Preventing Clinically Important Deterioration With Umeclidinium/Vilanterol Versus Bronchodilator Monotherapy in Patients With Chronic Obstructive Pulmonary Disease Free of Inhaled Corticosteroids: A Prospective Analysis of the EMAX Trial

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Background

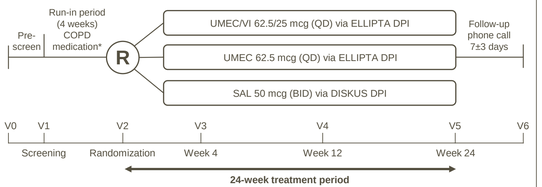
- Many patients with chronic obstructive pulmonary disease (COPD) on long-acting muscarinic antagonist (LAMA) or long-acting β_2-agonist (LABA) monotherapy continue to experience significant symptoms.[1]
- Previous studies have shown that ≥50% of patients receiving mono-bronchodilator therapy (with or without inhaled corticosteroids [ICS]) experience short-term worsening as measured by the clinically important deterioration (CID) composite endpoint; however, early optimization to dual-bronchodilator maintenance therapy reduces this risk.[2-7]
- Maintaining short-term disease stability and freedom from CID is also associated with sustained long-term treatment benefits and reduced future risk of exacerbations and mortality.[5,6,8,9]
- The original and most widely adopted definition of the CID composite endpoint includes one or more of: a first exacerbation, a trough forced expiratory volume in 1 second (FEV_1) decrease, and a deterioration in health status using St George's Respiratory Questionnaire (SGRQ). Alternative definitions with other components of deterioration, including the COPD Assessment Test (CAT) and Transition Dyspnea Index (TDI), have also been described.[4,7]
- This prospective analysis of the Early MAXimization of bronchodilation for improving COPD stability (EMAX) trial aimed to quantify the risk of a first CID in symptomatic ICS-free patients at low exacerbation risk receiving umeclidinium/vilanterol (UMEC/VI), UMEC, or salmeterol (SAL).

Methods

Study design

- The 24-week, double-blind, parallel-group EMAX trial randomized patients 1:1:1 to UMEC/VI 62.5/25 mcg once-daily via the ELLIPTA inhaler, UMEC 62.5 mcg once-daily via the ELLIPTA inhaler or SAL 50 mcg twice-daily via the DISKUS inhaler (**Figure 1**).[10,11]
- Full eligibility criteria have been described previously.[10] Briefly, patients were ≥40 years of age, ICS and LAMA/LABA free, current/former smokers, with a COPD diagnosis, a post-albuterol FEV_1 ≥30%–≤80% predicted, ≤1 moderate exacerbation in the previous year, and a CAT score ≥10.

Figure 1. Study design



*Patients were permitted to continue use of inhaled LAMA or LABA and/or study-provided salbutamol (rescue medication) as needed during the run-in period. BID, twice a day; DPI, dry powder inhaler; QD, once a day; R, randomization; V, visit

Endpoints and statistical analyses

- Risk of a first CID was assessed according to three a priori and one post hoc definitions:
  - A) A first exacerbation, and/or trough FEV_1 decrease from baseline of ≥100 mL, and/or deterioration in health status using SGRQ (≥4 units from baseline).
  - B) As above with CAT deterioration (≥2 units from baseline) replacing SGRQ deterioration.
  - C) A FEV_1-free CID definition including a first exacerbation, and/or SGRQ deterioration, and/or CAT deterioration, and/or a TDI deterioration (≥1 unit decrease from baseline).
  - D) A post hoc definition including a first exacerbation, and/or trough FEV_1 ≥100 mL decrease from baseline, and/or TDI ≥1 unit decrease from baseline.
- Pairwise statistical comparisons of the risk of CID were evaluated up to Day 168 and assessed using Cox proportional hazards model to compare UMEC/VI with UMEC and SAL.

Results

- The intent-to-treat population included 2425 patients (UMEC/VI: 812; UMEC: 804; SAL: 809); baseline patient demographics and clinical characteristics were similar between treatment arms (**Table 1**).[11]

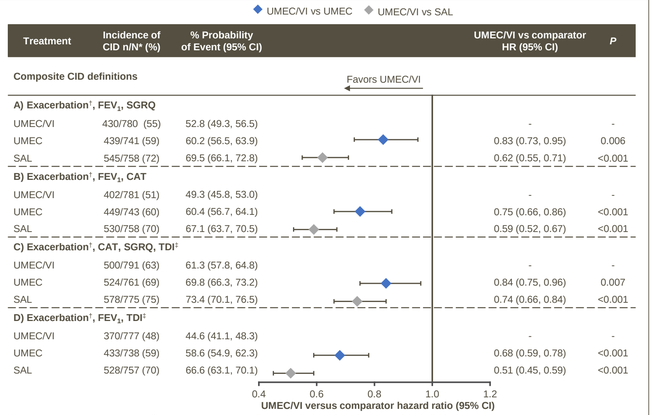
Table 1. Baseline demographics and clinical characteristics

