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Applying key learnings from the EMAX trial to clinical practice and future trial design in COPD

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ABSTRACT

Early MAXimisation of bronchodilation for improving COPD stability (EMAX) was a large, multicentre, multinational, randomised, double-blind, 24-week trial. EMAX evaluated the efficacy and safety of dual bronchodilator therapy with umeclidinium bromide (UMEC)/vilanterol (VI) versus monotherapy with either UMEC or salmeterol (SAL) in symptomatic patients with chronic obstructive pulmonary disease (COPD) at low exacerbation risk who were not taking concomitant inhaled corticosteroid (ICS).

EMAX generated evidence covering a wide range of patient-centred endpoints in COPD in addition to measures of lung function, clinical deterioration and safety. In addition, prospective and post hoc secondary analyses have generated clinically valuable information regarding the effects of baseline patient characteristics on treatment outcomes. Importantly, as concomitant ICS use was not permitted in this study, EMAX compared dual long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) therapy with LAMA or LABA monotherapy without potential confounding due to concurrent ICS use or withdrawal. EMAX demonstrated beneficial treatment effects of UMEC/VI over UMEC or SAL monotherapy as maintenance treatment across a range of different patient characteristics, with no forfeit in safety. Thus, the trial provided novel insights into the role of LAMA/LABA versus LABA and LAMA monotherapies as maintenance therapy for patients with symptomatic COPD at low risk of exacerbations. This article will explore the clinical implications of the main findings to date of the EMAX trial and consider the key learnings this trial offers for future trial design in COPD.

Abbreviations: AE, adverse event; ATS, American Thoracic Society; CAT, COPD Assessment Test; CI, confidence interval; CID, clinically important deterioration; CII, clinically important improvement; COPD, chronic obstructive pulmonary disease; CTS, Canadian Thoracic Society; EMAX, Early MAXimisation of bronchodilation for improving COPD stability; E-RS, Evaluating Respiratory Symptoms COPD; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GADS, Global Assessment of Disease Severity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; IC, inspiratory capacity; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LS, least squares; NICE, National Institute for Health and Care Excellence; NNT, number needed to treat; OR, odds ratio; PRO, patient-reported outcome; QALY, quality-adjusted life-years; SABA, short-acting β_2-agonist; SAC-TDI, self-administered computerised-Transition Dyspnoea Index; SAE, serious adverse event; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; UME, umeclidinium; VI, vilanterol.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) remains the third leading cause of death globally [1,2]. The disease is characterised by progressive airflow limitation and chronic respiratory symptoms including dyspnoea, cough and sputum production [2]. Persistent symptoms have a negative impact on health-related quality of life (HRQoL) and limit physical activity and work capacity [3–6]. Symptomatic patients are also at a greater risk of exacerbations, hospitalisation and death, even those without a recent history of exacerbations [7–9].

At present there is no consensus in treatment recommendations on the timing for initiation of long-acting antimuscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) combination therapy versus LAMA or LABA monotherapy for patients with symptomatic COPD [2,10,11]. The current Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report and Canadian Thoracic Society (CTS) guidelines recommend initial treatment with LAMA or LABA monotherapy for patients with symptomatic COPD at low risk of exacerbations [2,12]. In contrast, the American Thoracic Society (ATS) and UK National Institute for Health and Care Excellence (NICE) guidelines recommend initial maintenance therapy with dual bronchodilators for symptomatic patients [10,11]. The Early MAXimisation of bronchodilation for improving COPD stability (EMAX) trial addressed the evidence gap regarding the timing of dual bronchodilator therapy initiation by evaluating the efficacy and safety of dual versus mono-bronchodilator therapy in symptomatic patients with COPD and a low exacerbation risk (NCT03034915; GSK study 201749) [13].

Almost all clinical trials comparing LAMA/LABA with LAMA or LABA monotherapy have included a majority of patients using concurrent inhaled corticosteroid (ICS) at study entry. Concurrent ICS use can influence the efficacy of bronchodilator therapy (particularly LABA), or complicate interpretation of the evidence from studies when accounting for the impact of ICS withdrawal [14,15]. As concomitant ICS and/or LAMA/LABA use prior to study entry was not permitted in EMAX, it provided an ideal framework to compare dual LAMA/LABA therapy with LAMA or LABA monotherapy without potential confounding due to concurrent or withdrawal of ICS or stepping down combination therapies. Consequently, the trial provided important insights in an infrequently studied symptomatic population of patients with COPD not previously using ICS or combination therapy.

EMAX focused on the effects of LAMA/LABA therapy versus monotherapy on lung function, patient-reported outcomes (PROs) and short-term clinical deterioration. This approach facilitated a robust focus on early treatment to drive clinically relevant patient-centric improvements and/or prevent deteriorations in symptoms or health status in a population without a recent history of frequent exacerbations and no prior treatment with any inhaled combination therapy.

This article will present several unique findings from EMAX and explore the clinical implications of the main findings to date. In addition, the key learnings that can be drawn from EMAX to inform medical practice and future trial design in COPD are considered.

2. EMAX trial design and rationale

EMAX was a large, Phase IV, multicentre, multi-national, randomised, double-blind, 24-week trial comparing dual maintenance LAMA/LABA bronchodilation using umeclidinium bromide (UMEC)/vilanterol (VI) versus monotherapy with the LAMA UMEC or the LABA salmeterol (SAL) [13].

Patients were aged $\geq$40 years, current/former smokers with COPD, with a forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio <0.7, post-salbutamol FEV_1 $\geq$30 to $\leq$80% predicted (GOLD stage 2/3), COPD Assessment Test (CAT) score $\geq$10, with $\leq$1 moderate exacerbation and no severe exacerbations in the previous year. All patients utilised a rescue short-acting β_2 agonist (SABA; salbutamol) as-needed, and completed a nightly electronic diary (e-diary) to record SABA use and COPD symptoms on the 11-item Evaluating Respiratory Symptoms COPD (E-RS) questionnaire. ICS-containing therapy was not permitted for $\geq$6 weeks prior to randomisation or at any time during the study.

The primary endpoint was change from baseline in trough FEV_1 at Week 24. Secondary endpoints assessed over 24 weeks included self-administered-computerised-Transition Dyspnoea Index (SAC-TDI) score, E-RS total score, St George's Respiratory Questionnaire (SGRQ) total score, CAT score, daily rescue medication use, Global Assessment of Disease Severity (GADS), time-to-first moderate or severe exacerbation, risk of a first clinically important deterioration (CID), and on-treatment adverse events (AE) [13].

Of 2431 randomised patients, 2425 received study treatment and were included in the intent-to-treat (ITT) analysis. The mean age of this group was 64.6 years, 50% were current smokers at screening, 65% had previously received maintenance treatment with LAMA or LABA (49% and 17%, respectively) and 31% were maintenance-naïve at run-in. At baseline, mean post-salbutamol % predicted FEV_1 was 55.4%, mean CAT score was 19.2, mean SABA use was 2.2 puffs/day and 16% of patients had 1 moderate exacerbation in the previous year. The mean duration of COPD in the EMAX ITT population at baseline was 8.8 years.

