Single-Inhaler Triple Therapy Fluticasone Furoate/Umeclidinium/Vilanterol Improves Lung Function and Symptoms Compared With Tiotropium Monotherapy in Patients With Symptomatic Chronic Obstructive Pulmonary Disease at Risk of Exacerbations

Poster No. 805 (A4294)

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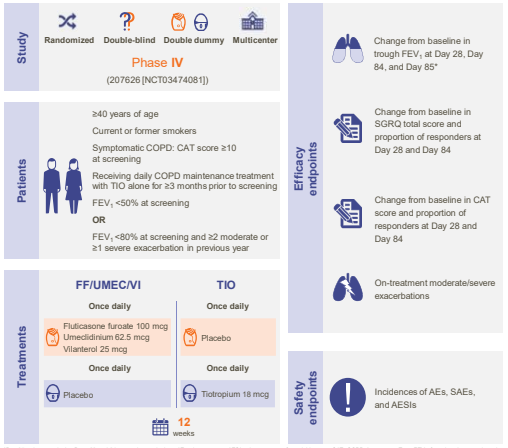
Introduction

- Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation and persistent respiratory symptoms and is a major cause of chronic morbidity and mortality throughout the world.[1]
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends stepwise escalation from monotherapy (long-acting muscarinic antagonist [LAMA] or long-acting β_2-agonist [LABA]) to dual therapy (LAMA/LABA or inhaled corticosteroid [ICS]/LABA) to triple therapy (ICS/LAMA/LABA) based on symptoms and exacerbations.[1]
- In clinical practice, escalation from monotherapy directly to triple therapy does occur;[2] however, recommendations are missing from treatment guidelines.
- Study 207626 (NCT03474081) evaluated the impact of once-daily single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI; an ICS/LAMA/LABA combination) versus once-daily tiotropium (TIO; a LAMA) on lung function and health status in patients with symptomatic COPD and moderate-to-very severe airflow limitation.

Methods



*Day 85: primary endpoint; Days 28 and 84: secondary endpoints. AE, adverse event; AESI, adverse event of special interest; CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; SAE, serious adverse event; SGRQ, St George's Respiratory Questionnaire

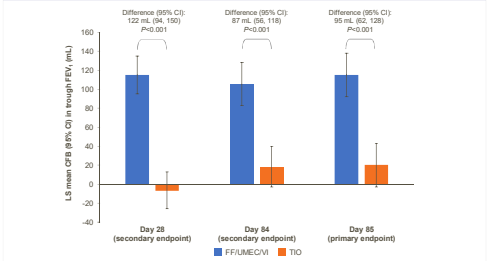
Results

Baseline characteristics and demographics were similar between the two treatment groups (ITT population)

	FF/UMEC/VI (N=400)	TIO (N=400)	Total (N=800)
Age, years, mean (SD)	66.2 (8.08)	66.1 (7.78)	66.2 (7.93)
Male, n (%)	274 (69)	269 (67)	543 (68)
BMI, kg/m², mean (SD)	27.5 (6.1)	27.2 (5.3)	27.4 (5.7)
Current smoker at screening, n (%)	189 (47)	192 (48)	381 (48)
Lung function at screening, mean (SD)			
Post-bronchodilator FEV_1*, L	1.434 (0.493)	1.443 (0.504)	1.439 (0.498)
Post-bronchodilator percent predicted FEV_1*, %	49.8 (14.0)	50.2 (14.2)	50.0 (14.1)
Post-bronchodilator FEV_1/FVC ratio*	0.493 (0.109)	0.502 (0.106)	0.498 (0.107)
Percent reversibility to salbutamol†, %	8.7 (13.4)	8.6 (11.6)	8.6 (12.5)
COPD exacerbations in the previous 12 months, n (%)			
Moderate COPD exacerbations			
0	145 (36)	151 (38)	296 (37)
1	44 (11)	40 (10)	84 (11)
≥2	211 (53)	209 (52)	420 (53)
Severe COPD exacerbations			
0	318 (80)	312 (78)	630 (79)
1	72 (18)	77 (19)	149 (19)
≥2	10 (3)	11 (3)	21 (3)
CAT score at screening, mean (SD)‡	20.7 (5.32)	20.5 (5.16)	20.6 (5.24)

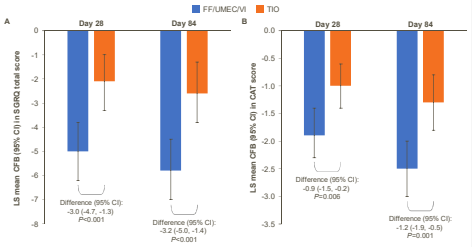
*FF/UMEC/VI n=397, TIO n=398, Total n=795. †FF/UMEC/VI n=392, TIO n=391, Total n=783. ‡FF/UMEC/VI n=399, TIO n=399, Total n=798.
BMI, body mass index; FVC, forced vital capacity; ITT, intent-to-treat; SD, standard deviation.

