Impact of Smoking Status on Improvements in Lung Function With Umeclidinium/Vilanterol Versus Fluticasone Propionate/Salmeterol in Patients With COPD

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Background

- In the US, 35%–50% of patients with chronic obstructive pulmonary disease (COPD) are current smokers.[1,2] Many patients with symptomatic COPD and a low risk of exacerbation continue smoking.
- Primary care physicians commonly prescribe a combination of an inhaled corticosteroid and a long-acting β_2-agonist (ICS/LABA) for patients with COPD, irrespective of smoking status.[3]
- Evidence suggests that the anti-inflammatory effects of preventative therapies such as ICS are diminished during ongoing exposure to tobacco smoke in patients with asthma and COPD.[4,5]
  - Consequently, the first-line use of ICS/LABA in symptomatic, low exacerbation risk patients with COPD who continue to smoke can be questioned.
- As decline in lung function is accelerated during continued smoking,[6] there is a need to assess if the use of long-acting muscarinic antagonist (LAMA)/LABA combination therapy is more effective than ICS/LABA in symptomatic, low exacerbation risk patients with COPD who actively smoke.
  - In two trials comparing the LAMA/LABA umeclidinium/vilanterol (UMEC/VI) with the ICS/LABA fluticasone propionate/salmeterol (FP/SAL), UMEC/VI resulted in improved lung function compared with FP/SAL in the intent-to-treat (ITT) population with moderate-to-severe symptomatic COPD without an exacerbation in the previous year.[7]
  - The objective of this integrated post hoc analysis of these two trials was to compare the efficacy and safety of UMEC/VI with FP/SAL in current and former smokers with a low risk of exacerbation.

Methods

Study design

- This was a post hoc integrated analysis (GSK study number: 209322) of two 12-week, multicenter, randomized, double-blind, double-dummy, parallel studies comparing UMEC/VI 62.5/25 mcg administered daily via the ELLIPTA inhaler and FP/SAL 250/50 mcg administered twice daily via the DISKUS inhaler [DB2114930/NCT01817764, DB2114951/NCT01879410].[7]

Patients

- Eligible patients had symptomatic (modified Medical Research Council dyspnea score ≥2), moderate-to-severe COPD (forced expiratory volume in 1 second [FEV_1] ≥30% and ≤70%) without a documented moderate/severe exacerbation in the year prior to screening.

Endpoints and assessments

- Lung function was evaluated in current and former smokers using the 0–24 hour weighted mean forced FEV_1 at Day 84.
- Secondary endpoints included trough FEV_1 and the proportion of patients achieving an increase in trough FEV_1 of ≥100 mL above baseline at Day 84.
- Adverse events (AEs) were also monitored.

Statistical analysis

- All reported analyses were conducted in the ITT population, which included all randomized patients who received ≥1 dose of study medication.
- 24 hour weighted mean FEV_1 was calculated from the pre-dose and post-dose spirometry measurements at 5 and 15 minutes and 1, 3, 6, 9, 12, 13, 15, 18, 23, and 24 hours after the morning dose.
  - Baseline was the mean of the two assessments made 30 mins and 5 mins pre-dose on Day 1.
  - An analysis of covariance (ANCOVA) model with covariates of study, baseline FEV_1 and treatment was used.
- Trough FEV_1 was analyzed using a mixed model repeated measures analysis with covariates of baseline FEV_1, day, treatment, day by baseline interaction and day by treatment interaction, where day is nominal.

Results

Patients

- A total of 1403 patients were included in the ITT population; 702 patients received UMEC/VI (48% current smokers) and 701 patients received FP/SAL (47% current smokers).
- Baseline demographics and clinical characteristics by smoking status are shown in **Table 1**.

Table 1. Demographics and clinical characteristics

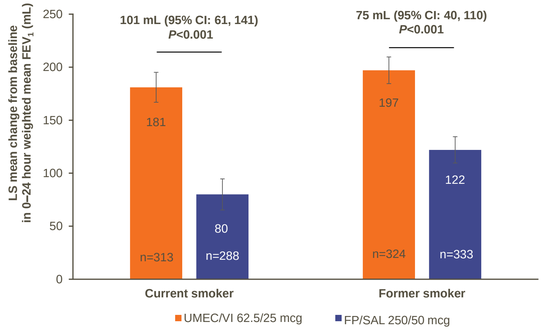
	Current smokers		Former smokers	
	UMEC/VI (N=338)	FP/SAL (N=329)	UMEC/VI (N=364)	FP/SAL (N=372)
Age, years, mean (SD)	60.4 (8.2)	60.9 (7.7)	65.2 (8.7)	65.9 (8.9)
Female, n (%)	101 (30)	98 (30)	84 (23)	95 (26)
Number of years smoked, mean (SD)	40.5 (10.2)	41.0 (9.7)	35.3 (11.7)	35.9 (11.6)
Smoking pack years*, mean (SD)	44.9 (21.9)	44.4 (22.2)	42.1 (25.4)	42.0 (27.7)
Post-albuterol FEV_1, mL, mean (SD)	1528 (434)†	1525 (462)‡	1412 (428)	1425 (473)
Post-albuterol % predicted FEV_1, mean (SD)	49.8 (10.8)†	49.8 (10.9)‡	48.9 (10.8)	49.3 (10.9)
Post-albuterol FEV_1/FVC, mean (SD)	49.1 (10.7)†	48.5 (10.5)‡	47.9 (10.7)	47.8 (10.8)
% reversibility to albuterol, mean (SD)	12.1 (12.5)†	12.8 (14.1)‡	12.5 (14.1)§	11.7 (13.1)

*Smoking pack years = number of cigarettes smoked per day/20) x number of years smoked; †n=337; ‡n=328; §n=363.
FVC, forced vital capacity; SD, standard deviation

Lung function

- At Day 84, UMEC/VI and FP/SAL resulted in improved 0–24 hour weighted mean FEV_1 compared with baseline in both current and former smokers (**Figure 1**).
  - UMEC/VI provided a significantly greater improvement from baseline than FP/SAL in both smoking status subgroups.
  - The observed between-treatment mean difference was greater in current smokers compared with former smokers (101 mL and 75 mL, respectively).