3. Key findings of the EMAX trial

3.1. Lung function

There were greater improvements in lung function with UMEC/VI dual therapy versus UMEC or SAL (Table 1) [13]. Least squares (LS) mean (95% confidence interval) change in trough FEV_1 from baseline at Week 24 (primary trial endpoint; 122 mL [106, 138] for UMEC/VI, 56 mL [39, 73] for UMEC and −19 mL [−35, −2] for SAL) was significantly greater with UMEC/VI versus UMEC by 66 mL (43, 89) and versus SAL by 141 mL (118, 164) ($p < 0.001$) [13].

3.2. Overall symptoms

Compared with either monotherapy, dual therapy was associated with significantly greater improvements in respiratory symptoms based on E-RS total scores at all time points, GADS score, and reduced need for rescue medication (Table 1) [13]. Responder analyses for symptom-based measures supported these findings (Table 1) [13,16].

3.3. Dyspnoea

There were significantly greater improvements in dyspnoea assessed using SAC-TDI score with UMEC/VI versus UMEC or SAL at Week 24 (Table 1) and at all time points. Responder analyses for SAC-TDI also showed improvements with UMEC/VI versus either monotherapy.

3.4. Health status

Despite the clear symptom benefit of UMEC/VI versus monotherapy, the effect on health status was less consistent. At Week 24, improvements in health status assessed using the SGRQ were significantly greater with UMEC/VI versus SAL but not versus UMEC monotherapy; responder analysis of SGRQ responders followed the same pattern (Table 1) [13]. In addition, at Week 24, there was no significant benefit for UMEC/VI over monotherapy on CAT score; however, responder rates were significantly greater with UMEC/VI versus either monotherapy (Table 1) [13]. One possible explanation for the limited differentiation between UMEC/VI and UMEC monotherapy on health status outcomes is that the SGRQ and CAT questionnaires assess domains that are less likely to demonstrate benefits of greater bronchodilation, such as fatigue. In contrast, questionnaires that focus only on COPD-related symptoms such as E-RS (assessing breathlessness, cough and sputum and chest

Table 1
Summary of efficacy outcomes from EMAX primary analysis [13,16].

Outcomes	UMEC/VI (n = 812)	UMEC (n = 804)	UMEC/VI vs UMEC		SAL (n = 809)	UMEC/VI vs SAL	
	LS mean change from baseline	LS mean change from baseline	LS mean treatment difference (95% CI)		LS mean change from baseline	LS mean treatment difference (95% CI)	
Lung function at Week 24							
Trough FEV_1, mL	122	56	**66 (43, 89); p < 0.001**		−19	**141 (118, 164); p < 0.001**	
Trough FVC, mL	125	46	**79 (42, 116); p < 0.001**		−64	**189 (152, 225); p < 0.001**	
Trough IC, mL	107	67	**41 (4, 77); p=0.028**		−9	**116 (80, 152); p < 0.001**	
Symptoms at Week 24							
SAC-TDI score	1.68	1.30	**0.37 (0.06, 0.68); p=0.018**		1.22	**0.45 (0.15, 0.76); p=0.004**	
E-RS respiratory symptoms total score[a]	−1.52	−0.99	**−0.53 (-0.95, -0.11); p=0.013**		−0.69	**−0.83 (-1.25, -0.42); p < 0.001**	
GADS, OR for improvement in response category[b]	–	–	**1.38 (1.14, 1.67); p=0.001**		–	**1.38 (1.14, 1.68); p=0.001**	
Use of rescue salbutamol, mean inhalations/day[c]	−0.61	−0.28	**−0.33 (-0.48, -0.18); p < 0.001**		−0.32	**−0.28 (-0.43, -0.14); p < 0.001**	
Health status							
SGRQ total score	−4.98	−5.23	0.25 (−1.07, 1.57); p = 0.709		−3.29	**−1.69 (-2.99, -0.39); p=0.011**	
CAT score	−3.5	−3.4	0 (−0.6, 0.6); p = 0.891		−2.9	−0.5 (−1.1, 0.1); p = 0.074	
Responder analysis at Week 24							
	n/N (%)	**n/N (%)**	**OR (95% CI)**	**NNT (95% CI)[h]**	**n/N (%)**	**OR (95% CI)**	**NNT (95% CI)[h]**
SAC-TDI responders[d]	403/806 (50)	332/799 (42)	**1.43 (1.17, 1.75); p < 0.001**	12 (8, 25)	330/807 (41)	**1.48 (1.21, 1.81); p < 0.001**	11 (7, 21)
E-RS responders[a,e]	290/809 (36)	219/800 (27)	**1.52 (1.22, 1.89); p < 0.001**	12 (8, 23)	217/808 (27)	**1.53 (1.23, 1.90); p < 0.001**	12 (8, 23)
SGRQ responders[f]	366/811 (45)	329/802 (41)	**1.21 (0.99, 1.48); p=0.063**	22 (-∞, −706) U (11, ∞)[i]	291/809 (36)	**1.49 (1.22, 1.83); p < 0.001**	11 (7, 21)
CAT responders[g]	447/812 (55)	385/804 (48)	**1.35 (1.11, 1.65); p=0.003**	14 (9, 38)	406/809 (50)	**1.23 (1.01, 1.50); p=0.037**	20 (10,259)

CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; e-diary, electronic diary; E-RS, Evaluating Respiratory Symptoms-COPD; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GADS, Global Assessment of Disease Severity, IC, inspiratory capacity; LS, least squares; OR, odds ratio; NNT, number needed to treat; SAC-TDI, self-administered computerised-Transition Dyspnoea Index; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

[a] Across Weeks 21–24.

[b] 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.

[c] Across Weeks 1–24.

[d] SAC-TDI responders were defined as a ≥1-unit improvement from baseline.

[e] E-RS responders were defined as a reduction of ≥2 from baseline.

[f] SGRQ responders were defined as a ≥4-point reduction from baseline.

[g] CAT responders were defined as a ≥2-unit improvement from baseline.

[h] NNT were calculated post hoc from the proportion of responders for each outcome.

[i] 95% CI encompassed both benefit and harm.

symptoms) or the TDI focal score showed incremental benefits of UMEC/VI over UMEC in EMAX (Table 1). Finally, EMAX was powered to detect changes in FEV_1 and SAC-TDI, but not in other PROs such as SGRQ total score and CAT score.

3.5. Exacerbations

UMEC/VI provided a significantly greater reduction in exacerbation risk than SAL, but not greater than UMEC [13]. A post hoc analysis also favoured UMEC/VI over LAMA or LABA monotherapy on the composite endpoint of time to a first moderate/severe exacerbation or early study withdrawal [17].

3.6. Clinically important deterioration (CID)

CID is a composite endpoint that assesses short-term disease worsening across multiple dimensions (lung function, health status, and exacerbations) [18,19]. Most previous studies have defined CID as any of a decline in FEV_1, decline in SGRQ or a first exacerbation [19]. In EMAX, the risk of disease worsening, as measured by the most commonly used definition of CID, was reduced with dual UMEC/VI versus UMEC or SAL. In the absence of a universally accepted definition, CID was also assessed using two alternative definitions. The first alternative definition included decline in FEV_1, CAT or a first exacerbation, and the second included decline in SGRQ, CAT or TDI, or a first exacerbation (FEV_1-free CID definition that is not influenced by changes in lung function) [19]. In EMAX, consistent results were obtained across all three CID definitions [13,17].

