Comparative Efficacy of Once-Daily Umeclidinium and Twice-Daily Salmeterol in Symptomatic Patients With Chronic Obstructive Pulmonary Disease Free of Inhaled Corticosteroids: Results from the EMAX Trial

Poster No. P509 (A3320)

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Background

- Long-acting muscarinic antagonist (LAMA) and long-acting β_2-agonist (LABA) monotherapies are currently recommended as first-line maintenance therapy in symptomatic patients with chronic obstructive pulmonary disease (COPD) at low risk of exacerbation.[1]
- Relief of COPD symptoms is similar when using LAMAs or LABAs; consequently, no clear choice of first-line therapy is advocated in low exacerbation risk patients.[1,2]
- Previous between-class LAMA and LABA comparator trials, such as the POET and INVIGORATE trials have included high exacerbation risk patients using concurrent inhaled corticosteroid (ICS) therapy, which may confound efficacy comparisons; therefore, studies in ICS-free patients are needed to determine whether the efficacy of LAMA and LABA therapies is similar in these patients.[3–6]
- The Early MAXimization of bronchodilation for improving COPD stability (EMAX) trial (NCT03034915; GSK study 201749) was designed to compare three different bronchodilators umeclidinium/vilanterol (UMEC/VI), UMEC and salmeterol (SAL), in symptomatic ICS-free patients at low exacerbation risk.
- UMEC was selected for comparison as it is a component of the dual bronchodilator and it has also demonstrated superior lung function benefits compared with tiotropium in ICS-treated and ICS-free patients with moderate-to-severe COPD.[7]
- Prior double-blind comparisons of UMEC and the once-daily LABA VI have indicated no symptom or health status benefits between the monotherapies.[8] However, as no once-daily LABAs are approved at a common dose in the EU and USA, this study selected the twice-daily LABA SAL, the only LABA approved at a standard dose in all countries participating in the study, to enable comparison between approved medicines.
- This prospective analysis of the EMAX trial presents the comparison between UMEC and SAL monotherapies, with data for UMEC/VI 62.5/25 mcg once daily compared with the monotherapies presented in Poster 212 (Abstract 2446).[9]

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 ELLIPTA inhaler, UMEC 62.5 mcg once daily via ELLIPTA inhaler or SAL 50 mcg twice daily via DISKUS inhaler following a 4-week run-in period on existing mono-bronchodilator maintenance therapy and/or short-acting bronchodilator rescue therapy.[10]
- Eligible patients were: ≥40 years of age; current/former smokers with a COPD diagnosis; post-albuterol forced expiratory volume in 1 second (FEV_1) ≥30%–≤80% predicted (Global Innitative for Chronic Obstructive Pulmonary Disease [GOLD] 2/3); a pre- and post-albuterol FEV_1/forced vital capacity (FVC) ratio of <0.7; a history of ≤1 moderate exacerbation in the previous year; a COPD Assessment Test (CAT) score ≥10 and were using a LAMA or LABA bronchodilator, but were not receiving ICS-containing therapy or LAMA/LABA combination treatment at screening.

Endpoints and assessments

- Lung function endpoints included change from baseline in trough FEV_1, FVC, and inspiratory capacity (IC) at Week 24.
- Patient-reported outcomes included change in symptoms from baseline and percentage of responders in self-administered computerized Transition Dyspnea Index (TDI), Evaluating Respiratory Symptoms-COPD (E-RS) and Subject Global Rating of Change in COPD Severity (SGRSI), and change in in quality of life from St George's Respiratory Questionnaire (SGRQ) and CAT.
- Use of rescue medication endpoints included the percentage of rescue albuterol-free days and mean inhalations of albuterol per day.
- Time-to-first moderate (requiring treatment with corticosteroids and/or antibiotics) and severe (requiring hospitalization) COPD exacerbations and time-to-first short-term clinically important deterioration (CID; a composite endpoint defined as: a ≥100 mL decrease from baseline in trough FEV_1; a ≥4 unit decrease in SGRQ total score from baseline or occurrence of a moderate/severe COPD exacerbation) were assessed.
- Adverse events (AEs) were recorded.

Statistical analysis

- The intent-to-treat population was analyzed for all reported endpoints and included all patients who were randomized who received ≥1 dose of study medication.
- Change from baseline was analyzed using mixed model repeated measures, proportion of responders was analyzed using a generalized linear mixed model, and time-to-first analysis was evaluated using Cox's proportional hazards model and Kaplan–Meier analysis. Hazard ratios (HR), odds ratios (OR) and 95% confidence intervals (CIs) were reported.

Results

Patients

- Overall, 804 and 809 patients received UMEC and SAL, respectively; baseline characteristics were similar between groups (**Table 1**).
  - Study completion rates for patients who received UMEC and SAL were 81% and 84%, respectively.

