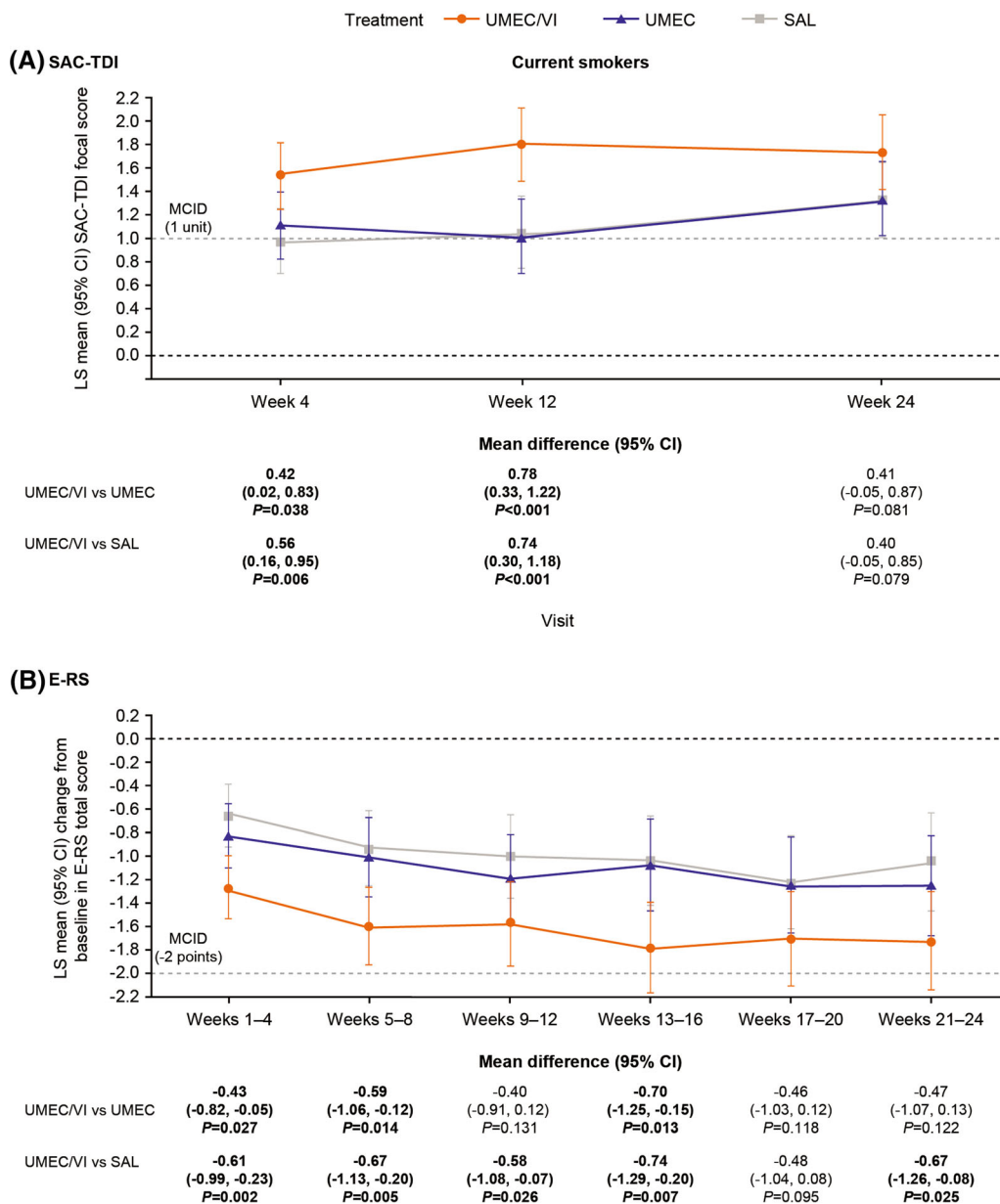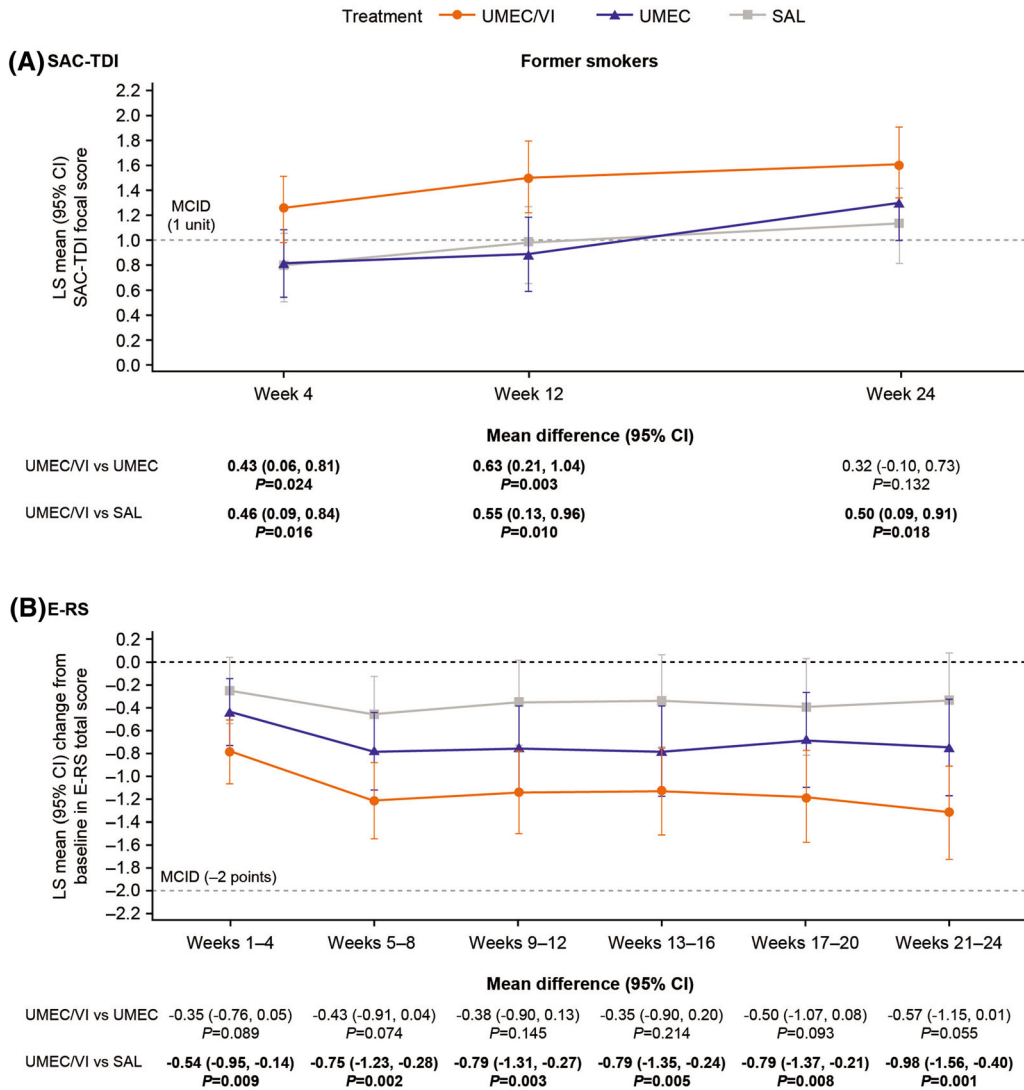
Fig. 2 **A** SAC-TDI focal score and **B** change from baseline in E-RS total score across all time points in current smokers. *CI* confidence interval, *E-RS* Evaluating Respiratory Symptoms–COPD, *LS* least squares, *MCID* minimum clinically important difference, *SAC-TDI* self-administered computerized Transition Dyspnea Index, *SAL* salmeterol, *SGRQ* St George's Respiratory Questionnaire, *UMEC* umeclidinium, *VI* vilanterol