3.7. Safety profile

EMAX demonstrated that the safety and tolerability profile of UMEC/VI was very similar to that of UMEC or SAL, with no evidence for increased risk of AEs/serious AEs (SAEs). The overall incidence of AEs/SAEs was similar across treatment groups, and the occurrence of drug-related AEs was low ($\leq$ 5%) for all therapies. The observed AEs were in line with those previously reported with long-acting bronchodilators [20]; the most frequent AE in all treatment groups was nasopharyngitis [13].

3.8. Cost effectiveness

An economic evaluation of the cost effectiveness of UMEC/VI versus UMEC and SAL from a UK perspective, based on post hoc EMAX trial data, has been conducted using the validated GALAXY model [21,22]. Over a 10-year horizon, dual therapy would provide more quality-adjusted life-years at a lower cost than either monotherapy (Fig. 1) [23]. Despite the higher treatment costs of UMEC/VI, the model predicted lower overall costs for dual therapy compared with UMEC or SAL due to lower healthcare costs (principally due to a predicted reduction in hospitalised exacerbations). Based on this modelling approach, symptomatic patients with COPD and no exacerbations in the prior year receiving UMEC/VI are expected to have improved survival and HRQoL outcomes compared with those receiving monotherapy, at a lower overall cost.

4. EMAX in a nutshell

The EMAX trial demonstrated the benefit of a fixed-dose combination of UMEC/VI over monotherapy with either UMEC or SAL as maintenance treatment in this patient population. This supports early initiation of dual bronchodilator maintenance therapy in symptomatic patients with COPD and a low exacerbation risk, as an alternative to stepwise management approaches. Importantly, dual bronchodilator therapy with UMEC/VI in this setting has a similar safety profile to monotherapy and is cost effective.

5. Implications for clinical practice

5.1. The efficacy of dual bronchodilator therapy is not compromised by smoking [24]

In a pre-specified subgroup analysis, the additional treatment benefit of UMEC/VI over UMEC or SAL on lung function and rescue medication use was apparent in both current and former smokers (Fig. 2) [24]. This suggests that the utility of dual bronchodilator therapy with UMEC/VI is not limited by smoking, in contrast with evidence suggesting that efficacy of ICS may be blunted in current smokers [25]. As such, dual therapy can be considered in both current and former smokers, alongside support for patients with smoking cessation.

5.2. Dual bronchodilator therapy may be considered as an initial treatment option for symptomatic patients across a range of symptom severities [26]

A post hoc fractional polynomial analysis explored the impact of

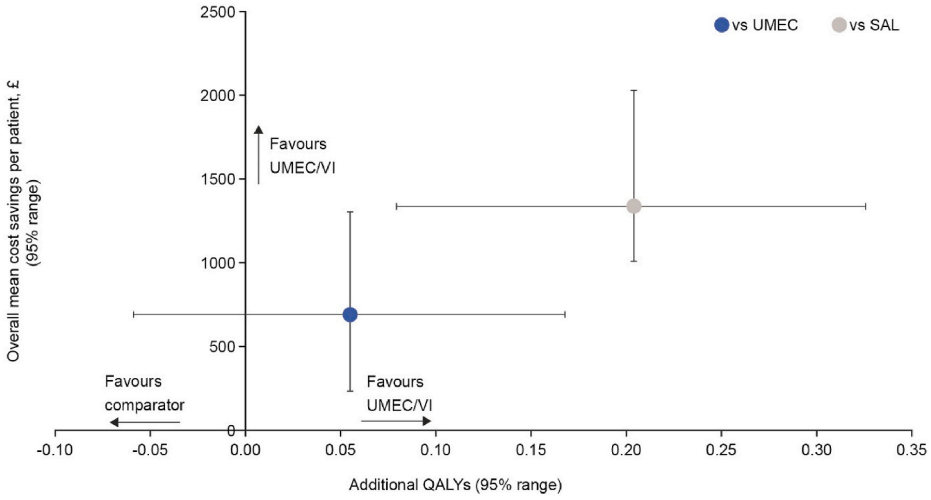

Fig. 1. Additional quality-adjusted life-years and overall mean cost savings per patient based on the GALAXY model predictions over a 10-year time horizon in a subgroup of patients without exacerbations in the year prior to study entry.
QALY, quality-adjusted life-year; UMEC, umeclidinium; SAL, salmeterol; VI, vilanterol.