FF/UMEC/VI led to statistically significant improvements in mean trough FEV_1 versus TIO at Day 28, Day 84, and Day 85 (ITT population)



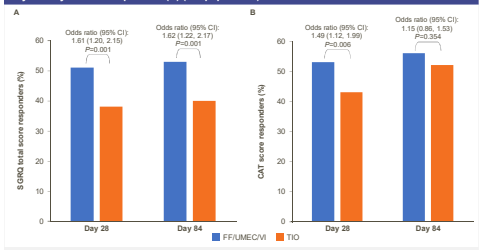
These analyses were performed using a repeated measures model with covariates of baseline value, geographical region, treatment and visit, with interaction terms of visit by treatment and visit by baseline value. CFB, change from baseline; CI, confidence interval; LS, least squares.

FF/UMEC/VI led to significantly greater improvements in (A) SGRQ total score and (B) CAT score versus TIO at both Day 28 and Day 84 (ITT population)



These analyses were performed using a repeated measures model with covariates of baseline value, geographical region, treatment and visit, with interaction terms of visit by treatment and visit by baseline.

The proportion of SGRQ responders was significantly higher with FF/UMEC/VI versus TIO at Day 28 and Day 84 (A), whereas statistical significance in favor of FF/UMEC/VI was achieved at Day 28 only for CAT responders (B) (ITT population)



These analyses were performed using a generalized linear mixed model with a logit link function and covariates of treatment group, geographical region, visit and baseline, with interaction terms of baseline by visit and treatment by visit. CAT responders had a CAT score at least 2 units below baseline; SGRQ responders had an SGRQ score at least 4 units below baseline.

- On-treatment moderate/severe exacerbations were experienced by:
  - **27 (7%)** patients treated with FF/UMEC/VI
  - **43 (11%)** patients treated with TIO.
- There were no new safety findings associated with the use of an ICS, a LAMA, and a LABA in combination.
  - Two patients died in the FF/UMEC/VI arm (cardiac arrest and cardiac failure) and one patient died in the TIO arm (hemorrhagic stroke). These were not considered to be related to study treatment.

Incidences of treatment-related adverse events were similar between treatment groups (ITT population)

	FF/UMEC/VI (N=400)		TIO (N=400)	
	n (%)	Rate [#]	n (%)	Rate [#]
AEs				
Any	127 (32)	2609.2 [236]	115 (29)	2695.2 [248]
Drug-related	11 (3)	199.0 [18]	4 (1)	228.2 [21]
Leading to permanent discontinuation or study withdrawal	7 (2)	110.6 [10]	3 (<1)	32.6 [3]
SAEs				
Any	13 (3)	187.9 [17]	10 (3)	130.4 [12]
Drug-related	0	0	0	0
Leading to permanent discontinuation or study withdrawal	4 (1)	44.2 [4]	3 (<1)	32.6 [3]
Fatal	2 (<1)	22.1 [2]	1 (<1)	10.9 [1]
AESIs				
Cardiovascular effects	11 (3)	143.7 [13]	11 (3)	195.6 [18]
Decreased BMD and associated fractures	2 (<1)	22.1 [2]	0	0
LRTI excluding pneumonia	0	0	1 (<1)	10.9 [1]
Pneumonia	3 (<1)	33.2 [3]	3 (<1)	32.6 [3]

Rate is the number of events per 1000 patient-years, calculated as the number of events x 1000 divided by the total treatment exposure.
BMD, bone mineral density; LRTI, lower respiratory tract infection.

Conclusions

- Once-daily single-inhaler FF/UMEC/VI triple therapy significantly improved lung function versus once-daily TIO monotherapy.
- Improvements in patient health status associated with FF/UMEC/VI therapy were seen at Day 28 and were sustained throughout the study.
- The safety profile of FF/UMEC/VI was similar to that of TIO, including the incidence of pneumonia.
- Few patients experienced a moderate/severe exacerbation in either treatment group, despite the population being at risk of exacerbation. While the study was not powered for exacerbations and was short in length, the proportion of patients who experienced a moderate/severe exacerbation was numerically lower with FF/UMEC/VI versus TIO.
- These results indicate that direct step-up from LAMA monotherapy to single-inhaler FF/UMEC/VI triple therapy is a viable option to improve outcomes in patients with symptomatic COPD who are at risk of exacerbations.

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1. GOLD Report 2020. Available from: http://goldcopd.org/ [last accessed February 2020].
2. Wolters Kluwer's Source Lx Database. Hierarchical Regimen Analysis (HRA) Application SLED report with filtering on patients Aged 18+ with COPD only. February 2011 to January 2012.

Disclosures

- This study was funded by GlaxoSmithKline (GSK study 207626/NCT03474081).
- NB, CC, TCC, KD, CH, MCK, DAL, NM, and C-QZ are employees of GSK and hold stocks and shares in GSK. DO receives personal fees from GSK. SB receives speaker fees from GSK and Boehringer Ingelheim, and previously participated in speaker's bureau for Sunovion Pharmaceuticals. DE is Principal Investigator – Vitalink Research. AP receives research grant and personal fees from Chiesi and GSK, and personal fees from AstraZeneca, Boehringer Ingelheim, Menarini, Mundipharma, Novartis, Sanofi, and Zambon. AP previously received personal fees from Merck Sharp & Dohme, and grants and personal fees from Teva. MK has nothing to disclose.
- Editorial support (in the form of writing assistance, including development of the initial draft based on author direction, assembling tables and figures, collating authors' comments, grammatical editing, and referencing) was provided by Anne Errichelli, DPhil, at Fishawack Indicia Ltd, UK, and was funded by GSK.

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Prepared for the American Thoracic Society Annual Meeting (2020)