Exacerbations and Disease Stability Outcomes

The risk of a first moderate/severe exacerbation (HR [95% CI]) with UMEC/VI versus UMEC was similar in current smokers (0.98 [0.65, 1.49]), but reduced in former smokers (0.70 [0.50, 1.00]). Compared with SAL, UMEC/VI significantly reduced the risk of a first moderate/severe exacerbation in both current (0.68 [0.46, 0.99]) and former smokers (0.60 [0.43, 0.85]).

In current smokers, the risk of a first CID was reduced with UMEC/VI versus UMEC for one of

Fig. 3 A SAC-TDI focal score and **B** change from baseline in E-RS total score across all time points in former smokers. *CI* confidence interval, *E-RS* Evaluating Respiratory Symptoms–COPD, *LS* least squares, *MCID* minimum clinically important difference, *SAC-TDI* self-administered computerized Transition Dyspnea Index, *SAL* salmeterol, *SGRQ* St George's Respiratory Questionnaire, *UMEC* umeclidinium, *VI* vilanterol

three CID definitions, and versus SAL for all three definitions, while in former smokers, UMEC/VI reduced CID risk versus UMEC and SAL for all three definitions (Fig. 7).

Effect of Smoking Status on Mean Improvements from Baseline

For four clinical outcomes of interest (trough FEV_1, SAC-TDI, rescue medication

inhalations/day, and SGRQ score), LS mean improvements in all treatment arms at week 24 were numerically larger in current smokers than former smokers, with the exception of SGRQ score in patients receiving SAL (Figs. 1, 2, 3, 5, 6, S2A). For trough FEV_1 in patients receiving UMEC/VI (Fig. 1), and for rescue medication inhalations/day in all treatment groups (Figs. 5a, 6a), there was no overlap in the 95% CIs between the subgroups, suggesting that
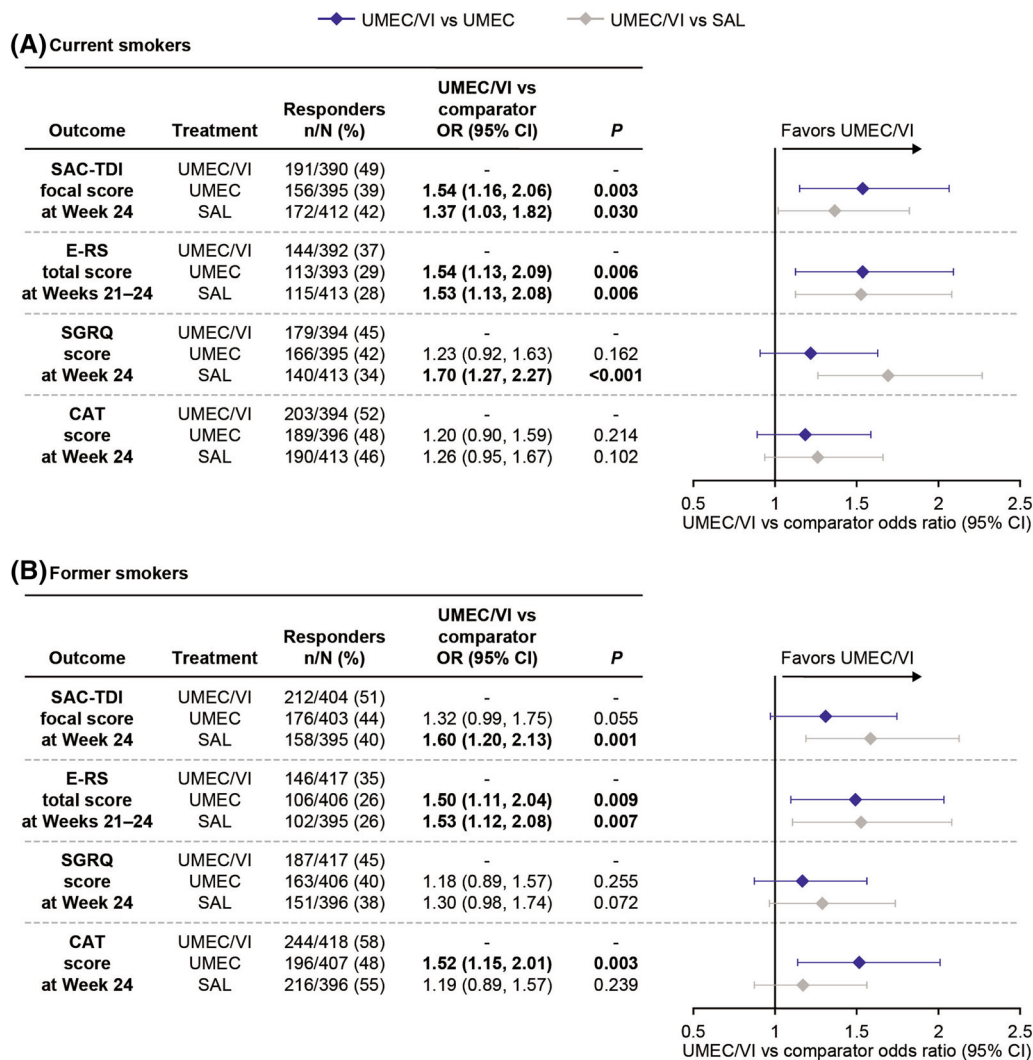
Fig. 4 Proportion of responders for symptoms and health status outcomes in **A** current smokers and **B** former smokers. *CAT* COPD Assessment Test, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *E-RS* Evaluating Respiratory Symptoms–COPD, *SAC-TDI* self-administered computerized Transition Dyspnea Index, *SAL* salmeterol, *SGRQ* St George's Respiratory Questionnaire, *UMEC* umeclidinium, *VI* vilanterol

current smokers may show greater improvements in lung function and larger reductions in rescue medication use than former smokers; for all other treatment groups and outcomes there was overlap in the 95% CIs between subgroups.

