InforMing the PAthway of COPD Treatment (IMPACT Study) – Single Inhaler Triple Therapy (Fluticasone Furoate/Umeclidinium/Vilanterol) Versus Fluticasone Furoate/Vilanterol and Umeclidinium/Vilanterol in Patients With COPD: Results Based on an Analysis of the North American Region

Poster No. P498 (A3309)

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Introduction

- Treatment for chronic obstructive pulmonary disease (COPD) aims to reduce symptoms, improve health status and exercise tolerance, and reduce the risk of exacerbations.[1] The current Global initiative for chronic Obstructive Lung Disease (GOLD) strategy document recommends treatment escalation to triple therapy with inhaled corticosteroid (ICS)/long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) for patients with recurrent exacerbations receiving LAMA/LABA or ICS/LABA therapy, and patients with persistent dyspnea on ICS/LABA therapy.[1]
- The recent InforMing the PAthway of COPD Treatment (IMPACT) study demonstrated that the once-daily ICS/LAMA/LABA combination of 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 compared with dual therapy with FF/VI (ICS/LABA) or UMEC/VI (LAMA/LABA) in patients with symptomatic COPD and a history of exacerbations.[2]
- Since IMPACT was a global study, post hoc analyses were conducted by geographic region to investigate potential differences to the overall findings from the intent-to-treat (ITT) population. Here, a post hoc analysis of patients in the IMPACT study from the North American (NA) region (USA, Canada, and Puerto Rico) is presented.

Methods

- IMPACT (GSK study CTT116855; NCT02164513) was a 52-week, randomized, double-blind, parallel-group, multicenter Phase III study comparing once-daily single-inhaler triple therapy 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 in patients ≥40 years of age with symptomatic COPD (COPD Assessment Test score ≥10) and ≥1 moderate/severe exacerbation in the previous year.[2]
- The primary endpoint was the annual rate of on-treatment moderate/severe exacerbations with FF/UMEC/VI versus FF/VI and UMEC/VI. Secondary endpoints included: time-to-first (TTF) moderate/severe exacerbation, trough forced expiratory volume in 1 second (FEV_1) and St George's Respiratory Questionnaire (SGRQ) at Week 52. Safety was also assessed. In this post hoc analysis, these outcomes were assessed in the subgroup of patients from the NA geographic region.
- Moderate exacerbations were defined as those requiring treatment with antibiotics and/or oral/systemic corticosteroids. Severe exacerbations were defined as events resulting in hospitalization or death.
- Exacerbation rates were analyzed using a generalized linear model assuming a negative binomial distribution; analysis of TTF moderate/severe exacerbation was performed using a Cox proportional hazards model; analyses of change from baseline in trough FEV_1 and SGRQ total score were performed using repeated measures models; SGRQ responder analysis was performed using a generalized linear mixed model with a logit link function.

Results

Patients

- Of the 10,355 patients in the ITT population, 2639 (25%) were from the NA region (91% [n=2406] were from the USA): 1071 in FF/UMEC/VI, 1046 in FF/VI, and 522 in UMEC/VI arms.
  - Compared with the ITT, the NA region had a lower proportion of male patients, and patients had a slightly higher body mass index (BMI) and slightly lower blood eosinophil counts (**Table 1**).

