Efficacy of Umeclidinium/Vilanterol Versus Umeclidinium or Salmeterol: A Number-Needed-to-Treat Analysis of the EMAX Trial

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EMAX TRIAL

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Background

- The relative treatment benefits with long-acting muscarinic antagonist/long-acting β_2-agonist (LAMA/LABA) combination therapy versus LAMA or LABA monotherapy have not been demonstrated in symptomatic, inhaled corticosteroid (ICS)-free patients with COPD who have a low risk of exacerbations.
- The number needed to treat (NNT) indicates the number of patients who need to be treated for one additional responder to be seen with one therapy versus another in a defined time period.[1–3]
  - Conversely, the number needed to harm (NNH) is the number of patients that need to be treated, for a defined time period, for one patient to experience an adverse outcome.[3]
- The NNT is often used by payors and decision makers to identify the benefits of a new therapy versus standard of care options.[2, 3]
- This analysis of the double-blind, placebo-controlled Early MAXimization of bronchodilation for improving COPD stability (EMAX) trial[4] evaluated the NNT and NNH in patients treated with umeclidinium/vilanterol (UMEC/VI) versus UMEC or salmeterol (SAL) over 24 weeks.

Methods

- The EMAX trial randomized patients 1:1:1 to 24 weeks of UMEC/VI 62.5/25 mcg once daily, UMEC 62.5 mcg once daily, or SAL 50 mcg twice daily.

Key inclusion criteria

- ≥40 years of age
- COPD diagnosis (ATS/ERS definition)
- Pre- and post-albuterol FEV_1/FVC ratio <0.7
- Post-albuterol FEV_1 ≥30–≤80% predicted GOLD stage 2/3)
- Current/former smokers (≥10 pack-years smoking history)
- COPD Assessment Test (CAT) score ≥10
- ≤1 moderate exacerbation and no severe exacerbations in the previous year

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

- Patient-reported symptoms were evaluated using self-administered computerized Transition Dyspnea Index (SAC-TDI), Evaluating Respiratory Symptoms-COPD (E-RS) score, and CAT score; health status was assessed using St George's Respiratory Questionnaire (SGRQ) score. Risk of a first moderate/severe exacerbation and a first clinically important deterioration (CID) were also assessed.
- Response was defined as: ≥100 mL increase in trough FEV_1 from baseline; ≥1-point improvement in SAC-TDI score; ≥2-point reduction from baseline in E-RS total score; ≥4-point reduction from baseline in SGRQ total score; ≥2-point reduction from baseline in CAT score.
- Odds ratios were calculated for UMEC/VI versus UMEC and versus SAL for the proportion of patients in the intent-to-treat population (all patients who received ≥1 dose of study treatment) with a clinically relevant response (responders) by each endpoint.
- A CID event was defined as one or more of: a ≥100 mL decrease in trough FEV1, ≥4-point reduction in SGRQ score, or a moderate/severe exacerbation.
- NNT were calculated from the proportion of responders for each outcome. NNH are shown in the opposite direction. If the confidence interval (CI) spans unity (∞), it therefore spans positive and negative treatment effects and encompasses both benefit and harm.
- Analyses were a priori except for FEV_1 response rates and NNT, which were post hoc.

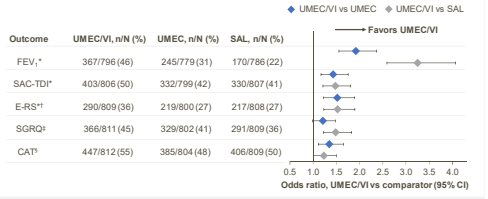
Results

Table 1. Patient demographics and clinical characteristics

Baseline characteristic	UMEC/VI (N=812)	UMEC (N=804)	SAL (N=809)
Age, years, mean (SD)	64.6 (8.4)	64.9 (8.5)	64.4 (8.5)
Female, n (%)	319 (39)	327 (41)	342 (42)
Current smoker at screening, n (%)	394 (49)	396 (49)	413 (51)
Moderate COPD exacerbation history in prior year,* n (%)	123 (15)	124 (15)	146 (18)
Duration of COPD, years, mean (SD)	8.8 (6.9)	7.8 (6.0)	8.3 (6.7)
Post-albuterol % predicted FEV_1, mean (SD)	54.9 (12.8)	55.9 (12.6)	55.6 (12.8)
GOLD spirometric grade,† n (%)			
2	518 (64)	529 (66)	522 (65)
3	294 (36)	271 (34)	286 (35)
FEV_1, mL, mean (SD)	1474 (513)	1503 (505)	1495 (533)
BDI score, mean (SD)	7.0 (1.8)	7.0 (1.9)	7.1 (1.8)
E-RS total score	10.7 (5.6)	10.7 (5.8)	10.4 (5.7)
SGRQ score, mean (SD)	44.5 (16.1)	45.0 (16.1)	44.6 (16.3)
CAT score, mean (SD)	19.1 (5.9)	19.3 (6.2)	19.3 (6.3)
Baseline rescue albuterol use, puffs/day, mean (SD)	2.2 (2.6)	2.1 (2.3)	2.2 (2.5)