Lung function

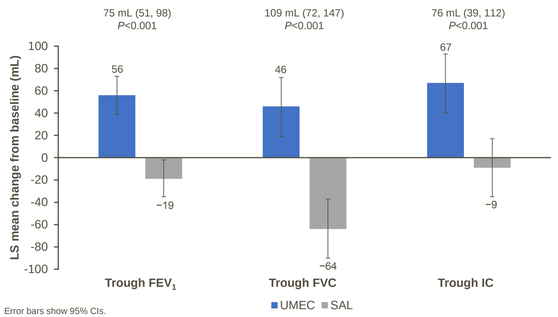
- UMEC demonstrated significantly greater improvements versus SAL in change from baseline in trough FEV_1, FVC, and IC from Week 4 (57 mL [95% CI, 35, 78], *P*<0.001; 98 mL [65, 132], *P*<0.001; 45 mL [12, 77], *P*=0.007, respectively), which were sustained through Week 24 (75 mL [51, 98]; 109 mL [72, 147]; 76 mL [39, 112], all *P*<0.001; **Figure 1**).

Table 1. Summary of patient demographics and baseline characteristics

Characteristic	UMEC (N=804)	SAL (N=809)
Age, years, mean (SD)	64.9 (8.5)	64.4 (8.5)
Female, n (%)	327 (41)	342 (42)
Current smoker at screening, n (%)	396 (49)	413 (51)
Smoking pack-years, mean (SD)	47.6 (25.9)	48.1 (25.8)
Post-albuterol FEV_1, mL, mean (SD)	1609 (503)	1600 (523)
Post-albuterol % predicted FEV_1, mean (SD)	55.9 (12.6)	55.6 (12.8)
Post-albuterol FEV_1/FVC, mean ratio (SD)	0.52 (0.10)	0.52 (0.10)
% reversibility to albuterol, mean (SD)	10.2 (13.3)	10.7 (13.3)
Moderate COPD exacerbation history in prior year*, n (%)	124 (15)	146 (18)
GOLD grade†, n (%) 2 3	 529 (66) 271 (34)	 522 (65) 286 (35)
COPD duration, years, mean (SD)	7.8 (6.0)	8.3 (6.7)
Baseline FEV_1, mL, mean (SD)	1503 (505)	1495 (533)
BDI score, mean (SD)	7.0 (1.9)	7.1 (1.8)
Baseline CAT score, mean (SD)	19.3 (6.2)	19.3 (6.3)
Baseline rescue albuterol, puffs/day, mean (SD)	2.1 (2.3)	2.2 (2.5)

*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 were excluded from the trial; †an additional 4 patients (<1%) with GOLD grade 1 were randomized (UMEC n=3; SAL n=1).
BDI, baseline dyspnea index; SD, standard deviation

Figure 1. Change from baseline in lung function parameters at Week 24



Error bars show 95% CIs.
LS, least squares

Symptoms

- There were no statistically significant differences between UMEC and SAL for TDI and SGRSI at Week 24 and for E-RS score and albuterol use at Weeks 1–24 (**Table 2**).
- No statistically significant differences were seen in the proportions of responders for TDI and E-RS total score between the two treatment groups.

Health-related quality of life

- Change from baseline at Week 24 in SGRQ was significantly greater for UMEC versus SAL with a greater proportion of SGRQ responders in the UMEC treatment group (UMEC 41% vs SAL 36%; odds ratio [95% CI]: 1.23 [1.00, 1.51], *P*=0.045). There were no statistically significant between-treatment differences in change from baseline in SGRQ score or responder rates at Weeks 4 and 12 (**Table 2, Figure 2**) or in change from baseline in CAT score or responder rates at Week 24 (**Table 2**).

COPD exacerbations and short-term CID

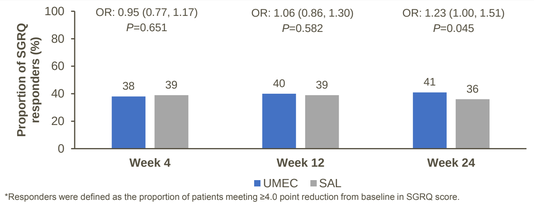
- The probability of experiencing a first moderate/severe exacerbation or a first CID up to Day 168 was lower in patients receiving UMEC versus SAL (**Figure 3**).
- There was no statistically significant difference in the risk of a first moderate/severe exacerbation for UMEC versus SAL (HR [95% CI]: 0.80 [0.62, 1.02]; *P*=0.067); however, risk of a first CID significantly favored UMEC (HR [95% CI]: 0.78 [0.69, 0.89]; *P*<0.001) (**Figure 3**).