Safety

A similar percentage of patients in each treatment arm reported on-treatment AEs and SAEs, and these percentages were similar in current

and former smokers (Table 3). There were no drug-related SAEs in current or former smokers. There were four fatal SAEs in each subgroup, none of which were considered treatment-related.

DISCUSSION

This prespecified analysis of the EMAX trial suggests that both current and former smokers experienced larger improvements in lung
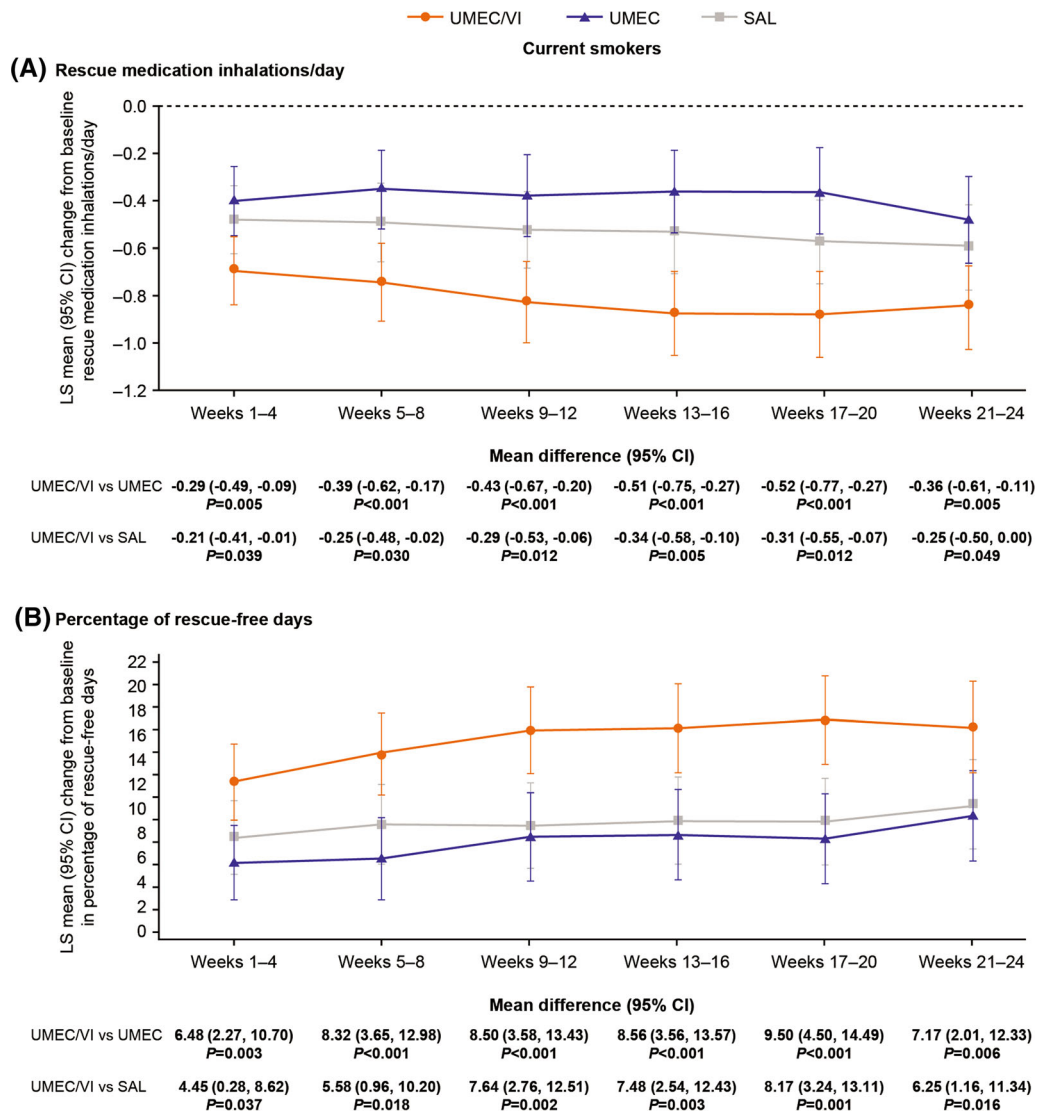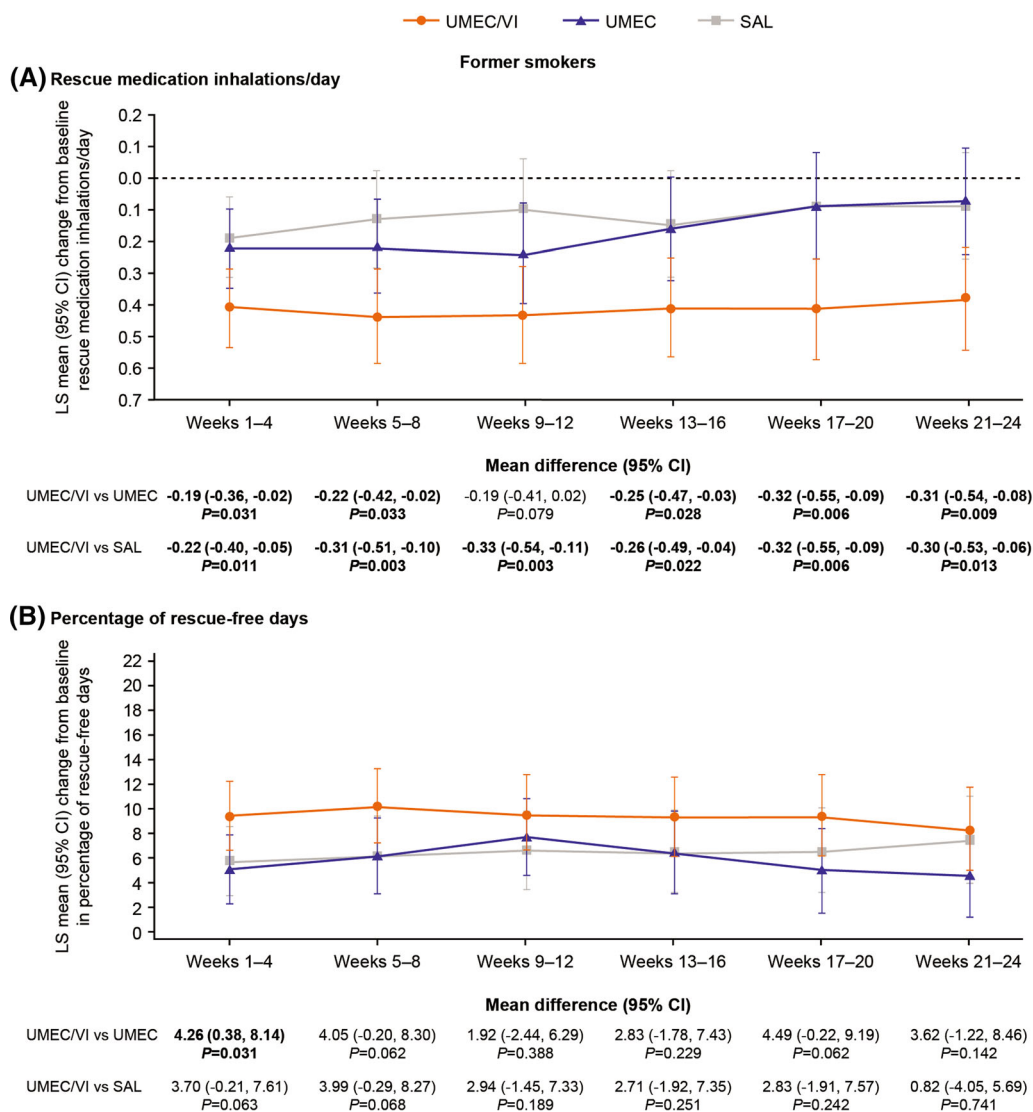
Fig. 5 Change from baseline in **A** rescue medication inhalations/day and **B** percentage of rescue-free days across all time points in current smokers. *CI* confidence interval, *LS* least squares, *SAL* salmeterol, *UMEC* umeclidinium, *VI* vilanterol

function and reductions in daily rescue medication use with UMEC/VI versus UMEC or SAL. The study was not powered to investigate subgroups and care should be taken when interpreting the results. However, consistent directional improvements with UMEC/VI versus monotherapy were also observed for other symptoms outcomes (SAC-TDI and E-RS). Furthermore, patients receiving UMEC/VI also had greater odds of improvements exceeding the MCID for SAC-TDI and E-RS total score in current and former smokers compared with UMEC

and SAL. A generally reduced risk of moderate/severe exacerbations was observed with UMEC/VI compared with monotherapy in both subgroups, which is consistent with the findings in the ITT population [21]. However, longer studies are typically needed to fully investigate treatment effect on exacerbations and the EMAX trial included a relatively small proportion of patients with a history of moderate exacerbations in the past year (16% in the ITT population). Former smokers also demonstrated a reduced risk of a CID with UMEC/VI