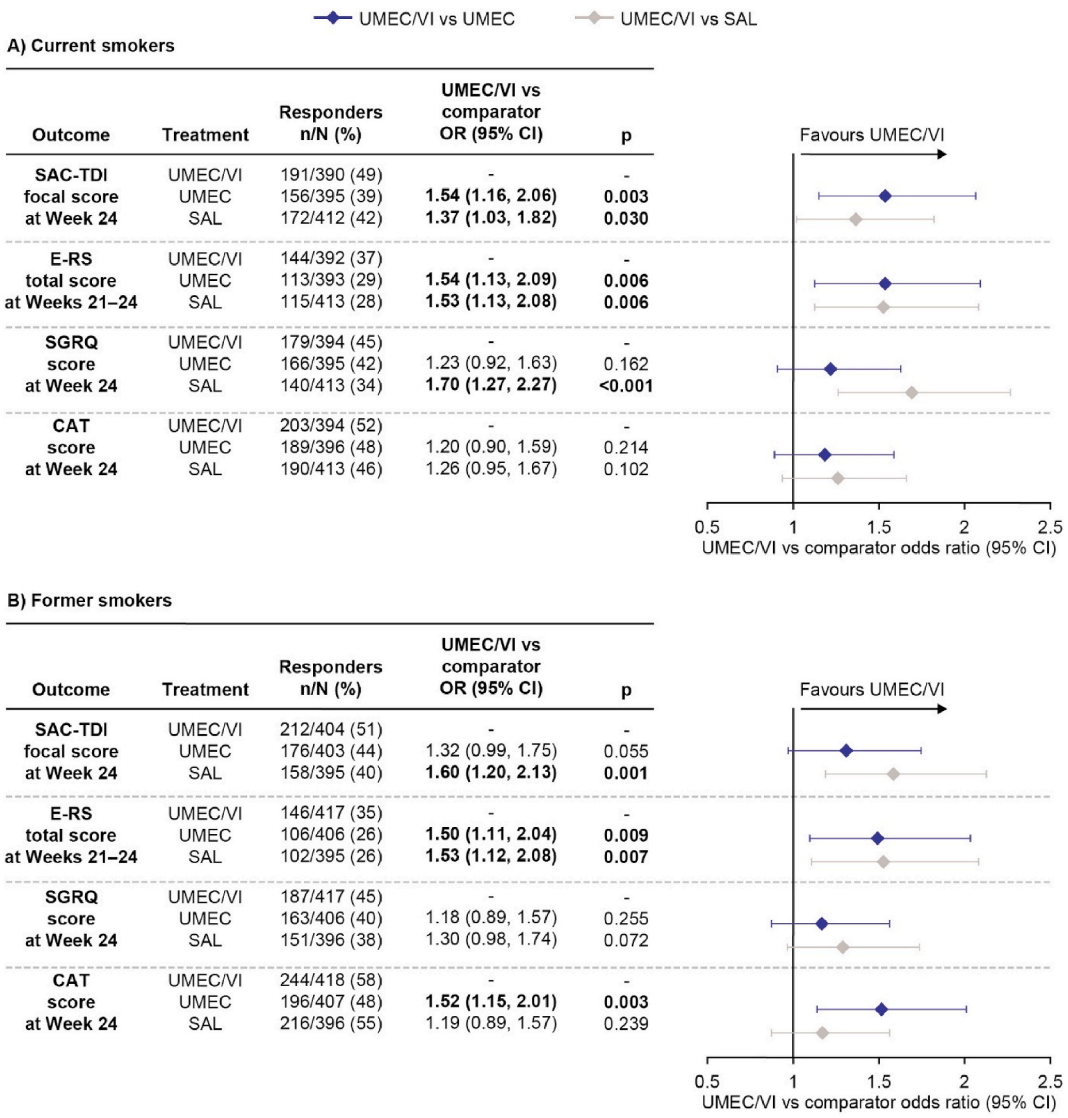

Fig. 2. Treatment effects in current versus former smokers.
CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms-COPD; OR, odds ratio; SAC-TDI, self-administered computerised-Transition Dyspnoea Index; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.
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symptom severity at baseline (assessed using CAT scores) on treatment effects, without categorising the patients by low and high CAT scores. This analysis showed that the greatest benefits of dual therapy on lung function and symptoms outcomes were seen in patients with CAT scores across the range of 10–21, although benefits were seen at scores up to 30 (Fig. 3). Therefore, LAMA/LABA dual therapy may be considered as an initial treatment option for patients with symptomatic COPD at low exacerbation risk across a range of symptom severities, not just for those with more severe symptoms [26].

5.3. Dual bronchodilator therapy is an appropriate treatment option for patients with symptomatic COPD at low risk of exacerbation across the full range of reversibility [27]

The relationship between reversibility to short-acting bronchodilators and longer-term response to maintenance bronchodilator therapy was also investigated using post hoc fractional polynomial analyses. Higher levels of reversibility at screening were associated with greater improvements in lung function and symptoms with all three treatments (Fig. 4) [27]. Despite this, improvements in lung function and E-RS total scores and reductions in the need for rescue medication were greater with UMEC/VI versus monotherapy regardless of the level of reversibility to short-acting bronchodilators at screening [27].

5.4. Initial dual bronchodilator therapy can be considered as an alternative to stepwise management in both treatment-naïve and previously treated symptomatic patients with COPD at low risk of exacerbation [28]

A pre-specified subgroup analysis of maintenance-treated and maintenance-naïve patients explored the impact of prior bronchodilator therapy on efficacy outcomes [28]. Both subgroups had greater improvements in lung function and symptoms with UMEC/VI compared with UMEC or SAL monotherapy (Fig. 5). In addition, for four key endpoints (FEV_1, SAC-TDI, SABA use and SGRQ), improvements from baseline were numerically greater in maintenance-naïve versus maintenance-treated patients for all treatment arms. These findings

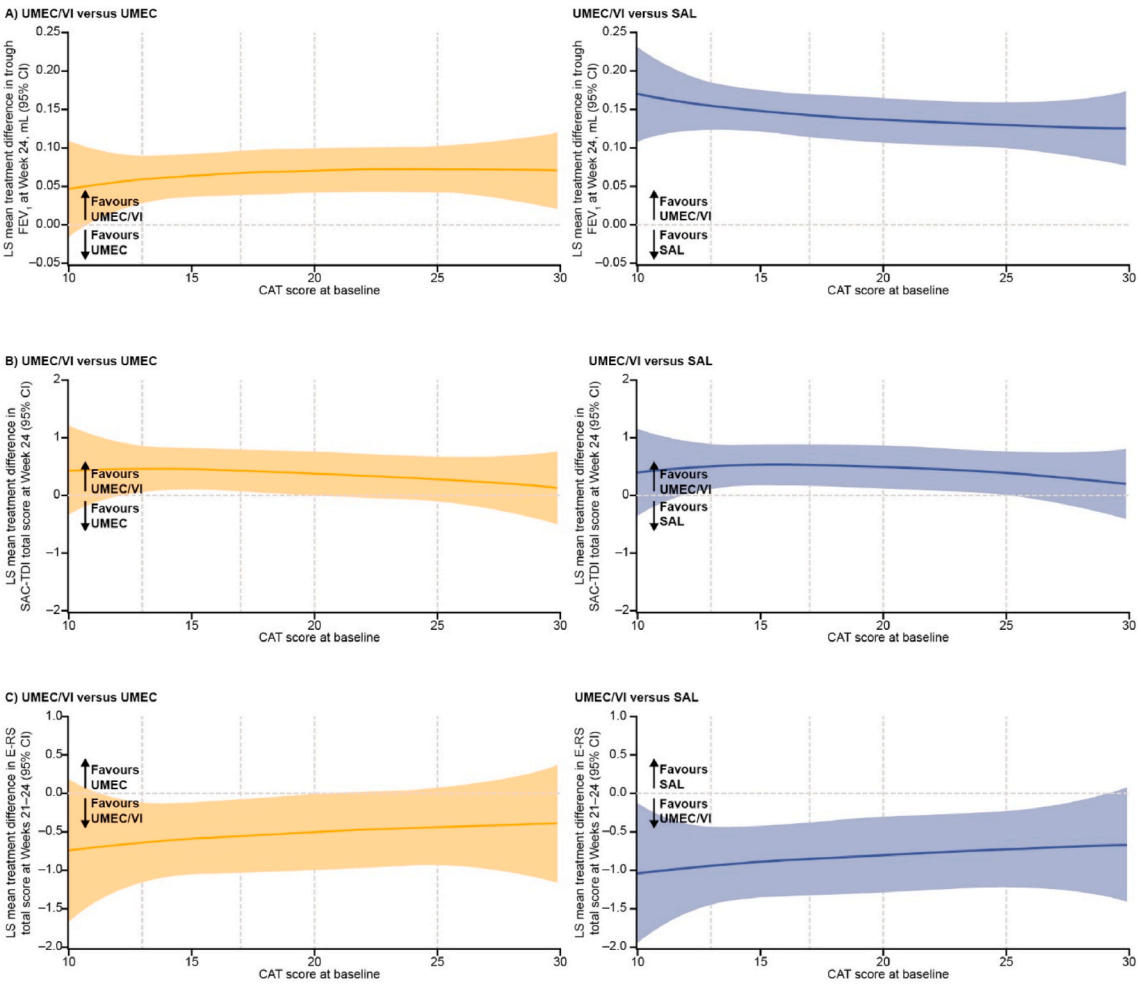

Fig. 3. Improvement in trough FEV_1, SAC-TDI focal score and E-RS total score at Week 24 according to CAT score at baseline.
Vertical dotted lines indicate quintiles of CAT score. Fractional polynomial analyses were carried out across the full range of baseline CAT scores. However, the results are presented for the range of CAT scores 10–30 as there were few patients with CAT scores >30.
CAT, COPD Assessment Test, CI, confidence interval; COPD, chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms-COPD; FEV_1, forced expiratory volume in 1 s; LS, least squares; SAC-TDI, self-administered computerised-Transition Dyspnoea Index; SAL, salmeterol; UMEC, umeclidinium; VI, vilanterol.
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suggest that dual therapy with UMEC/VI can be considered in all symptomatic maintenance-naive patients with COPD at low risk of exacerbation as an alternative to the stepwise approach of initiating treatment with one bronchodilator and adding a second if symptoms persist [28].

