The IMPACT Trial: Single Inhaler Triple Therapy Fluticasone Furoate/Umeclidinium/Vilanterol Versus Fluticasone Furoate/Vilanterol and Umeclidinium/Vilanterol in Patients With COPD: Results on Rescue Use and Nighttime Awakenings

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Introduction

- Triple therapy with an inhaled corticosteroid, a long-acting muscarinic antagonist and a long-acting β_2-agonist (ICS/LAMA/LABA) is recommended in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) management strategy for chronic obstructive pulmonary disease (COPD) in patients with clinically significant symptoms despite treatment with an ICS/LABA or LAMA/LABA and who are at increased risk of exacerbations.[1]
- Reduction in rescue medication use is an indicator of symptomatic benefits in patients with COPD and is associated with improvements in clinical outcomes such as lung function, breathlessness and health status, and reduction in exacerbation rates.[2]
- Nighttime awakenings due to COPD symptoms are associated with decreased health status and may increase the need for rescue medication. This suggests that nighttime awakenings could be used as a marker of disease control (as is done in asthma[3]) and that reducing the frequency of these events may positively affect health status.[4,5]
- The recent InforMing the PAthway of COPD Treatment (IMPACT) trial demonstrated that once-daily single inhaler triple therapy (SITT) containing fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) resulted in a lower rate of moderate/severe exacerbations and improved lung function and health-related quality of life (HRQoL) compared with dual therapy with FF/VI or UMEC/VI in patients with symptomatic COPD and a history of exacerbations.[6] Based on data from IMPACT, we evaluated the effect of FF/UMEC/VI versus FF/VI and UMEC/VI on rescue medication use and nighttime awakenings due to COPD.

Methods

- IMPACT (GSK study CTT116855; NCT02164513) was a Phase III, 52-week, randomized, double-blind, parallel-group, multicenter study comparing once-daily SITT with FF/UMEC/VI 100/62.5/25 mcg with once-daily dual therapy with FF/VI 100/25 mcg or UMEC/VI 62.5/25 mcg administered via the ELLIPTA inhaler.[6]
- Eligible patients were ≥40 years of age with symptomatic COPD (COPD Assessment Test [CAT] score ≥10) and a history of ≥1 moderate/severe exacerbation in the previous year.
- The primary endpoint was the annual rate of on-treatment moderate/severe exacerbations with FF/UMEC/VI versus FF/VI and UMEC/VI. Other pre-specified efficacy endpoints included: change from baseline in use of rescue medication (salbutamol) (occasions per day), change from baseline in percentage of rescue-free days, and change from baseline in the mean number of nighttime awakenings per night due to COPD symptoms.
- Patients were provided with rescue medication to be used on an as-needed basis throughout the study.
- Use of rescue medication and number of nighttime awakenings due to COPD symptoms were captured in eDiarys completed daily by the patients and collected throughout the 52-week study.
- Analysis was performed by 4-weekly periods in the intent-to-treat (ITT) population using a repeated measures model with covariates of treatment group, smoking status (Screening), geographical region, 4-weekly time period, baseline, and baseline-by-4-weekly time period and treatment group by 4-weekly time period interactions.

Results

Patients

- A total of 10,355 patients were included in the ITT population.
- Baseline demographics and clinical characteristics were similar across the three treatment groups (**Table 1**).

Rescue medication use

- A statistically significant reduction in the number of occasions of rescue medication use/week in each 4-weekly period was seen with FF/UMEC/VI compared with both FF/VI and UMEC/VI (all *P*<0.001; **Figure 1**).
  - At Weeks 49–52, the between-treatment difference in least squares (LS) mean change from baseline in the number of occasions of rescue medication use/week was -1.96 (95% confidence interval [CI]: -2.59, -1.33; *P*<0.001) for FF/UMEC/VI versus FF/VI and -2.10 (95% CI: -2.87, -1.33; *P*<0.001) for FF/UMEC/VI versus UMEC/VI.

Table 1. Baseline demographics and clinical characteristics (ITT population)

	FF/UMEC/VI (N=4151)	FF/VI (N=4134)	UMEC/VI (N=2070)
Age, years, mean (SD)	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)
Female, n (%)	1385 (33)	1386 (34)	714 (34)
Former smoker, n (%)	2715 (65)	2711 (66)	1342 (65)
Post-bronchodilator FEV_1 % predicted, mean (SD)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)
Exacerbation history in prior 12 months, n (%)			
≥2 moderate exacerbations	1967 (47)	1921 (46)	989 (48)
≥1 severe exacerbation	1087 (26)	1069 (26)	515 (25)
CAT score, mean (SD)	20.1 (6.1)	20.1 (6.1)	20.2 (6.2)
No. of occasions of rescue medication use/week, mean (SD)	10.9 (13.5)	11.5 (13.7)	10.9 (13.1)
% of rescue-free days, mean (SD)	45.6 (43.0)	43.3 (43.1)	44.6 (43.0)
Nighttime awakenings/week due to COPD, mean (SD)	4.8 (6.8)	4.9 (6.8)	4.8 (6.7)

