Efficacy and Safety of Inhaled Umeclidinium/Vilanterol in COPD According to Level of Airflow Limitation: A Post Hoc Analysis

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Asmus MJ[1]*, Tombs L[2], Ray R[1], Naya I[3], Boucot I[3]

[1]US Medical Affairs, GSK, Research Triangle Park, NC, USA; [2]Precise Approach Ltd, contingent worker on assignment at GSK, Stockley Park West, Uxbridge, Middlesex, UK; [3]Global Respiratory Franchise, GSK, Brentford, Middlesex, UK; *At the time of the study

Background

- Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation.[1] Airflow limitation in COPD can be classified as mild, moderate, severe or very severe based on post-bronchodilator forced expiratory volume in 1 second (FEV_1) as defined by the 2019 Global initiative for chronic Obstructive Lung Disease (GOLD) strategy.[1]
- The long-acting bronchodilator combination umeclidinium/vilanterol (UMEC/VI) delivered by the ELLIPTA dry powder inhaler (DPI) has been demonstrated to improve lung function and health-related quality of life compared with a range of maintenance medications and reduce the risk of a first exacerbation versus placebo in patients with moderate to very severe COPD.[2–6]
- Data from in vitro investigations of the ELLIPTA DPI suggest that deposition and performance is independent of a patient's airflow limitation[7]; consequently, a direct comparison of the efficacy and safety of UMEC/VI delivered via the ELLIPTA DPI in patients with differing degrees of airflow limitation would be informative.
- The objective of this study was to compare the efficacy and safety profile of inhaled UMEC/VI delivered via the ELLIPTA DPI with other maintenance medications in patients with COPD among subgroups of patients with moderate (GOLD 2) and severe/very severe (GOLD 3/4) airflow limitation.

Methods

Primary studies

- This was a post hoc intent-to-treat integrated analysis (GSK ID: 208125) of seven, randomized, double-blind COPD clinical trials (NCT01316900,[2] NCT01316913,[2] NCT01313650,[3] NCT01817764,[4] NCT01879410,[4] NCT02152605,[5] and NCT01777334[6]).
- Key patient eligibility criteria from the primary studies included being ≥40 years of age, having a smoking-pack history ≥10 years, and evidence of fixed airway obstruction. In one study, patients with a history of exacerbations in the year before screening were excluded.[4]

Integrated analysis

- Patients included in this analysis received once-daily UMEC/VI 62.5/25 mcg administered via the ELLIPTA DPI, twice-daily fluticasone propionate/salmeterol (FP/SAL) 250/50 mcg administered via the DISKUS DPI, once-daily tiotropium (TIO) 18 mcg administered via the Handihaler DPI or once-daily placebo administered via the ELLIPTA DPI.
- Patients were analyzed in subgroups according to airflow limitation as defined by the 2018 GOLD strategy document: moderate (GOLD 2) or severe/very severe (GOLD 3/4), ≥50%–<80% or ≥30%–<50% of predicted post-bronchodilator FEV_1, respectively.[8]
- Endpoints included change from baseline in trough FEV_1 and proportion of FEV_1 responders (defined as a change from baseline in trough FEV_1 ≥100 mL) on Days 28, 56, and 84. The incidence of adverse events (AEs) over 12 weeks was reported.
- Trough FEV_1 was analyzed using mixed model repeated measures on each subgroup level separately. The proportion of FEV_1 responders was analyzed using a generalized linear mixed model. Covariates for these analyses were study, treatment, smoking status at screening, baseline FEV_1 (mean of 30 min and 5 min pre-dose on Day 1), visit, visit by baseline, and visit by treatment interactions.

Results

Patients

- In total, 4341 patients were included in this analysis (GOLD 2, n=2039; GOLD 3/4, n=2302). Of these, 2242 received UMEC/VI, 700 received FP/SAL, 871 received TIO, and 528 received placebo.
- Patient demographics and baseline characteristics by GOLD grade (**Table 1**) were similar across treatment groups (data not shown).

Table 1. Patient demographics

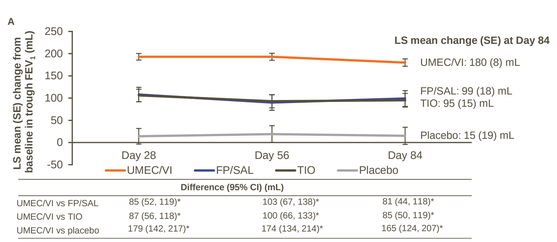
Characteristic	GOLD 2 (N=2039)	GOLD 3/4 (N=2302)
Age, years, mean (SD)	62.9 (9.1)	63.3 (8.4)
Female, n (%)	691 (34)	643 (28)
Current smoker at screening, n (%)	1070 (52)	1113 (48)
Smoking pack-years, mean (SD)	43.2 (25.2)	45.3 (25.5)

SD, standard deviation

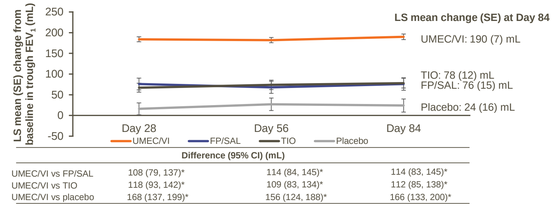
Lung function

- Statistically significant improvements in trough FEV_1 from baseline were observed with UMEC/VI versus all treatment groups at all time points in both GOLD 2 and GOLD 3/4 subgroups (**Figure 1**).
  - Improvements from baseline in trough FEV_1 with FP/SAL and TIO were significantly lower (80 mL–110 mL) than UMEC/VI at all time points in both the GOLD 2 and GOLD 3/4 subgroups.