Characteristic	UMEC/VI (N=812)	UMEC (N=804)	SAL (N=809)	Total (N=2425)
Age, years, mean (SD)	64.6 (8.4)	64.9 (8.5)	64.4 (8.5)	64.6 (8.5)
Female, n (%)	319 (39)	327 (41)	342 (42)	988 (41)
Current smoker at screening, n (%)	394 (49)	396 (49)	413 (51)	1203 (50)
Smoking pack-years, mean (SD)	49.4 (27.7)	47.6 (25.9)	48.1 (25.8)	48.4 (26.5)
Post-albuterol FEV_1, mL, mean (SD)	1577 (506)	1609 (503)	1600 (523)	1595 (511)
Post-albuterol % predicted FEV_1, mean (SD)	54.9 (12.8)	55.9 (12.6)	55.6 (12.8)	55.4 (12.7)
COPD duration, years, mean (SD)	8.8 (6.9)	7.8 (6.0)	8.3 (6.7)	8.3 (6.6)
Baseline FEV_1, mL, mean (SD)	1474 (513)	1503 (505)	1495 (533)	1491 (517)
BDI score, mean (SD)	7.0 (1.8)	7.0 (1.9)	7.1 (1.8)	7.0 (1.9)
Baseline CAT score, mean (SD)	19.1 (5.9)	19.3 (6.2)	19.3 (6.3)	19.2 (6.1)
Baseline SGRQ total score, mean (SD)	44.5 (16.1)	45.0 (16.1)	44.6 (16.3)	44.7 (16.2)
Moderate COPD exacerbation history in prior year*, n (%)	123 (15)	124 (15)	146 (18)	393 (16)

*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).
BDI, baseline dyspnea index; SD, standard deviation

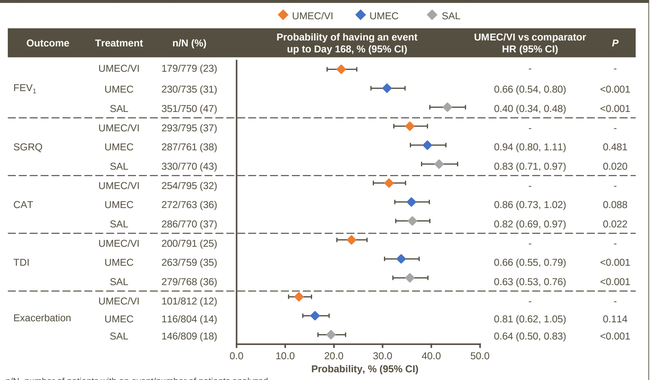
- The probability of a short-term CID was high for all treatments (44.6%–73.4%).
- The probability of a CID event was lower for UMEC/VI compared with UMEC and SAL for all four CID definitions (**Figure 2**).
- In prospective analyses, UMEC/VI significantly reduced the risk of a first CID versus UMEC (16%–25%; P<0.01) and SAL (26%–41%; P<0.001) (**Figure 2**).
- The greatest reduction in risk was seen for the CID definition using exacerbation, FEV_1, or TDI, with which UMEC/VI significantly reduced the risk of a first CID compared with both UMEC (32%) and SAL (49%) (both P<0.001) (**Figure 2**).

Figure 2. Risk of a first CID up to Day 168 across multiple composite definitions



*N, patients with at least 1 post baseline assessment (not including exacerbations) for at least one of the individual components or patients who had an exacerbation; †moderate/severe exacerbation; ‡ assessed using a self-administered computerized version.
CI, confidence interval; HR, hazard ratio; n, number of patients with an event

Figure 3. Percent probability of individual component CID event types to Day 168



n/N, number of patients with an event/number of patients analyzed

- The probability of an exacerbation event was low across all treatments (13%–19%), whereas the probabilities of other types of CID events were higher (UMEC/VI [22%–36%], UMEC [31%–39%], and SAL [36%–43%]) (**Figure 3**).
- UMEC/VI significantly reduced the risk of all individual CID component events versus SAL (P<0.05), and the FEV_1 and TDI components versus UMEC (P<0.001) (**Figure 3**).
  - The probability of deterioration in FEV_1 or TDI among patients receiving UMEC/VI was 22% and 24%, compared with 31% and 34% for UMEC and 43% and 36% for SAL (**Figure 3**).

Conclusions

- This first prospective analysis of CID comparing a LAMA/LABA with monotherapy confirmed a high incidence of short-term worsening within 6 months.
- UMEC/VI consistently provided increased protection from this short-term worsening versus UMEC and SAL.
- These findings were consistent for all four short-term composite CID definitions examined, including the CID definition without decrease in FEV_1.
- These findings provide additional evidence to support the early intensification of bronchodilator therapy in symptomatic low-risk patients with COPD to prevent short-term worsening, which indicates potential treatment failure.

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Disclosures

IN, IB, DAL, CC, and PJ are employees of GlaxoSmithKline (GSK) and hold stocks and shares in GSK. MLW was an employee of GSK at the time of the study. LT is a contingent worker on assignment at GSK. FM has received research grants for participating in multicenter trials for AstraZeneca, Boehringer Ingelheim, GSK, Sanofi, and Novartis, and has received unrestricted research grants and personal fees from Boehringer Ingelheim, Grifols, and Novartis. LB has received honoraria for giving a lecture or attending an advisory board for Airsonett, ALK-Abello, AstraZeneca, Boehringer, Chiesi, GSK, Meda, Novartis, and Teva. EK has attended advisory boards for Amphastar, Boehringer Ingelheim, Cipla, GSK, Mylan, Novartis, Sunovion, Teva, and Theravance and has received personal fees from Boehringer Ingelheim, Forest, Novartis, Teva, and Theravance. CFV has been an advisor for and/or received personal fees and/or grants from AstraZeneca, Bayer-Schering, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, GSK, Grifols, Menarini, MSD, Mundipharma, Novartis, Pfizer, and Teva. ELLIPTA and DISKUS are owned by/licensed to the GSK group of companies.

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