Fig. 6 Change from baseline in **A** rescue medication inhalations/day and **B** percentage of rescue-free days across all time points in former smokers. *CI* confidence interval, *LS* least squares, *SAL* salmeterol, *UMEC* umeclidinium, *VI* vilanterol

versus both monotherapies, while current smokers showed a consistent reduction in risk versus SAL. All treatments demonstrated a similar AE profile in both subgroups. Overall, these findings are consistent with a treatment benefit of dual bronchodilators compared with monotherapy in patients with COPD who are current or former smokers.

Current smokers demonstrated greater improvements from baseline in lung function with UMEC/VI and daily rescue medication use on all treatments compared with former

smokers, with no overlap in the 95% CIs for the two subgroups. This difference in treatment outcomes may be related to baseline differences between the subgroups; current smokers had a more severe symptom burden than former smokers, as demonstrated by higher baseline E-RS, CAT, and SGRQ scores, although mean baseline FEV_1 was higher in current smokers. The difference in baseline symptom severity may be related to the smaller proportion of current smokers receiving bronchodilator therapy during run-in compared with former
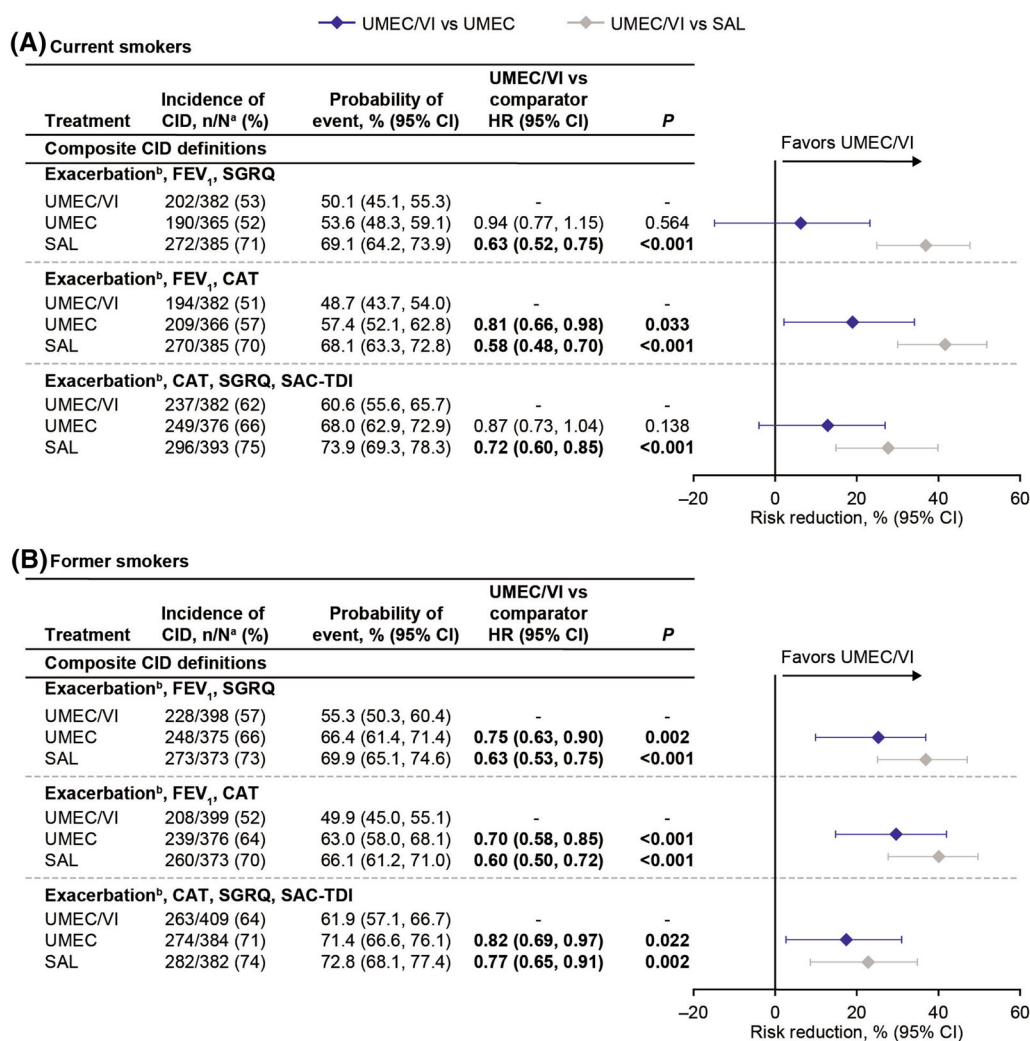
Fig. 7 Risk of a first CID in **A** current smokers and **B** former smokers. [a]n/N number of patients with an event/number of patients with at least one post-baseline assessment (not including exacerbations) for at least one of the individual components or patients who had an exacerbation; [b]moderate/severe exacerbation. *CAT* COPD Assessment Test, *CI* confidence interval, *CID* clinically important deterioration, *COPD* chronic obstructive pulmonary disease, FEV_1 trough forced expiratory volume in 1 s, *HR* hazard ratio, *SAC-TDI* self-administered computerized Transition Dyspnea Index, *SAL* salmeterol, *SGRQ* St George's Respiratory Questionnaire, *UMEC* umeclidinium, *VI* vilanterol