Rate and risk of on-treatment moderate/severe exacerbations

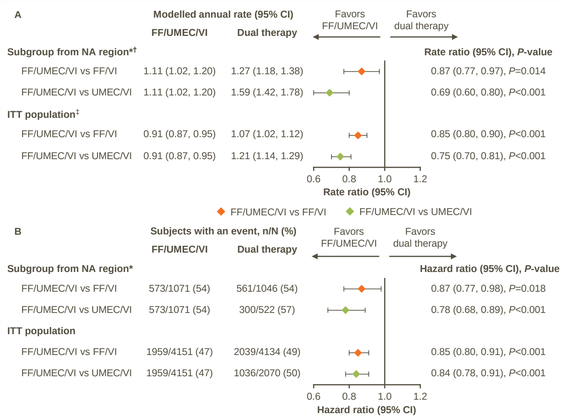
- In the subgroup of patients from the NA region, FF/UMEC/VI demonstrated a statistically significant reduction in the annual rate of on-treatment moderate/severe exacerbations versus FF/VI (13% reduction; 95% confidence interval [CI]: 3, 23; *P*=0.014) and UMEC/VI (31% reduction; 95% CI: 20, 40; *P*<0.001).
- Based on the TTF analysis, a statistically significant reduction in the risk of experiencing a moderate/severe exacerbation was observed with FF/UMEC/VI versus FF/VI (13% reduction; 95% CI: 2.3, 22.7; *P*=0.018) and UMEC/VI (22% reduction; 95% CI: 10.6, 32.4; *P*<0.001) in the subgroup of patients from the NA region.
- These findings were consistent with those in the ITT population (**Figure 1**).

Table 1. Baseline characteristics (NA region and ITT populations)

	NA region			ITT		
	FF/UMEC/VI (N=1071)	FF/VI (N=1046)	UMEC/VI (N=522)	FF/UMEC/VI (N=4151)	FF/VI (N=4134)	UMEC/VI (N=2070)
Age, mean (SD), years	65.1 (8.2)	65.1 (8.6)	65.1 (8.7)	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)
Male, n (%)	531 (50)	520 (50)	279 (53)	2766 (67)	2748 (66)	1356 (66)
BMI, mean (SD), kg/m²	28.4 (7.0)	28.6 (6.9)	28.3 (6.3)	26.6 (6.2)	26.7 (6.1)	26.6 (5.9)
Smoking status, n (%)						
Former smoker	670 (63)	633 (61)	308 (59)	2715 (65)	2711 (66)	1342 (65)
Current smoker	401 (37)	413 (39)	214 (41)	1436 (35)	1423 (34)	728 (35)
Post-bronchodilator FEV_1 % predicted, mean (SD)	44.1 (15.2)	44.2 (14.6)	44.8 (14.8)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)
Exacerbation history in prior 12 months, n (%)						
<2 moderate and 0 severe	356 (33)	351 (34)	180 (34)	1198 (29)	1242 (30)	616 (30)
≥2 moderate or ≥1 severe	715 (67)	695 (66)	342 (66)	2953 (71)	2892 (70)	1454 (70)
Baseline blood eosinophil count (cells/μL), mean (SD)	196 (177)	214 (269)	205 (197)	219 (232)	223 (239)	227 (226)

SD, standard deviation

Figure 1. (A) Rate and (B) risk (TTF) of on-treatment moderate/severe exacerbations



*Post hoc analysis; †N=2639 (FF/UMEC/VI, n=1071; FF/VI, n=1046; UMEC/VI, n=522); ‡N=10,355 (FF/UMEC/VI, n=4151; FF/VI, n=4134; UMEC/VI, n=2070).

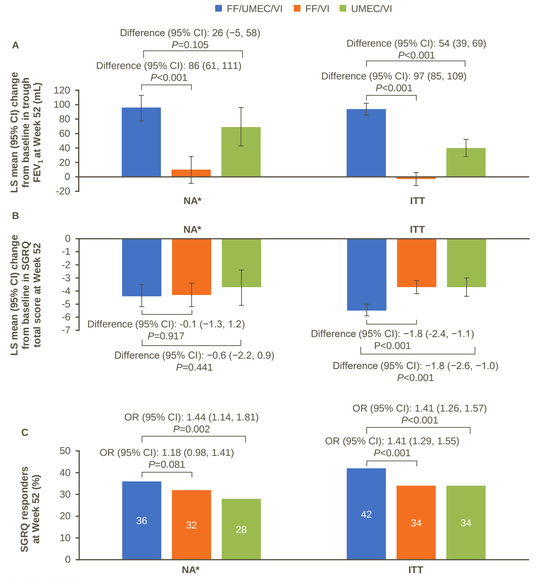
Change from baseline in trough FEV_1 at Week 52

- Consistent with the ITT population, in the NA patient subgroup, FF/UMEC/VI demonstrated statistically significant improvements in change from baseline in trough FEV_1 at Week 52 compared with FF/VI (difference: 86 mL; *P*<0.001). Change from baseline in trough FEV_1 at Week 52 favored FF/UMEC/VI over UMEC/VI in the NA subgroup, but the between-treatment difference was not significant (26 mL; *P*=0.105; **Figure 2A**).