5.5. Among symptomatic patients with COPD at low risk of exacerbation, maintenance-naïve patients may not necessarily be those with less severe symptoms or recently diagnosed COPD

In EMAX, maintenance-naïve patients had been diagnosed with COPD for a similar length of time as their maintenance-treated counterparts, yet both subgroups had similar baseline symptom severity as indicated by CAT scores [28]. This is perhaps unexpected, as it might be assumed that treatment-naïve patients would be recently diagnosed or those with mild symptoms; however, the mean duration of COPD was 8.3 years in this subgroup [28]. This suggests inadequate assessment or undertreatment of symptomatic patients in current clinical practice.

5.6. Monitoring early improvement with dual bronchodilator therapy can enable accurate prediction of longer-term patient wellbeing [29]

COPD is characterised by a progressive decline in lung function beyond that expected due to normal aging, particularly in the early stages of the disease course [30]. Early optimisation of treatment to help control symptoms and improve quality of life is therefore an important aim of clinical management [2,30,31], and from a patient's perspective early improvement in symptoms after initiation of therapy would be beneficial. A post hoc analysis showed that improvements in E-RS scores and rescue medication use were apparent as early as Day 2 with all treatments in the EMAX trial (Fig. 6) [29]. Treatment differences between UMEC/VI and either monotherapy plateaued by Week 4–8 and were sustained throughout Weeks 21–24 (Fig. 6). Improvements were consistently greater with UMEC/VI compared with monotherapy. For all treatments, most patients (60–85%) retained their responder/non-responder status from Weeks 1–4 to Weeks 21–24. Given the rapid and sustained improvements seen in this analysis, monitoring early responses to bronchodilator treatment within approximately 4–8 weeks may help clinicians to make predictions about the longer-term success of their management strategy, and to act early on

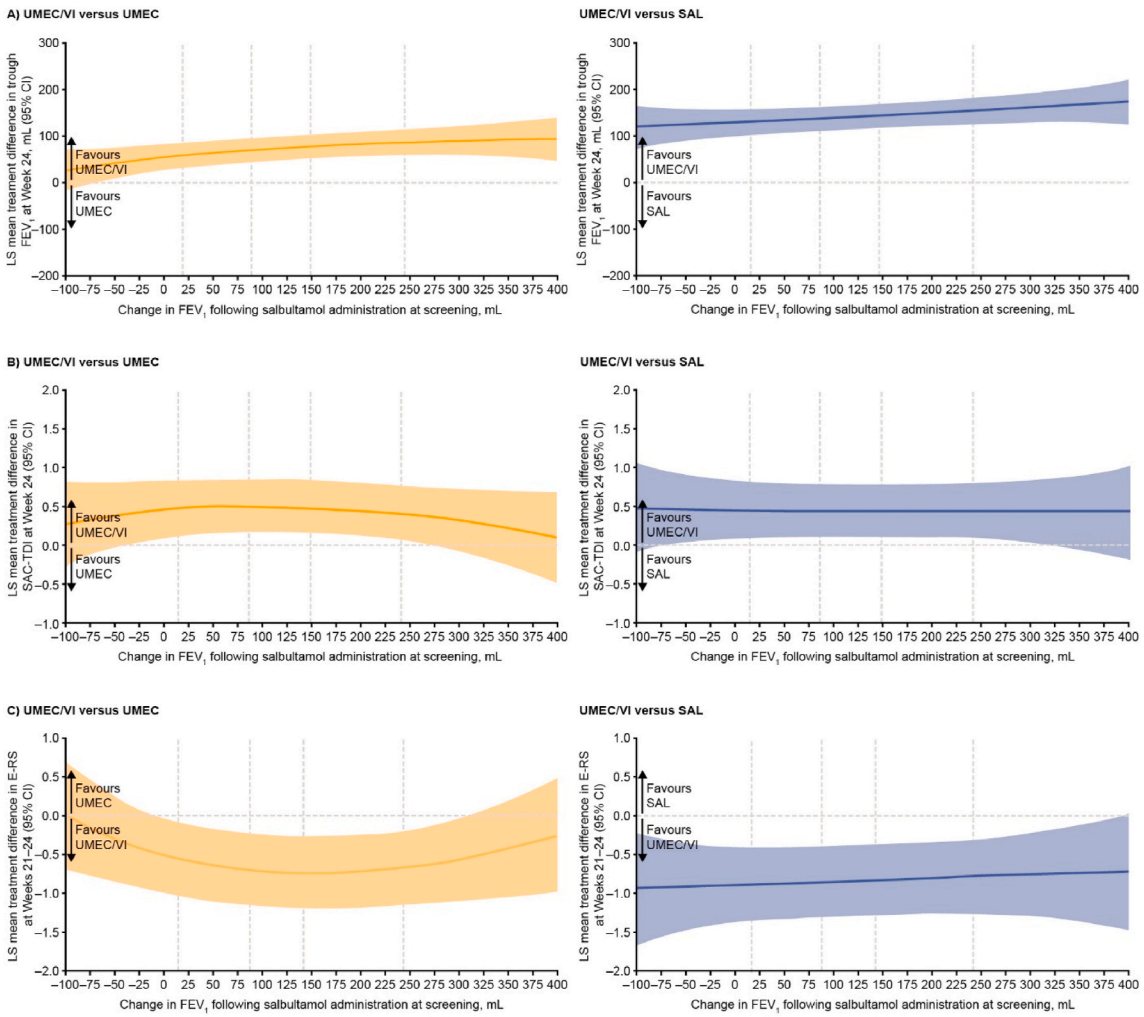

Fig. 4. Improvement in trough FEV_1, SAC-TDI focal score and E-RS total score at Week 24 according to reversibility to salbutamol at screening.
Vertical dotted lines indicate quintiles reversibility to salbutamol at baseline. Fractional polynomial analyses were carried out for the full range of reversibility to salbutamol at baseline (-850–896 mL). However, results are presented for the range -100–400 mL, as there were few patients with reversibility to salbutamol outside this range.
CI, confidence interval; E-RS, Evaluating Respiratory Symptoms-COPD; FEV_1, forced expiratory volume in 1 s; LS, least squares; SAC-TDI, self-administered computerised-Transition Dyspnoea Index; SAL, salmeterol; UMEC, umeclidinium; VI, vilanterol.
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any necessary adjustments to optimise their patients' outcomes [29].