smokers, since these undertreated patients may be expected to show greater improvements when initiating treatment at the start of the trial.

On the basis of time-to-first-event analyses, both current and former smokers generally demonstrated a reduced risk of exacerbations and disease worsening (CID) with UMEC/VI versus UMEC or SAL. This treatment effect was particularly prominent in former smokers, who had a reduced risk of exacerbations and CID across all definitions with UMEC/VI versus both monotherapies. In contrast, current smokers had consistently reduced risk with UMEC/VI versus SAL, but only showed a benefit for one of three CID definitions compared with UMEC, and risk of a first exacerbation was similar between the UMEC/VI and UMEC treatment

Table 3 Adverse events

	Current smokers			Former smokers		
	UMEC/VI (*n* = 394)	UMEC (*n* = 396)	SAL (*n* = 413)	UMEC/VI (*n* = 418)	UMEC (*n* = 407)	SAL (*n* = 396)
AE, *n* (%)						
AE	163 (41)	163 (41)	160 (39)	152 (36)	153 (38)	154 (39)
Treatment-related AE	13 (3)	12 (3)	13 (3)	16 (4)	25 (6)	14 (4)
AE leading to study withdrawal	15 (4)	17 (4)	13 (3)	17 (4)	20 (5)	13 (3)
SAE, *n* (%)						
Nonfatal SAE	26 (7)	22 (6)	19 (5)	20 (5)	9 (2)	19 (5)
Treatment-related nonfatal SAE	0	0	0	0	0	0
Fatal SAE[a]	3 (< 1)	1 (< 1)	0	1 (< 1)	3 (< 1)	0
Treatment-related fatal SAE	0	0	0	0	0	0
Most frequent AEs[b], *n* (%)						
Nasopharyngitis	40 (10)	50 (13)	51 (12)	28 (7)	37 (9)	33 (8)
Upper respiratory tract infection	8 (2)	5 (1)	9 (2)	11 (3)	7 (2)	11 (3)
Influenza	8 (2)	3 (< 1)	7 (2)	12 (3)	6 (1)	11 (3)
Back pain	6 (2)	9 (2)	7 (2)	4 (< 1)	4 (< 1)	8 (2)
Cough	6 (2)	3 (< 1)	4 (< 1)	8 (2)	8 (2)	6 (2)
Bronchitis	5 (1)	2 (< 1)	5 (1)	6 (1)	9 (2)	7 (2)
Headache	6 (2)	5 (1)	3 (< 1)	4 (< 1)	12 (3)	3 (< 1)
COPD	5 (1)	4 (1)	2 (< 1)	3 (< 1)	6 (1)	8 (2)
Oropharyngeal pain	7 (2)	5 (1)	2 (< 1)	1 (< 1)	6 (1)	7 (2)
Hypertension	4 (1)	3 (< 1)	4 (< 1)	4 (< 1)	9 (2)	1 (< 1)
Sinusitis	7 (2)	3 (< 1)	8 (2)	1 (< 1)	4 (< 1)	1 (< 1)
Nausea	1 (< 1)	6 (2)	3 (< 1)	3 (< 1)	5 (1)	3 (< 1)
Dyspnea	0	3 (< 1)	0	3 (< 1)	7 (2)	6 (2)
Dizziness	4 (1)	6 (2)	2 (< 1)	0	2 (< 1)	1 (< 1)

