InforMing the PAthway of COPD Treatment (The IMPACT Study): Single Inhaler Triple Therapy (Fluticasone Furoate/Umeclidinium/Vilanterol) Versus Fluticasone Furoate/Vilanterol and Umeclidinium/Vilanterol in Patients With COPD: An Analysis Based on Baseline COPD Medication Use

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Introduction

- The current Global initiative for chronic Obstructive Lung Disease (GOLD) strategy document recommends escalation to triple therapy with inhaled corticosteroid (ICS)/long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) for patients with chronic obstructive pulmonary disease (COPD) who experience recurrent exacerbations on LAMA/LABA or ICS/LABA therapy, or persistent dyspnea on ICS/LABA therapy.[1]
- The recent InforMing the PAthway of COPD Treatment (IMPACT) study demonstrated that once-daily single-inhaler triple therapy with 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 (ICS/LABA) or UMEC/VI (LAMA/LABA) in patients with symptomatic COPD and a history of exacerbations on current COPD maintenance therapy.[2]
- It is of interest to evaluate whether the benefits of triple therapy versus dual therapy demonstrated in the IMPACT study are influenced by prior COPD medication. This post hoc analysis of IMPACT evaluated efficacy outcomes based on COPD medication at screening.

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 and 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.[1]
- 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 annual rate of on-treatment severe exacerbations, lung function (mean change from baseline in trough forced expiratory volume in 1 second [FEV_1]) and HRQoL (St George's Respiratory Questionnaire [SGRQ] total score) at Week 52.
  - Post hoc analyses of these primary and secondary endpoints were conducted for FF/UMEC/VI versus UMEC/VI and FF/VI for the following baseline COPD medication subgroups (defined by treatment use within 3 days prior to and including the screening visit): ICS+LAMA+LABA; LAMA+LABA; ICS+LABA; and LAMA.
  - The study was not powered to analyze between-treatment differences in these outcomes by subgroups.
- 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 negative binomial distribution. Trough FEV_1 and SGRQ total score were analyzed using repeated measures models.

Results

Patients

- Patient baseline demographics and clinical characteristics are described in **Table 1**. The most frequently reported COPD medications at screening were ICS+LABA+LAMA and ICS+LABA.

Rates of on-treatment moderate/severe exacerbations

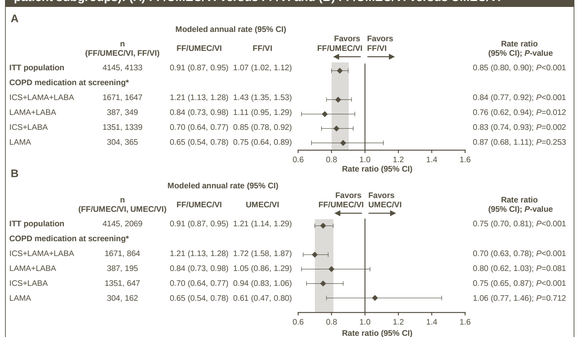
- Consistent with results in the intent-to-treat (ITT) population, FF/UMEC/VI significantly reduced annual moderate/severe exacerbation rates versus FF/VI and UMEC/VI in patients on ICS+LAMA+LABA or ICS+LABA at screening (**Figure 1A** and **1B**).
- In patients on LAMA+LABA at screening, FF/UMEC/VI significantly reduced annual moderate/severe exacerbation rates compared with FF/VI (**Figure 1A**); a reduction was also seen versus UMEC/VI but this was not statistically significant (**Figure 1B**).
  - The small number of patients in this subgroup contributed to wide confidence intervals (CIs) and may explain why statistical significance was not consistently observed (**Figure 1B**).
- There were no statistically significant differences in annual moderate/severe exacerbation rates with FF/UMEC/VI versus both comparators in patients on LAMA at screening (**Figure 1A** and **1B**).