Change from baseline in SGRQ total score and proportion of SGRQ responders at Week 52

- In the NA patient subgroup, all treatments improved mean SGRQ total score at Week 52 from baseline. No between-treatment differences were observed (FF/UMEC/VI vs FF/VI: −0.1 [*P*=0.917]; FF/UMEC/VI vs UMEC/VI: −0.6 [*P*=0.441]; **Figure 2B**).
- The proportion of SGRQ responders at Week 52 was significantly higher with FF/UMEC/VI than UMEC/VI (*P*=0.002) in the NA patient subgroup, consistent with the results in the ITT population (**Figure 2C**). No significant difference was observed with FF/UMEC/VI versus FF/VI in the NA subgroup.

Figure 2. (A) Change from baseline in trough FEV_1 (mL), (B) Change from baseline in SGRQ total score and (C) SGRQ responders at Week 52



*Post hoc analysis.
SGRQ responders are patients with a ≥4-unit decrease from baseline in SGRQ total score.
LS, least squares; OR, odds ratio

Safety

- In the NA patient subgroup, the safety profile of FF/UMEC/VI was similar to that of FF/VI and UMEC/VI; no new safety signals were identified for the use of FF, UMEC and VI in combination (**Table 2**). These results are in line with those in the ITT population.[2]

Table 2. Incidence of on-treatment adverse events (NA region)

AE incidence, n (%)	FF/UMEC/VI n=1071	FF/VI n=1046	UMEC/VI n=522
Any on-treatment AE	790 (74)	739 (71)	360 (69)
On-treatment AESI			
Anticholinergic syndrome (SMQ)	67 (6)	43 (4)	15 (3)
Asthma/bronchospasm (SMQ)	15 (1)	19 (2)	6 (1)
Cardiovascular effects	147 (14)	135 (13)	59 (11)
LRTI excluding pneumonia	42 (4)	36 (3)	29 (6)
Pneumonia	99 (9)	86 (8)	20 (4)
Urinary retention	6 (<1)	7 (<1)	2 (<1)
Any on-treatment SAE	264 (25)	228 (22)	124 (24)
Pneumonia SAE	53 (5)	44 (4)	12 (2)
Any on-treatment fatal SAE	18 (2)	15 (1)	13 (2)
Pneumonia fatal SAE	2 (<1)	1 (<1)	2 (<1)

AE, adverse event; AESI, adverse event of special interest (AEs which have specified areas of interest for FF, UMEC, or VI, or for patients with COPD); LRTI, lower respiratory tract infection; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients; SAE, serious adverse event; SMQ, Standardized MedDRA Query

Conclusions

- In this subgroup of patients from the IMPACT study randomized in the NA region, FF/UMEC/VI demonstrated significant improvements in the rate and risk of moderate/severe exacerbations compared with FF/VI and UMEC/VI. Improvement in lung function was seen with FF/UMEC/VI versus FF/VI and the proportion of SGRQ responders was higher with FF/UMEC/VI versus UMEC/VI.
- Across the three treatment arms, the safety profile was consistent with the ITT population and previous data.
- Overall the results from this regional subgroup analysis are consistent with the findings in the overall ITT population and confirm the efficacy and safety profile of FF/UMEC/VI in subjects enrolled in North America.

References

1. GOLD report 2019. Available at https://goldcopd.org/gold-reports/. [last accessed 01 February 2019].
2. Lipson DA, et al. *N Engl J Med* 2018;378:1671–80.

Disclosures

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