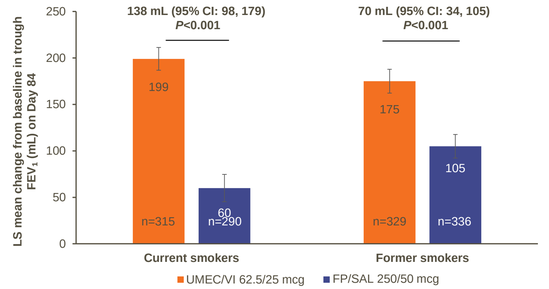
Figure 1. Change from baseline in 0–24 hour weighted mean FEV_1 at Day 84



Error bars represent the standard error of the mean. LS, least squares

- Improvements from baseline in trough FEV_1 were also seen with both UMEC/VI and FP/SAL in current and former smokers at Day 84 (**Figure 2**).
  - UMEC/VI resulted in significantly greater improvements from baseline than FP/SAL in both smoking status subgroups at all timepoints.
  - The observed between-treatment mean difference was greater in current than former smokers (138 mL and 70 mL, respectively).

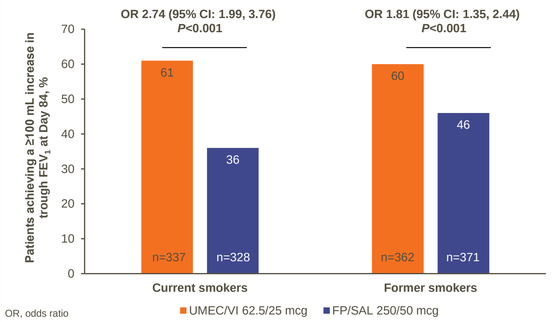
Figure 2. Change from baseline in trough FEV_1 at Day 84



Error bars represent the standard error of the mean.

- At Day 84, a significantly higher proportion of UMEC/VI- than FP/SAL-treated patients achieved a clinically meaningful improvement in trough FEV_1 of ≥100 mL above baseline (**Figure 3**).
  - The observed improvement provided by UMEC/VI over FP/SAL in trough FEV_1 was greater in current than former smokers.

Figure 3. Proportion of patients achieving an increase from baseline of ≥100 mL in trough FEV_1 at Day 84



OR, odds ratio

Safety

- AEs were reported in 27% and 29% of current smokers with UMEC/VI and FP/SAL, respectively; 29% of former smokers experienced AEs with both treatments (**Table 2**).
- Headache and viral upper respiratory tract infection were the most common AEs for both treatments in both current and former smokers (**Table 2**).
- In current smokers, pneumonia occurred in <1% (1/338) of patients in the UMEC/VI subgroup and 2% (5/329) of patients in the FP/SAL subgroup. In former smokers, pneumonia occurred in <1% (2/364) of patients in the UMEC/VI subgroup and 1% (3/372) of patients in the FP/SAL subgroup (**Table 2**).

Table 2. On-treatment AEs

	Current smokers		Former smokers	
	UMEC/VI (N=338)	FP/SAL (N=329)	UMEC/VI (N=364)	FP/SAL (N=372)
On-treatment AEs, n (%)				
Any	92 (27)	95 (29)	105 (29)	109 (29)
On-treatment AEs reported by ≥2% of patients on any treatment, n (%)				
Headache	23 (7)	22 (7)	24 (7)	17 (5)
Viral upper respiratory tract infection	8 (2)	4 (1)	14 (4)	10 (3)
Influenza	3 (<1)	5 (2)	3 (<1)	2 (<1)
Oral candidiasis	0	6 (2)	0	1 (<1)
Pneumonia	1 (<1)	5 (2)	2 (<1)	3 (<1)
Dyspnea	0	0	5 (1)	6 (2)
Back pain	2 (<1)	4 (1)	7 (2)	4 (1)

Conclusions

- In patients with symptomatic, moderate-to-severe COPD, and low risk of exacerbation, UMEC/VI provided greater improvement in lung function compared with FP/SAL, regardless of smoking status. However, the magnitude of the treatment benefit favoring UMEC/VI versus FP/SAL was greater in current smokers.
- These data are consistent with the placement of bronchodilators as the foundation treatment in this population and provide further evidence to support the Global initiative for chronic Obstructive Lung Disease (GOLD) recommendation to use bronchodilators over ICS/LABA in this population.[8]
- Both treatments were well tolerated in current and former smoker subgroups.
- These results support the hypothesis that smoking diminishes the benefits of ICS/LABA in patients with COPD, potentially due to relative steroid resistance, and supports the use of UMEC/VI 62.5/25 mcg to improve lung function in low exacerbation risk patients with COPD, regardless of smoking status.

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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.

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