Table 1. Patient demographics (ITT population)

	FF/UMEC/VI (N=4151)	FF/VI (N=4134)	UMEC/VI (N=2070)
Age, mean (SD) years	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)
Gender, % male	67	66	66
BMI, mean (SD) kg/m²	26.6 (6.2)	26.7 (6.1)	26.6 (5.9)
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)
COPD medication at screening*, n (%)			
ICS+LAMA+LABA	1672 (40)	1647 (40)	864 (42)
LAMA+LABA	389 (9)	349 (8)	196 (9)
ICS+LABA	1354 (33)	1340 (32)	647 (31)
LAMA	304 (7)	365 (9)	162 (8)
Lung function (post-bronchodilator)			
Screening FEV_1, mean (SD) L	1.275 (0.488)	1.272 (0.486)	1.268 (0.481)
FEV_1 % predicted, mean (SD)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)
SGRQ total score, mean (SD)	50.8 (16.8)	50.7 (17.0)	50.2 (16.7)

*Between day of screening -3 days and date of screening (inclusive). BMI, body mass index; SD, standard deviation

Figure 1. Rates of on-treatment moderate/severe exacerbations (ITT analysis and patient subgroups): (A) FF/UMEC/VI versus FF/VI and (B) FF/UMEC/VI versus UMEC/VI

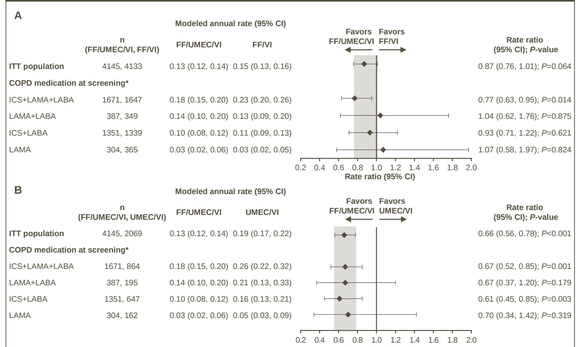


*Between day of screening -3 days and date of screening (inclusive). Gray areas represent treatment effect (95% CI) in the ITT population.

Rates of on-treatment severe exacerbations

- In the ITT population, reduction in exacerbation rates favored FF/UMEC/VI over both FF/VI and UMEC/VI but the comparison was only significant versus UMEC/VI (**Figure 2A** and **2B**).
- FF/UMEC/VI significantly reduced severe exacerbation rates versus FF/VI in patients on ICS+LAMA+LABA at screening; between-treatment comparisons in other patient subgroups were non-significant (**Figure 2A**).
- FF/UMEC/VI significantly reduced severe exacerbation rates versus UMEC/VI in patients on ICS+LAMA+LABA or ICS/LABA at screening; between-treatment comparisons in other patient subgroups favored FF/UMEC/VI but were non-significant (**Figure 2B**).

Figure 2. Rates of on-treatment severe exacerbations (ITT analysis and patient subgroups): (A) FF/UMEC/VI versus FF/VI and (B) FF/UMEC/VI versus UMEC/VI



*Between day of screening -3 days and date of screening (inclusive). Gray areas represent treatment effect (95% CI) in the ITT population.

Table 2. Change from baseline in trough FEV_1 (mL) and SGRQ score at Week 52 (ITT analysis and patient subgroups)