FEV_1, forced expiratory volume in 1 second; SD, standard deviation

Figure 1. (A) LS mean and (B) LS mean change from baseline in mean number of occasions of rescue use per week by 4-weekly periods

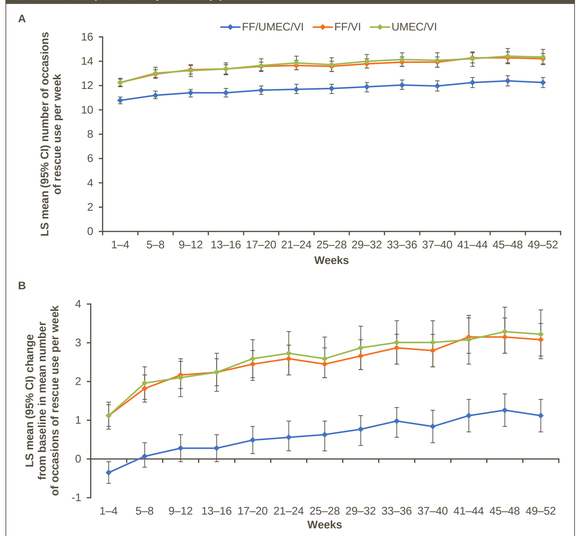


Figure 2. (A) LS mean percentage and (B) LS mean change from baseline in percentage of rescue-free days by 4-weekly periods

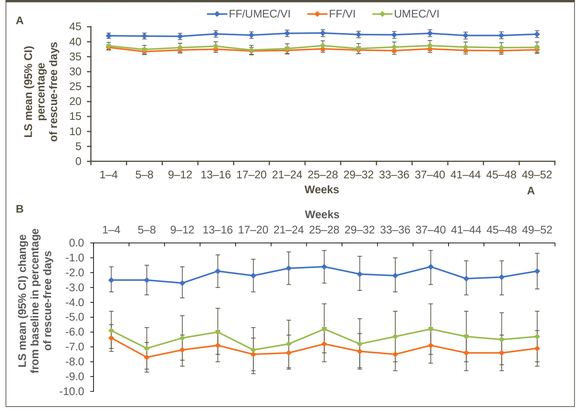
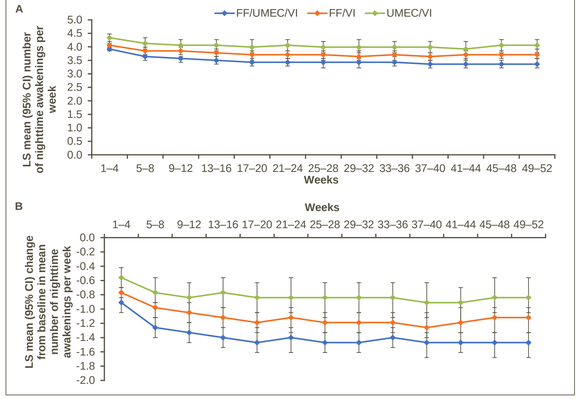


Figure 3. (A) LS mean and (B) LS mean change from baseline in mean number of nighttime awakenings per week by 4-weekly periods



- FF/UMEC/VI also led to more rescue-free days compared with FF/VI and UMEC/VI, with statistically significant treatment differences at each 4-weekly time period for both comparisons (all *P*<0.001; **Figure 2**).
  - At Weeks 49–52, the between-treatment difference in LS mean change from baseline in percentage of rescue-free days was 5.2% (95% CI: 3.5, 6.9; *P*<0.001) for FF/UMEC/VI versus FF/VI and 4.4% (95% CI: 2.3, 6.5; *P*<0.001) for FF/UMEC/VI versus UMEC/VI.

Nighttime awakenings

- Statistically significant reductions in LS mean change from baseline in number of nighttime awakenings were seen at all 4-weekly time points (*P*<0.05) for FF/UMEC/VI compared with FF/VI except in Weeks 1–4 (*P*=0.070) and Weeks 33–36 (*P*=0.056) (**Figure 3**).
- For FF/UMEC/VI versus UMEC/VI, statistically significant reductions in LS mean change from baseline in number of nighttime awakenings per week were observed at all 4-weekly time periods (all *P*<0.001; **Figure 3**).
  - At Weeks 49–52, the between-treatment difference in LS mean change from baseline in number of nighttime awakenings per week was -0.35 (95% CI -0.56, -0.07; *P*=0.005) for FF/UMEC/VI versus FF/VI and -0.70 (95% CI -0.98, -0.35; *P*<0.001) for FF/UMEC/VI versus UMEC/VI.

Safety

- Safety data have been previously published.[6] The safety profile of FF/UMEC/VI was similar to that of FF/VI and UMEC/VI, with no new identified safety signals.[6]

Conclusions

- These results from the IMPACT trial demonstrate the benefits of FF/UMEC/VI versus FF/VI and UMEC/VI on the clinically relevant patient-reported outcomes of rescue medication use and nighttime awakenings.
- The findings underscore a consistent efficacy profile with once-daily FF/UMEC/VI compared with FF/VI and UMEC/VI across a range of COPD endpoints.

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