Figure 1. LS mean (SE) change from baseline in trough FEV_1 in patients with A) GOLD 2 and B) GOLD 3/4 COPD



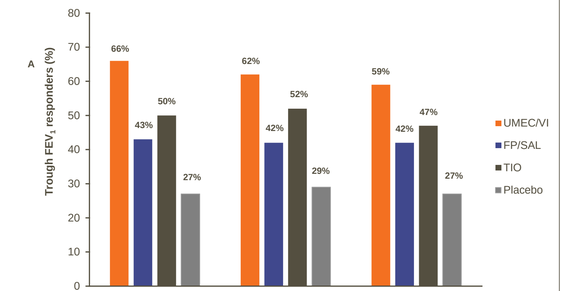
Difference (95% CI) (mL)	Day 28	Day 56	Day 84
UMEC/VI vs FP/SAL	85 (52, 119)*	103 (67, 138)*	81 (44, 118)*
UMEC/VI vs TIO	87 (56, 118)*	100 (66, 133)*	85 (50, 119)*
UMEC/VI vs placebo	179 (142, 217)*	174 (134, 214)*	165 (124, 207)*



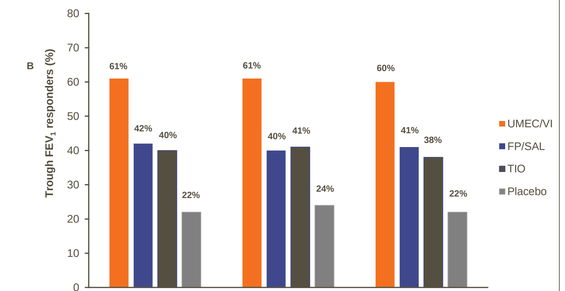
Difference (95% CI) (mL)	Day 28	Day 56	Day 84
UMEC/VI vs FP/SAL	108 (79, 137)*	114 (84, 145)*	114 (83, 145)*
UMEC/VI vs TIO	118 (93, 142)*	109 (83, 134)*	112 (85, 138)*
UMEC/VI vs placebo	168 (137, 199)*	156 (124, 188)*	166 (133, 200)*

*P<0.001.
CI, confidence interval; LS, least squares; SE, standard error

Figure 2. Proportion of trough FEV_1 responders in patients with A) GOLD 2 and B) GOLD 3/4 COPD



Odds ratio (95% CI)	Day 28	Day 56	Day 84
UMEC/VI vs FP/SAL	2.61 (1.94, 3.50)*	2.27 (1.69, 3.04)*	2.04 (1.52, 2.74)*
UMEC/VI vs TIO	2.21 (1.68, 2.89)*	1.73 (1.32, 2.26)*	1.74 (1.33, 2.28)*
UMEC/VI vs placebo	4.89 (3.45, 6.93)*	3.74 (2.66, 5.26)*	3.64 (2.57, 5.15)*



Odds ratio (95% CI)	Day 28	Day 56	Day 84
UMEC/VI vs FP/SAL	2.09 (1.58, 2.78)*	2.24 (1.68, 2.98)*	2.10 (1.58, 2.79)*
UMEC/VI vs TIO	2.74 (2.14, 3.49)*	2.58 (2.03, 3.29)*	2.79 (2.18, 3.57)*
UMEC/VI vs placebo	5.13 (3.66, 7.19)*	4.50 (3.24, 6.26)*	4.74 (3.39, 6.62)*

*P<0.001.

- A greater proportion of patients treated with UMEC/VI (59%–66%) were FEV_1 responders compared with patients treated with FP/SAL (40%–43%), TIO (38%–51%), and placebo (22%–27%) at all time points and across GOLD airflow limitation subgroups (**Figure 2**).
  - The odds of a patient being an FEV_1 responder were statistically significantly (P<0.001) greater with UMEC/VI compared with FP/SAL, TIO, and placebo in both GOLD 2 and GOLD 3/4 subgroups.
  - The odds of a patient being an FEV_1 responder with UMEC/VI versus TIO were numerically higher in the GOLD 3/4 subgroup compared with the GOLD 2 subgroup.

Safety

- The safety profiles of all treatments were similar and consistent between airflow limitation severity subgroups at 12 weeks.
  - The most common AEs, regardless of airflow limitation severity subgroup or treatment, were headache (≤10% of patients) and viral upper respiratory tract infection (≤8% of patients).
  - The incidence of serious AEs was 2%–6% across treatment groups and airflow limitation severity, with only one fatal AE reported (pneumonia in a patient with GOLD 3/4 COPD treated with FP/SAL).

Conclusions

- In stable symptomatic patients with a low exacerbation risk, UMEC/VI delivered via the ELLIPTA DPI consistently provided clinically important improvements in lung function over other COPD maintenance medications and placebo at all time points.
- After 12 weeks on-treatment, the odds of responding favorably were increased 1.7–2.8-fold with UMEC/VI versus either FP/SAL or TIO. Patients with severe/very severe airflow limitation at baseline (GOLD 3/4) showed greater improvements in lung function with UMEC/VI versus TIO or placebo than those with moderate airflow limitation (GOLD 2).
- This post hoc analysis suggests that clinically relevant improvements in lung function with UMEC/VI delivered via the ELLIPTA DPI are likely to be independent of a patient's baseline airflow limitation.

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Disclosures

- IN, IB, and RR are employees of GlaxoSmithKline (GSK) and hold GSK stocks/shares. LT is a contingent worker on assignment at GSK. MJA was an employee of GSK at the time of the study and holds GSK stocks/shares. ELLIPTA and DISKUS are owned by/licensed to the GSK group of companies. HandiHaler is a registered trademark of Boehringer Ingelheim International GmbH.

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