5.7. *Early monitoring of treatment response in patients with COPD should include assessment across multiple PROs [32]*

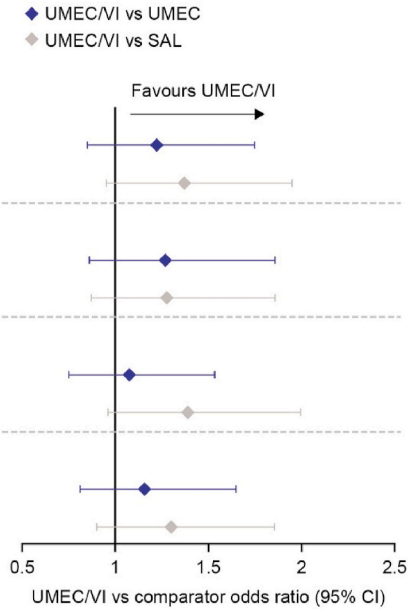
In the EMAX trial, patients often demonstrated improvements exceeding the minimal clinically important difference in only one or two PROs, showing that these measures are not entirely interchangeable, as they assess different dimensions of COPD [32]. For example, there was better concordance between SGRQ and CAT than between SGRQ and E-RS. For this reason, a composite endpoint of clinically relevant improvement across multiple PROs may be more reliable for detecting broader symptom improvement than a single PRO measure. Indeed, a post hoc analysis of EMAX data showed that patients who achieved clinically important improvement (CII; defined as reaching a clinically relevant threshold of improvement in ≥2 PROs) by Week 4 were highly likely to sustain such responses to Week 24, and had lower risk of deterioration than patients who did not achieve CII at Week 4 (Fig. 7) [32]. Patients who were CII responders after 4 weeks were more likely (odds ratio [95% confidence interval]: 4.09 [3.44, 4.86], $p < 0.001$) to be responders at Week 24 versus CII non-responders at Week 4, and were less likely to deteriorate over the remaining duration of the trial [32]. Overall, more patients treated with UMEC/VI showed response on ≥2 PROs compared with patients receiving UMEC or SAL [32]. While use of multiple PROs may not be practicable in routine clinical practice, these data suggest that a comprehensive symptomatic assessment such as CAT is required to reliably identify patients who do or do not respond to their prescribed treatment.

5.8. *Monitoring of SABA use is important to identify a potential need for treatment adjustment [33]*

A pre-specified subgroup analysis of the EMAX trial showed that the enhanced treatment effect observed with UMEC/VI versus UMEC or SAL may be smaller in patients with high SABA use, particularly for symptoms outcomes [33]. As such, clinicians should be aware of high levels of SABA use, since this is more likely in patients with more severe symptomatic COPD; escalation of maintenance therapy should be considered for these patients [33].

A) MN

Outcome	Treatment	Responders n/N (%)	UMEC/VI vs comparator OR (95% CI)	p
SAC-TDI focal score at Week 24	UMEC/VI	122/249 (49)	-	-
	UMEC	110/250 (44)	1.22 (0.85, 1.75)	0.278
	SAL	103/249 (41)	1.36 (0.95, 1.96)	0.095
E-RS total score at Weeks 21–24	UMEC/VI	96/249 (39)	-	-
	UMEC	83/249 (33)	1.27 (0.87, 1.85)	0.215
	SAL	82/249 (33)	1.28 (0.88, 1.86)	0.204
SGRQ score at Week 24	UMEC/VI	117/250 (47)	-	-
	UMEC	114/250 (46)	1.07 (0.75, 1.53)	0.705
	SAL	99/249 (40)	1.39 (0.97, 2.00)	0.072
CAT score at Week 24	UMEC/VI	132/250 (53)	-	-
	UMEC	126/250 (50)	1.15 (0.81, 1.65)	0.438
	SAL	118/249 (47)	1.30 (0.91, 1.86)	0.151



B) MT

Outcome	Treatment	Responders n/N (%)	UMEC/VI vs comparator OR (95% CI)	p
SAC-TDI focal score at Week 24	UMEC/VI	281/557 (50)	-	-
	UMEC	222/549 (40)	1.56 (1.22, 1.99)	**<0.001**
	SAL	227/558 (41)	1.54 (1.21, 1.97)	**<0.001**
E-RS total score at Weeks 21–24	UMEC/VI	194/560 (35)	-	-
	UMEC	136/551 (25)	1.64 (1.26, 2.14)	**<0.001**
	SAL	135/559 (24)	1.65 (1.26, 2.15)	**<0.001**
SGRQ score at Week 24	UMEC/VI	249/561 (44)	-	-
	UMEC	215/552 (39)	1.28 (1.00, 1.64)	**0.047**
	SAL	192/560 (34)	1.54 (1.20, 1.97)	**<0.001**
CAT score at Week 24	UMEC/VI	315/562 (56)	-	-
	UMEC	259/554 (47)	1.46 (1.15, 1.85)	**0.002**
	SAL	288/560 (51)	1.21 (0.95, 1.53)	0.116

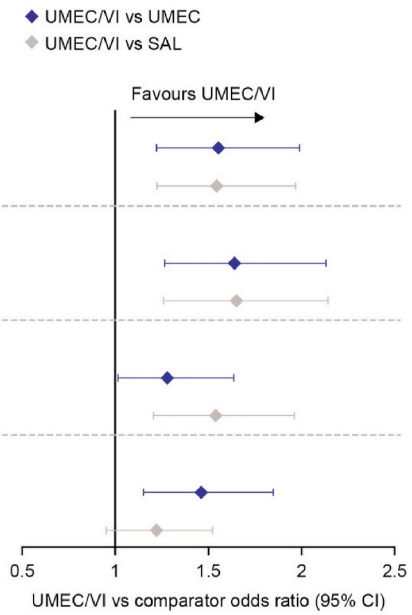


Fig. 5. Comparative treatment effects in maintenance-naïve versus maintenance-treated patients.
CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms-COPD; MN, maintenance naive; MT. maintenance-treated; OR, odds ratio; SAC-TDI, self-administered computerised-Transition Dyspnoea Index; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.
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6. Implications for clinical trials

6.1. Clinical trials can recruit patient populations that reflect clinical practice and therefore provide informative data to shape advances in patient care

In contrast to registrational studies, Phase IV trials recruit patients whose demographic and clinical characteristics may be more representative of those seen in clinical practice and may provide clinically relevant data to address specific unanswered research questions. For example, by including patients with COPD who have previously not received maintenance treatment, the EMAX trial enabled a greater understanding of the characteristics, needs and outcomes of this population, and prior assumptions about management to be reviewed and perhaps challenged. Furthermore, the EMAX trial was designed to exclude ICS use. This removed a key confounding factor in the comparison of LAMA/LABA with LABA or LAMA [14,15], and selected a rarely studied patient group.

