Predicting Improvements in COPD with Clinically Important Improvements in Patient-Reported Outcomes: A Post Hoc Analysis of the EMAX Trial

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EMAX TRIAL

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Background

- Patient-reported outcomes (PROs) in COPD measure different aspects of disease impact and are not interchangeable.[1] Consequently, monitoring improvement in multiple PROs may offer a more comprehensive assessment of clinically important improvement (CII) and better capture the overall impact of treatment.
- This post hoc analysis of the Early MAXimization of bronchodilation for improving COPD stability (EMAX) trial describes the likelihood of achieving CII in the first and last month of treatment to evaluate whether early CII responses to treatment in PROs may be predictive of a longer-term response.

Methods

- The 24-week, double-blind, parallel-group EMAX trial randomized patients with symptomatic COPD and low exacerbation risk not receiving inhaled corticosteroids 1:1:1 to umeclidinium/vilanterol (UMEC/VI) 62.5/25 mcg once daily, UMEC 62.5 mcg once daily, or salmeterol (SAL) 50 mcg twice daily for 24 weeks.[2]
- Achievement of concordant CII was defined in individual patients as a minimum clinically important difference (MCID) response in ≥2 of the PRO measures at the same timepoint: self-administered computerized Transition Dyspnea Index (SAC-TDI) focal score, Evaluating Respiratory Symptoms–COPD (E-RS) total score, St George's Respiratory Questionnaire (SGRQ) total score and COPD Assessment Test (CAT) total score (**Table 1**).
  - PRO responders were assessed a priori at Weeks 4 and 24 for SAC-TDI focal score, SGRQ total score, and CAT total score, and at Weeks 1–4 and 21–24 for E-RS total score.
- Changes in Global Assessment of Disease Severity (GADS) were assessed at Weeks 4 and 24 on a seven-point Likert scale ('Much Better', 'Better', 'Slightly Better', 'No Change', 'Slightly Worse', 'Worse', 'Much Worse') versus baseline.
  - Improvement in GADS was achieved when better response categories ('Much Better', 'Better' or 'Slightly Better') were reported.
- Occurrence of a CID event (defined as any one of: a ≥1-point decrease in SAC-TDI focal score, ≥4-point increase in SGRQ score, ≥2-point increase in CAT score, or a first moderate/severe exacerbation) was also assessed.

Table 1. MCID improvement for PRO responses

PRO	MCID for improvement (PRO responders)
SAC-TDI focal score	≥1-point increase[3]
E-RS total score	≥2-point reduction[4]
SGRQ total score	≥4-point reduction[5]
CAT total score	≥2-point reduction[6]

Results

Clinically important improvement (CII)

- At both Weeks 4 and 24, a greater proportion of patients receiving UMEC/VI achieved CII compared with patients receiving UMEC or SAL (**Figure 1**).
- The proportion of patients with CII at Week 4 who maintained this response at Week 24 was higher among those receiving UMEC/VI (72%) compared with UMEC (67%) or SAL (66%).

Improvement in Global Assessment of Disease Severity (GADS)

- A greater proportion of patients who achieved CII (2, 3, or 4 PRO responses) at Week 4, reported improved disease severity (GADS) from baseline at Weeks 4 and 24 compared with patients who did not achieve CII (0 or 1 PRO response) (**Figure 2**).
- Odds of improvement in GADS at Weeks 4 and 24 increased with the number of PRO responses at Week 4; all ordered ORs were significant versus patients with 0 PRO responses (**Table 3**).

Clinically important improvement (CII) as a predictor of disease worsening

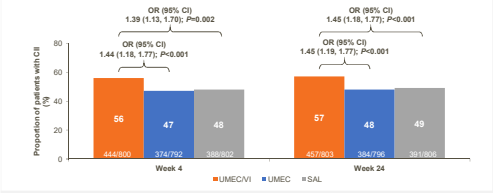
- The proportion of patients experiencing a CID after Day 30 decreased with increasing number of positive PRO responses at Week 4. Fewer patients with CII at Week 4 experienced a CID event after Week 4 compared with patients without CII (**Figure 3**).