	FF/UMEC/VI (N=4151)	FF/VI (N=4134)		UMEC/VI (N=2070)	
	LS mean (95% CI) change from baseline	LS mean (95% CI) change from baseline	Difference (FF/UMEC/VI vs FF/VI); *P*-value	LS mean (95% CI) change from baseline	Difference (FF/UMEC/VI vs UMEC/VI); *P*-value
Trough FEV_1 (mL)					
ITT	94 (86, 102)	−3 (−12, 6)	97 (85, 109); *P*<0.001	40 (28, 52)	54 (39, 69); *P*<0.001
COPD medication at screening*					
ICS+LAMA+LABA	52 (40, 64)	−65 (−78, −52)	116 (99, 134); *P*<0.001	−6 (−24, 11)	58 (36, 79); *P*<0.001
LAMA+LABA	57 (32, 82)	−56 (−84, −28)	113 (76, 151); *P*<0.001	−14 (−51, 23)	71 (26, 116); *P*=0.002
ICS+LABA	131 (116, 145)	47 (32, 62)	84 (63, 105); *P*<0.001	86 (64, 108)	44 (18, 71); *P*=0.001
LAMA	151 (116, 185)	34 (2, 66)	117 (70, 164); *P*<0.001	58 (10, 105)	93 (34, 152); *P*=0.002
SGRQ total score					
ITT	−5.5 (−5.9, −5.0)	−3.7 (−4.2, −3.2)	−1.8 (−2.4, −1.1); *P*<0.001	−3.7 (−4.4, −3.0)	−1.8 (−2.6, −1.0); *P*<0.001
COPD medication at screening*					
ICS+LAMA+LABA	−3.3 (−4.0, −2.6)	−1.5 (−2.2, −0.7)	−1.8 (−2.8, −0.8); *P*<0.001	−1.6 (−2.7, −0.6)	−1.6 (−2.9, −0.4); *P*=0.010
LAMA+LABA	−2.7 (−3.9, −1.4)	−1.0 (−2.4, 0.5)	−1.7 (−3.6, 0.2); *P*=0.078	−1.2 (−3.1, 0.7)	−1.5 (−3.8, 0.8); *P*=0.195
ICS+LABA	−8.1 (−9.0, −7.3)	−5.8 (−6.7, −5.0)	−2.3 (−3.5, −1.1); *P*<0.001	−6.3 (−7.5, −5.0)	−1.9 (−3.4, −0.3); *P*=0.018
LAMA	−6.5 (−8.1, −4.9)	−3.5 (−4.9, −2.0)	−3.1 (−5.2, −0.9); *P*=0.006	−4.2 (−6.3, −2.0)	−2.4 (−5.0, 0.3); *P*=0.086

*Between day of screening -3 days and date of screening (inclusive). LS, least squares

Risk (time-to-first analysis) of on-treatment moderate/severe exacerbations

- FF/UMEC/VI significantly reduced the risk (time-to-first) of a moderate/severe exacerbation in patients on ICS+LAMA+LABA or ICS/LABA at screening versus FF/VI and UMEC/VI.
- The point estimates favored FF/UMEC/VI over FF/VI with regards to the risk (time-to-first) of moderate/severe exacerbations in those on LAMA/LABA or LAMA at baseline but were not statistically significant. No differences were seen in these subgroups between FF/UMEC/VI and UMEC/VI.

Change from baseline in trough FEV_1 at Week 52

- In line with the results for the ITT population, significant improvements in lung function were seen with FF/UMEC/VI versus both comparators regardless of COPD medication use at screening (**Table 2**).

HRQoL improvements at Week 52

- At Week 52, FF/UMEC/VI demonstrated statistically significant improvements in mean SGRQ total score versus both comparators in the ITT population (**Table 2**).
- Consistent with results in the ITT population, FF/UMEC/VI significantly improved SGRQ total score at Week 52 versus both comparators in patients on ICS+LAMA+LABA or ICS+LABA at screening, and versus FF/VI in patients on LAMA at screening (**Table 2**). Other comparisons favored FF/UMEC/VI but were not significant.

Safety

- Safety data have been previously published.[2] The safety profile of FF/UMEC/VI was similar to that of FF/VI and UMEC/VI, with no new identified safety signals.[2]

Conclusions

- Consistent with the overall ITT population results, benefits of FF/UMEC/VI versus FF/VI and UMEC/VI were demonstrated across several COPD endpoints in patients on ICS+LAMA+LABA or ICS+LABA at screening.
- Benefits on annual rates of moderate/severe exacerbations and lung function were seen in patients on LAMA+LABA at screening for FF/UMEC/VI versus FF/VI. Significant lung function benefits were also observed in this subgroup for FF/UMEC/VI versus UMEC/VI, while the point estimate for reduction in annual rates of moderate/severe exacerbations favored FF/UMEC/VI over UMEC/VI but was not significant, potentially due to the small number of patients in this subgroup resulting in wide CIs.
- In patients on LAMA at screening, benefits of FF/UMEC/VI were demonstrated on lung function and HRQoL versus FF/VI, and on lung function versus UMEC/VI. No significant between-treatment differences were observed for other COPD endpoints for FF/UMEC/VI versus FF/VI and UMEC/VI in this subgroup.

References

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

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