Table 2. Change from baseline and proportion of responders in symptom, health-related quality of life, and rescue medication use outcomes

Outcome	UMEC n	UMEC LS mean CFB (95% CI)	SAL n	SAL LS mean CFB (95% CI)	UMEC vs SAL Mean difference (95% CI)	*P*-value
TDI*	636	1.30 (1.08, 1.53)	673	1.22 (1.00, 1.44)	0.08 (−0.23, 0.39)	0.610
E-RS total score†	621	−0.99 (−1.29, −0.69)	653	−0.69 (-0.98, −0.39)	−0.30 (−0.72, 0.12)	0.159
SGRQ total score*	636	−5.23 (−6.18, −4.28)	674	−3.29 (−4.22, −2.36)	−1.94 (−3.27, −0.61)	0.004
CAT score*	633	−3.4 (−3.9, −3.0)	669	−2.9 (−3.4, −2.5)	−0.5 (−1.1, 0.1)	0.107
% albuterol-free days‡	799	6.55 (4.42, 8.68)	805	7.68 (5.55, 9.80)	−1.13 (−4.14, 1.88)	0.463
Mean albuterol inhalations/day‡	799	−0.28 (-0.38, −0.17)	805	−0.32 (−0.43, −0.22)	0.05 (−0.10, 0.19)	0.520
SGRSI*,§, n, %	638	393 (62)‖	674	413 (61)‖	1.00 (0.82, 1.22)**	0.971
Outcome	**UMEC n**	**UMEC Responders, n (%)**	**SAL n**	**SAL Responders, n (%)**	**UMEC vs SAL Odds ratio (95% CI)**	***P*-value**
TDI*	799	332 (42)	807	330 (41)	1.03 (0.84, 1.27)	0.755
E-RS†	800	219 (27)	808	217 (27)	1.00 (0.80, 1.26)	0.969
SGRQ*	802	329 (41)	809	291 (36)	1.23 (1.00, 1.51)	0.045
CAT*	804	385 (48)	809	406 (50)	0.91 (0.75, 1.11)	0.363

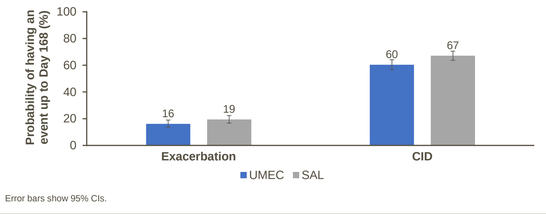
*At Week 24; †at Weeks 21–24; ‡at Weeks 1–24; §overall assessment of change in COPD severity was rated using a seven-point Likert scale ('Much Better', 'Better', 'Slightly Better', 'No Change', 'Slightly Worse', 'Worse', 'Much Worse'); ‖patients reporting an improvement; **ordered response ratios were reported as odds of better response category.

Figure 2. Proportion of SGRQ responders* at Weeks 4, 12, and 24



*Responders were defined as the proportion of patients meeting ≥4.0 point reduction from baseline in SGRQ score.

Figure 3. Percent probability of first moderate/severe exacerbation and short-term CID at Day 168



Error bars show 95% CIs.

Safety

- The incidence and type of AEs and serious AEs were similar between groups.
- In total, 37 (5%) and 27 (3%) drug-related AEs occurred in the UMEC and SAL groups, respectively.
  - Nasopharyngitis was the most common on-treatment AE in both UMEC (11%) and SAL (10%) treatment groups.
  - There were no treatment-related serious AEs.

Conclusions

- In the EMAX trial, once-daily UMEC consistently improved all lung function measures compared with twice-daily SAL throughout the 6-month observation period.
- These marked differences in lung function failed to translate into consistent symptom or health-related quality of life benefits between the LAMA and LABA monotherapies. These data support the GOLD 2019 strategy document suggestion that either a LAMA or LABA monotherapy may be used as first-choice treatment in GOLD group B patients.[1]
- Other than for SGRQ, there were no differences in patient-reported outcomes between UMEC and SAL; however, risk of a CID was lower for UMEC versus SAL.
- These pre-specified data highlight the limited scope for detecting improvements between monotherapy bronchodilators in low-risk symptomatic patients with COPD, but suggest that the improved lung function observed with UMEC compared with SAL may be associated with preventing clinically important deteriorations.

References

1. Global Initiative for Chronic Obstructive Lung Disease. 2019 Report. Available from: https://goldcopd.org/wp-content /uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf [last accessed January 2019]; 2. Kew KM, et al. *Cochrane Database Syst Rev* 2014;(3):CD010844; 3. Decramer ML, et al. *Lancet Respir Med* 2013;1(7):524–33; 4. Vogelmeier C, et al. *N Engl J Med* 2011;364(12):1093–1103; 5. Donohue JF, et al. *Int J Chron Obstruct Pulmon Dis* 2017;12:367–81; 6. Buhl R, et al. *Eur Respir J* 2015;45(4):969–79; 7. Feldman G, et a. *Int J Chron Obstruct Pulmon Dis* 2016;11:719–30; 8. Donohue JF, et al. *Respir Med* 2013;107:1538–4; 9. Maltais F, et al. *ATS 2019*; Poster 212 (Abstract 2446); 10. Jones P, et al. *Thorax* 2018;73(Suppl 4):A235–6.

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 and holds stock and shares in GSK. 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.

Acknowledgments

- This study was funded by GSK (study 201749; NCT03034915).
- Editorial support (in the form of writing assistance, including development of the initial draft based on author direction, assembling tables and figures, collating authors' comments, grammatical editing, and referencing) was provided by Katie White, PhD, at Fishawack Indicia Ltd, UK, and was funded by GSK.