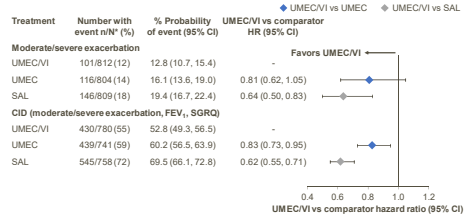
*Number of exacerbations requiring oral or systemic corticosteroids and/or antibiotics in 12 months prior to screening (patients with >1 moderate exacerbation or with a severe exacerbation [requiring hospitalization] were excluded); †An additional 4 patients (<1%) with GOLD grade 1 were randomized (UMEC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

Figure 1. Comparative incidence and odds ratio of response rates for symptoms and health-related quality of life outcomes at Week 24



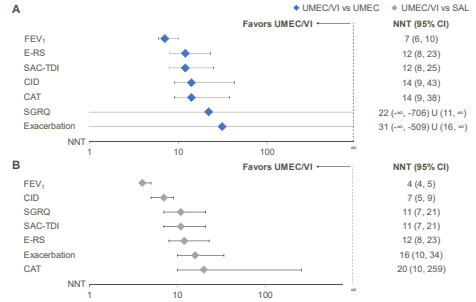
*P<0.001 for FEV_1, SAC-TDI, E-RS:COPD, UMEC/VI vs UMEC or SAL; †E-RS response at Weeks 21–24; ‡P=0.063 and P<0.001 for UMEC/VI vs UMEC and SAL, §P=0.003 and 0.037 for CAT UMEC/VI vs UMEC and SAL, respectively.
n/N, number of responders/number of patients with analyzable data

Figure 2. Hazard ratio for a first moderate/severe exacerbation or CID at Week 24



*N, 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. HR, hazard ratio

Figure 3. NNT for FEV_1, symptoms, health status, and exacerbation measures for UMEC/VI versus (A) UMEC and (B) SAL at Week 24*



Horizontal bars represent the 95% CI; NNH are observed where the CIs include unity (∞), thereby encompassing both benefit and harm;
*E-RS at Weeks 21–24; exacerbations and CID up to Day 168.

Patients

- Demographics and baseline characteristics are shown in **Table 1**.

Outcomes

- The proportions of responders for FEV_1, SAC-TDI, E-RS, and CAT were significantly higher with UMEC/VI than UMEC or SAL (**Figure 1**). UMEC/VI also provided significant improvements in the proportion of SGRQ responders versus SAL, but not UMEC.
- Patients receiving UMEC/VI had a lower risk of a moderate/severe exacerbation and CID than those receiving UMEC or SAL; however, this was not significant on exacerbations for UMEC/VI versus UMEC (**Figure 2**).
- Over 24 weeks, UMEC/VI resulted in a lower NNT versus UMEC for all outcomes except SGRQ and exacerbations, for which the 95% CI encompassed both benefit and harm (**Figure 3**).
  - No NNH values were observed as point estimates for any endpoints with UMEC/VI versus monotherapy.
  - Across all outcomes fewer patients needed to be treated with UMEC/VI for one additional responder versus SAL.
  - For the majority of endpoints, the NNT was lower for comparisons of UMEC/VI versus SAL than for comparisons of UMEC/VI versus UMEC.
  - Of the seven outcomes analyzed, the NNT most in favor of UMEC/VI versus UMEC or SAL was observed for FEV_1 responder rate.

Conclusions

- These findings demonstrate increased rates of clinically meaningful improvements in FEV_1, symptoms, and health-related quality of life with UMEC/VI compared with LAMA or LABA monotherapy in symptomatic, ICS-free patients at low risk of exacerbations.
  - The NNT reported here for a MCID in FEV_1, SAC-TDI, and SGRQ with UMEC/VI versus UMEC are consistent with values reported in a meta-analysis of previous UMEC/VI studies, including patients with moderate to very severe COPD.[5]
- The NNT presented here for UMEC/VI versus LAMA or LABA therapy over 24 weeks may provide additional guidance to physicians making maintenance therapy choices.

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