Table 2. Baseline characteristics

Characteristic	ITT (N=2425)	Without CII <2 positive PROs (N=1211)	With CII ≥2 positive PROs (N=1211)	*P*-value
Age, years, mean (SD)	64.6 (8.5)	64.6 (8.4)	64.6 (8.5)	0.956
Female, n (%)	988 (41)	481 (40)	506 (42)	0.321
Moderate COPD exacerbation in prior year,* n (%)	393 (16)	204 (17)	188 (16)	0.408
Duration of COPD, years, mean (SD)	8.3 (6.6)	8.2 (6.4)	8.4 (6.7)	0.408
Use of a LABD during run in, n (%)	1576 (65)	883 (73)	790 (65)	**<0.001**
GOLD spirometric grade,† n (%)				
2	1569 (65)	784 (65)	783 (65)	0.966
3	851 (35)	424 (35)	426 (35)	
Trough FEV_1, mL, mean (SD)	1491 (517)	1505 (516)	1476 (518)	0.164
Patient-rated disease severity, n (%)				
Mild	411 (17)	235 (19)	175 (14)	**0.002**
Moderate	1672 (69)	818 (68)	854 (71)	
Severe	320 (13)	147 (12)	173 (14)	
Very severe	19 (<1)	9 (<1)	9(<1)	
BDI score, mean (SD)	7.0 (1.9)	7.1 (1.9)	7.0 (1.8)	0.109
E-RS total score, mean (SD)	10.6 (5.7)	10.3 (5.8)	10.9 (5.7)	**0.008**
SGRQ total score, mean (SD)	44.7 (16.2)	42.8 (15.9)	46.6 (16.2)	**<0.001**
CAT total score, mean (SD)	19.2 (6.1)	18.2 (5.8)	20.2 (6.3)	**<0.001**

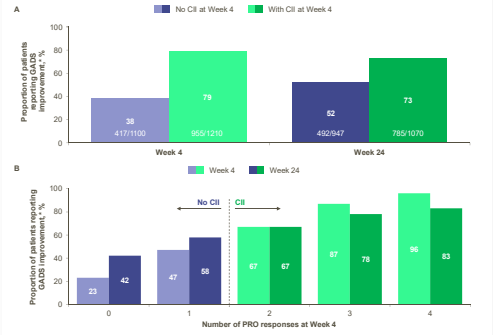
*Number of exacerbations requiring oral or systemic corticosteroids and/or antibiotics (moderate) in 12 months prior to screening (patients with >1 moderate exacerbation or with a severe exacerbation [requiring hospitalization] were excluded); †an additional 4 (<1%) patients with GOLD grade 1 were randomized.
BDI, baseline dyspnea index; CII, clinically important improvements; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABD, long-acting bronchodilator

Figure 1. Proportion of patients with CII (response in ≥2 PROs) at Weeks 4 and 24



OR (95% CI) were obtained using a generalized linear mixed model with treatment as an explanatory variable and visit, baseline SGRQ score, baseline CAT score, BDI focal score, baseline E-RS score, geographical region, number of bronchodilators per day during run-in, visit by baseline SGRQ score, visit by baseline CAT score, visit by BDI focal score, visit by baseline E-RS score and visit by treatment interactions included as covariates. OR, odds ratio.

Figure 2. Relationship between the number of positive PRO responses at Week 4 and improvement from baseline in disease severity (GADS) at Weeks 4 and 24



*GADS was rated by patients at Weeks 4 and 24 compared with baseline using a seven-point Likert scale: 'much better', 'better', 'slightly better', 'no change', 'slightly worse', 'worse', 'much worse'.

Conclusions

- Patients who achieved CII at Week 4 were more likely to have future improvement in GADS at Week 24 and a lower risk of CID compared with patients who did not achieve CII at Week 4.
- This suggests that early assessment of concordant clinical responses to treatment may be predictive of longer-term improvements in patient-perceived symptoms, as well as increased stability of treatment responses.
- In addition, this study shows that physicians can obtain useful information about treatment efficacy by using a standardized approach to ask patients about improvements in their COPD.

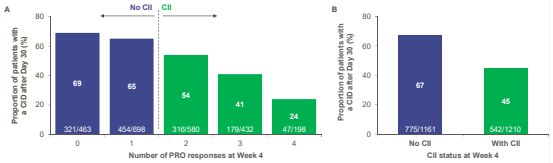
Table 3. Improvement from baseline in GADS at Weeks 4 and 24 by PRO responses at Week 4

Ordered OR* (95% CI) of a better GADS response category versus 0 PRO responses at Week 4

	Number of positive PRO responses			
	1 PRO	2 PROs	3 PROs	4 PROs
Week 4	2.91 (2.30, 3.69); *P*<0.001	6.67 (5.18, 8.61); *P*<0.001	15.96 (12.07, 21.10); *P*<0.001	42.07 (29.58, 59.83); *P*<0.001
Week 24	1.87 (1.47, 2.38); *P*<0.001	2.64 (2.06, 3.39); *P*<0.001	4.10 (3.12, 5.40); *P*<0.001	5.50 (3.88, 7.78); *P*<0.001

*Ordered OR (95% CI) were obtained using a generalized linear model with covariates of number of PRO responses, treatment, number of bronchodilators per day during run-in and geographical region.

Figure 3. Relationship between the number of PRO responses at Week 4 and the proportion of patients with a CID event after Day 30



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