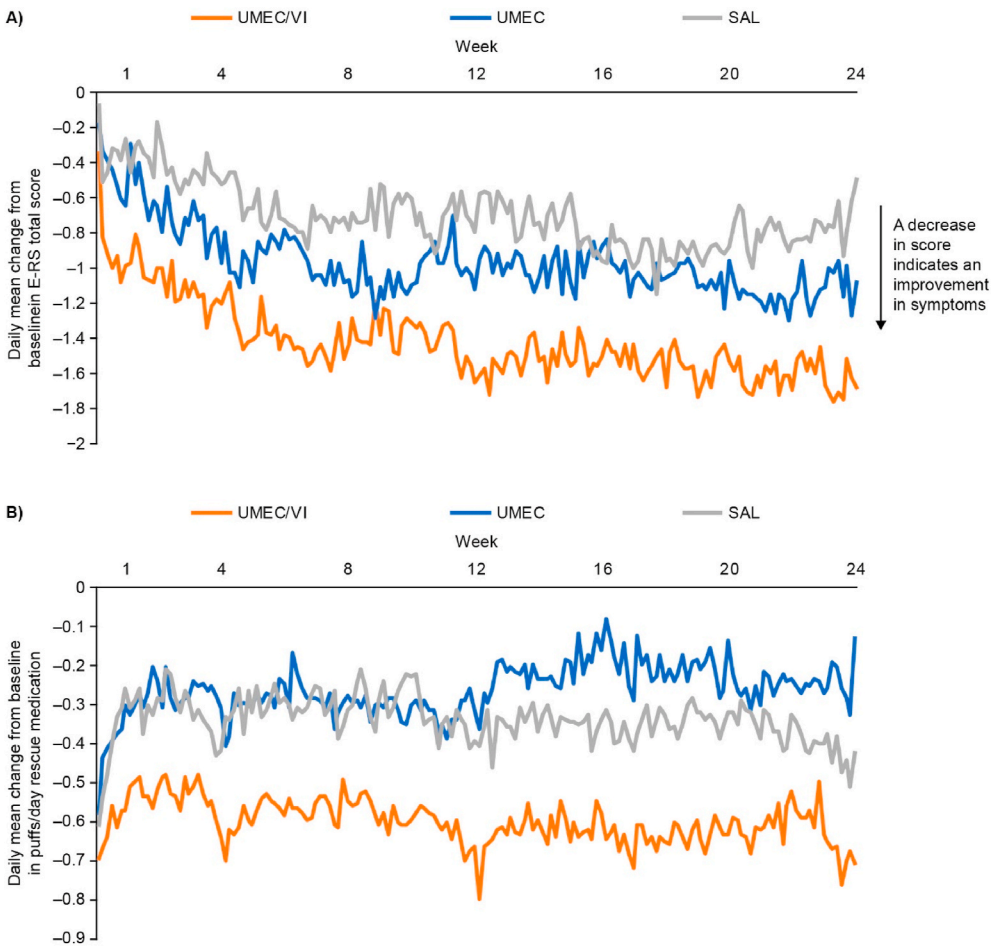

Fig. 6. Daily mean change from baseline in A) E-RS total score and B) rescue medication use (puffs/day).
Analyses for Weeks 21–24 were pre-specified, and for Weeks 1, 4 and 8 were conducted post hoc.
COPD, chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms-COPD; SAL, salmeterol; UMEC, umeclidinium; VI, vilanterol.
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6.2. Endpoints in a clinical trial should be tailored to the patient population rather than standardised across trials

Given the heterogeneity of the disease, COPD trials should aim to generate data that can inform the most appropriate treatment strategy according to specific patient characteristics and needs. EMAX included a range of outcomes that enabled characterisation of the relative benefits of the treatments on symptoms and health status, including onset and time-to-maximal effect. This was possible because the endpoints in EMAX were tailored to test the effect of treatments principally targeted for symptom improvement in symptomatic patients. It is therefore important to design trials with appropriate endpoints for the specific patient population rather than adhering to an identical set of standardised endpoints.

6.3. Composite endpoints can be informative for predicting longer-term exacerbation or deterioration outcomes

EMAX was the first trial to prospectively evaluate the CID composite endpoint as an indicator of short-term disease worsening. Three different definitions of CID were included, amalgamating exacerbations with measures of lung function, symptoms, and health status to give a wider view on the ability of treatment to reduce the risk of deterioration [13]. One of these definitions excluded changes in FEV_1, acknowledging the possibility for fluctuations in symptoms to occur independent of changes in lung function. Similarly, the composite measure of CII enabled measurement of meaningful treatment response and prediction of improved longer-term outcomes in EMAX [32]. Another composite endpoint combined exacerbations and early study withdrawal, which may mitigate some of the biases caused by early trial withdrawal [17,34]. UMEC/VI consistently provided benefits across the composite endpoints examined, suggesting that there is a broad benefit of treatment with UMEC/VI dual therapy over monotherapy.

6.4. The duration of the trial should be considered carefully

Symptomatic benefits of bronchodilators can be seen within a month of starting treatment [32]. For EMAX, the 24-week study duration was considered adequate due to demonstrate sustained medium-term clinically relevant improvements in lung function and patient-centric PROs in response to bronchodilator treatment. A sustained reduction in moderate or severe exacerbation risk was also achieved with UMEC/VI versus SAL, but not versus UMEC, consistent with other studies showing consistent reductions in exacerbation risk with LAMA/LABA versus LABA but not LAMA [35]. This was an unexpected finding in a 24-week trial, as a longer study would typically be required to evaluate outcomes such as exacerbations and disease progression.

6.5. Fractional polynomial analyses are valuable for evaluating relationships between patient characteristics and treatment response

Fractional polynomial analysis was used in the post hoc evaluations of EMAX subgroups based on baseline CAT score and reversibility, and on concurrent SABA use [26,27,33]. This method delivers broader insights than conventional subgroup analyses as it allows modelling of non-linear relationships, and thereby provides a more nuanced assessment of treatment differences across covariate values than dichotomised analyses, better reflecting the diversity seen in clinical practice [33]. For