Table 3 continued

	Current smokers			Former smokers		
	UMEC/VI (n = 394)	UMEC (n = 396)	SAL (n = 413)	UMEC/VI (n = 418)	UMEC (n = 407)	SAL (n = 396)
Depression	2 (< 1)	6 (2)	2 (< 1)	0	0	2 (< 1)

AE adverse event, *COPD* chronic obstructive pulmonary disease, *SAE* serious adverse event, *SAL* salmeterol, *UMEC* umeclidinium, *VI* vilanterol

[a] A total of 8 fatal SAEs were reported, 4 each in the UMEC/VI (any cardiac disorder: n = 3, and pneumonia: n = 1) and UMEC (any cardiac disorder: n = 1, and any respiratory, thoracic and mediastinal disorder: n = 3) treatment groups across both smoking status subgroups; none were considered treatment-related by the investigators

[b] Includes all on-treatment AEs occurring in at least 2% of any treatment group

arms in current smokers. However, the UMEC arm showed the highest rates of early discontinuation in the ITT population (UMEC/VI: 12%; UMEC: 19%; SAL: 16%) [21], which may have biased the analysis of exacerbations in favor of UMEC [26]. The small reduction in exacerbations and CID risk for two definitions with UMEC/VI versus UMEC in current smokers may therefore be an anomaly related to the excess early dropouts on the UMEC group, and to the low proportion of patients with an exacerbation in the prior year in the EMAX population. In support of this, treatment differences for the non-exacerbation components of the CID composite (FEV$_1$, SGRQ, CAT, and SAC-TDI) were generally similar or larger in current smokers than in former smokers. Previous studies have also shown similar effects of LAMA monotherapy on lung function and symptoms outcomes in current and former smokers [18, 19, 27].

This analysis of EMAX provides longer-term evidence of similar efficacy and safety of LAMA/LABA therapy in current and former smokers, consistent with the findings of a post hoc analysis of the 12-week FLIGHT studies [20]. Taken together, the evidence suggests that dual-bronchodilator therapy is a suitable maintenance treatment option for both current and former smokers with COPD. Nonetheless, smoking cessation is an important aspect of the management of COPD, and should be encouraged for all patients who smoke [4]. An important aim of future studies will be to determine

whether dual-bronchodilator therapy can help to minimize long-term risk and deterioration in lung function; this is particularly pertinent in former smokers, who have an elevated risk of mortality and a greater rate of lung function decline than nonsmokers [5, 6, 9].

A strength of this study is that EMAX selected an ICS-free population of patients with COPD, allowing a prospective assessment of the efficacy of dual and mono-bronchodilators independent of the potentially confounding effect of variable ICS use that has been noted in previous trials [12, 28]. However, a major limitation is that there were differences in patient characteristics between current and former smokers, which are consistent with a more severe COPD symptom burden and less frequent use of COPD maintenance therapy among current smokers. These baseline differences limit the conclusions that can be drawn regarding the effect of smoking status on long-acting bronchodilator efficacy, although our results do support greater efficacy of UMEC/VI compared with UMEC or SAL in both subgroups. In addition, only approximately 16% of the overall population had a history of exacerbations in the prior year, which together with the 24-week duration of the study may have limited the ability of the analysis to fully confirm reductions in exacerbation risk. Furthermore, the study was not powered to detect treatment differences in the smoking status subgroups.

CONCLUSION

In this analysis of the EMAX trial, dual-bronchodilator treatment with UMEC/VI provided improvements in lung function and reduced rescue medication use and was similarly well tolerated compared with UMEC and SAL monotherapy in both current and former smokers. Directional improvements with UMEC/VI versus monotherapy were observed in both subgroups for other symptoms outcomes (SAC-TDI and E-RS) and the risk of moderate/severe exacerbations. Current smokers showed greater overall benefits than former smokers with all three treatments. These findings suggest that dual-bronchodilator therapy is a suitable treatment option for symptomatic patients with COPD, regardless of their smoking status.

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Compliance with Ethics Guidelines. This study was performed according to the 1964 Declaration of Helsinki and its later amendments, and received appropriate ethical approval (Supplementary Table S1). All patients provided written informed consent at either the pre-screening or screening visit.

Data Availability. The datasets generated during and/or analyzed during the current study are available from www. clinicalstudydatarequest.com.

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