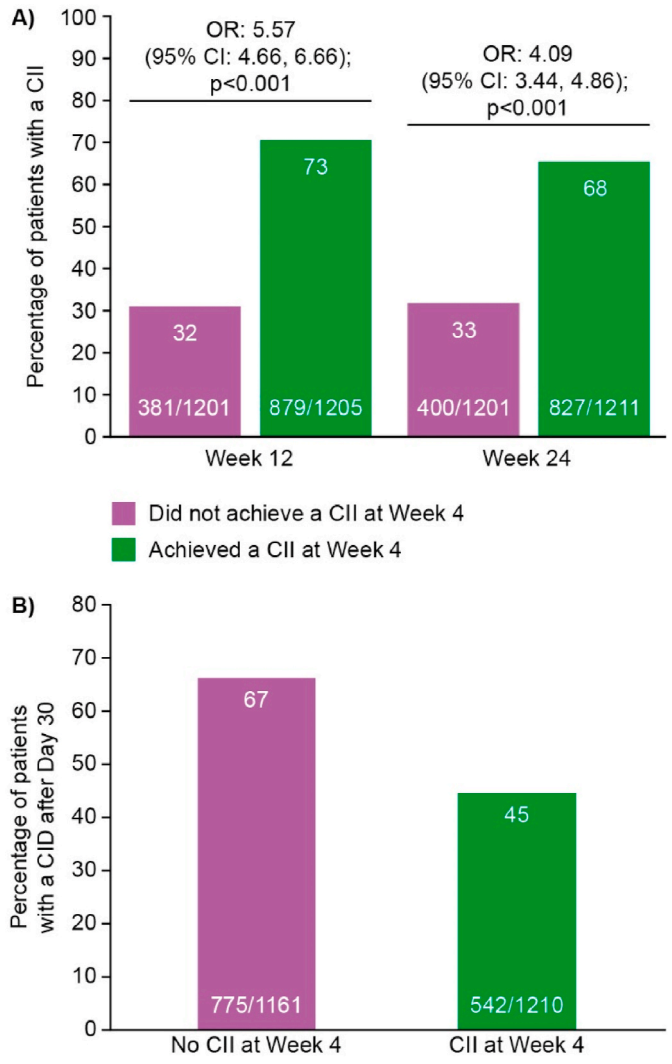

Fig. 7. Proportion of patients achieving A) a CII at Weeks 12 and 24 stratified by the achievement of a CII at Week 4 and B) a CID after Day 30 by achievement of a CII at Week 4 [32].
CI, confidence interval; CID, clinically important deterioration CII, clinically important improvement; OR, odds ratio.
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example, fractional polynomial modelling allowed assessment of treatment response across the full range of bronchodilator reversibility in EMAX and across the full range of CAT scores at baseline. These analyses avoided dichotomising the data with arbitrary cut-off points to categorise patients as reversible or non-reversible, or by symptom severity (e.g. CAT score <20 and ≥20) [26,27]. Modelling of baseline covariates as continuous variables in this manner produces more informative data than categorising patients into arbitrary subgroups, and better reflects the diversity seen in clinical practice. However, a limitation of fractional polynomial modelling is that the analysis becomes less informative at the extreme ends of the included range because there are few patients with extreme values.

6.6. Daily monitoring of SABA use and E-RS symptom scores on an e-diary allows rapid assessment of treatment benefit [33]

Overuse of rescue medication can lead to increased risk of AEs and poorer outcomes [33,36–39]. In addition, over-reliance on SABA use (>4 puffs daily) may partially confound assessments of symptom and health status improvement PROs, including SAC-TDI, E-RS, CAT and SGRQ scores [33]. Monitoring overuse of SABA in clinical studies is key to ensure appropriate patient care [37,40] and avoid confounding of efficacy results [33]. Use of a daily e-diary as part of a clinical trial in which the patient records SABA use and E-RS score can alert investigators to SABA overuse, and furthermore can alert investigators to patients experiencing exacerbations. SABA use tends to be correlated with degree of lung function decline and severity of symptoms [33,41], and as such is a valuable and under-utilised surrogate endpoint in clinical studies of COPD. In addition, a new composite endpoint integrating simultaneous SABA, airflow and symptom improvement could be helpful to evaluate overall clinical wellbeing of patients with COPD.

7. Additional considerations

It should be noted that the EMAX trial recruited patients with symptomatic COPD (CAT ≥10) at low exacerbation risk. Therefore, any recommendations made regarding treatment strategies relate specifically to this patient population. Similarly, as EMAX compared UMEC/VI against UMEC and SAL, extrapolating findings from the EMAX trial to other therapies is not appropriate. Nor did the EMAX trial compare UMEC/VI with other LAMA/LABA maintenance treatments; however, head-to head studies and Bayesian network meta-analyses have previously made comparisons between available LAMA/LABAs [42,43].

The EMAX trial has allowed multiple subgroup analyses to identify differential responses between specified treatment groups, but extrapolating from group data to individual patients remains challenging. A tool to help clinicians apply findings from clinical research to the assessment and management of individual patients, similar to widely used cardiovascular risk calculators, would be beneficial for the treatment of patients with COPD. Composite endpoints such as CID that are based on individual patient changes in outcomes already monitored in routine clinical practice could be useful in this context.

Subgroup analyses are informative but have inherent limitations due to smaller sample sizes, unprotected randomisation and potential group differences that may confound results. EMAX was powered for trough FEV_1 and SAC-TDI, but not for any other PROs and composite endpoints discussed in this review [13]. The relatively short 24-week duration of the trial is another limitation, at least with regard to the evaluation of disease progression and exacerbation risk. A longer-term trial with the same study design, perhaps extending over 3 years of treatment, would be critical to robustly examine the impact of the different bronchodilator therapies on exacerbations and disease progression and define the long-term effects of early treatment optimisation on patient outcomes.

8. Conclusions

EMAX has shown that patients with COPD at low risk of exacerbations may have a high symptom burden, and as such may be at elevated risk of deterioration and poor outcomes. The reported findings support treatment initiation with LAMA/LABA or early escalation to dual

therapy in this symptomatic population with CAT scores ≥10 [13,32]. Avoiding deterioration is a key aim for COPD management and optimising early intervention may have the potential to improve prognosis in symptomatic patients [30,31].

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Author contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval of the version to be published. **François Maltais:** Writing - Review & Editing, Investigation. **Claus F. Vogelmeier:** Writing - Review & Editing, Investigation. **Edward M. Kerwin:** Writing - Review & Editing, Investigation. **Leif H. Bjermer:** Writing - Review & Editing, Investigation. **Paul W. Jones:** Writing - Review & Editing, Investigation, Methodology, Conceptualisation. **Isabelle H. Boucot:** Writing - Review & Editing, Investigation. **David A. Lipson:** Writing - Review & Editing, Investigation, Methodology, Conceptualisation. **Lee Tombs:** Writing - Review & Editing, Formal analysis, Investigation, Methodology, Conceptualisation. **Chris Compton:** Writing - Review & Editing, Investigation, Methodology, Conceptualisation. **Ian P. Naya:** Writing - Review & Editing, Investigation, Methodology, Conceptualisation.

Provide a statement demonstrating the originality and clinical relevance of your paper

While treatment guidelines for patients with symptomatic COPD at low risk of exacerbations recommend maintenance therapy with long-acting bronchodilators, there is currently no consensus on the timing for initiation of LAMA or LABA monotherapy versus LAMA/LABA dual therapy. There is limited evidence on the efficacy and safety of LAMA or LABA monotherapy versus LAMA/LABA dual therapy in patients with COPD not taking ICS. Our review article responds to this evidence gap by providing an overview of insights from the EMAX trial, which investigated outcomes with umeclidinium bromide/vilanterol dual therapy versus UMEC (LAMA) or SAL (LABA) monotherapy in patients with symptomatic COPD at low risk of exacerbations who were not taking concomitant ICS.

Building on prospective evidence from the EMAX trial, which has been published previously (Maltais F et al. Respir Res 2019; 20 [1]:238), we present an overview of valuable data from post hoc analyses and an original discussion of the clinical implications of these findings. We have analysed treatment effects across ranges of bronchodilator reversibility, symptom severity, and rescue medication use, smoking status, and maintenance status at baseline to identify which patients gained the greatest benefit from treatment with dual therapy versus monotherapy. These findings are based on subgroup analyses as well as fractional polynomial analyses with continuous transformations of baseline characteristics, an approach that eliminates the need for subgroups defined by arbitrary cut-off points to better reflect the diversity seen in clinical practice. We also use several composite endpoints to provide a broadened view of trends in short-term deterioration or improvement across treatment groups. Finally, we reflect on the lessons learned from EMAX that could benefit future trial design in COPD. In EMAX, treatment with umeclidinium bromide/vilanterol dual therapy resulted in greater treatment benefits across a wide range of patient characteristics, highlighting the need for the inclusion of a representative patient population in clinical trials. In addition, carefully selected endpoints allowed for characterisation of treatment effects in the patient population of interest.

Overall, our review presents the findings from EMAX in a structured format that is easily accessible and highly relevant for both healthcare professionals involved in clinical trial design, and those who treat patients with COPD.

Disclosures

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