The IMPACT Trial: Single Inhaler Triple Therapy Fluticasone Furoate/Umeclidinium/Vilanterol Versus Fluticasone Furoate/Vilanterol and Umeclidinium/Vilanterol in Patients With COPD: Analysis According to Smoking Status

Poster No. P528 (A3339)

Halpin DMG[1], Bardsley S[2], Criner GJ[3], Dransfield MT[4], Han MK[5], Jones CE[6], Kilbride S[7], Lomas DA[8], Martinez FJ[9], Pascoe SJ[10*], Singh D[11], Wise RA[12], Lipson DA[10,13], Lange P[14]

[1]Department of Respiratory Medicine, Royal Devon and Exeter Hospital, Exeter, UK; [2]GSK, Stevenage, UK; [3]Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA; [4]Division of Pulmonary, Allergy, and Critical Care Medicine, Lung Health Center, University of Alabama at Birmingham, Birmingham, AL, USA; [5]University of Michigan, Pulmonary & Critical Care, Ann Arbor, MI, USA; [6]GSK, Research Triangle Park, NC, USA; [7]GSK, Uxbridge, UK; [8]UCL Respiratory, University College London, London, UK; [9]Weill Cornell Medicine, New York, NY, USA; [10]GSK, Collegeville, PA, USA; [11]Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, University of Manchester, Manchester University NHS Foundation Trust, Manchester, UK; [12]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [13]Perelman School of Medicine, University of Pennsylvania, PA, USA; [14]Department of Public Health, University of Copenhagen, Copenhagen, Denmark; *Affiliation at the time of the study

Introduction

- The Global initiative for chronic Obstructive Lung Disease (GOLD) management strategy recommends inhaled corticosteroid, long-acting muscarinic antagonist, long-acting β_2-agonist (ICS/LAMA/LABA) triple therapy for patients with chronic obstructive pulmonary disease (COPD) who have clinically significant symptoms despite treatment with an ICS/LABA or LAMA/LABA and are at increased risk for exacerbations.[1]
- Smoking is one of the main risk factors for COPD,[1] and a high proportion of patients with symptomatic COPD are current smokers.[2–4] Evidence suggests that continued cigarette smoking impairs response to ICS.[5–7]
- The InforMing the PAthway of COPD Treatment (IMPACT) trial investigated the effects of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI), FF/VI and UMEC/VI in patients with symptomatic COPD.[8]
- As IMPACT evaluated treatment arms with both ICS-containing and non-ICS-containing COPD maintenance therapies, between-treatment comparisons could be made to determine any differences in the efficacy profile of triple versus dual therapy in current and former smokers. Here, we report efficacy and safety results from the IMPACT trial according to smoking status at screening.

Methods

Study design

- IMPACT (GSK study CTT116855; NCT02164513) was a 52-week, randomized, double-blind, parallel-group, multicenter, Phase III study comparing the efficacy and safety of 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.
- 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. Secondary endpoints included change from baseline in St George's Respiratory Questionnaire (SGRQ), trough forced expiratory volume in 1 second (FEV_1), and mean Transition Dyspnea Index (TDI) focal score at Week 52. Adverse events of special interest (AESIs) were also recorded.
- 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.
- This pre-specified analysis evaluated the rate of on-treatment moderate/severe COPD exacerbations by smoking status at screening using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), geographical region, and post-bronchodilator percent predicted FEV_1 (Screening) for former smokers and current smokers separately. Former smokers were patients who had not smoked for >6 months prior to the screening visit. Any change in smoking status during the course of the study was not considered in this analysis. Post hoc analyses were performed on trough FEV_1, SGRQ total score, and TDI focal score by smoking status at screening. Safety was also assessed.
- All reported endpoints were assessed in the intent-to-treat (ITT) population.

Results

Patients

- In total, 10,355 patients were included in the ITT population; 4151 patients who received FF/UMEC/VI (35% [n=1436] current smokers), 4134 who received FF/VI (34% [n=1423] current smokers), and 2070 who received UMEC/VI (35% [n=728] current smokers).
- Baseline demographics and clinical characteristics were broadly similar across treatment groups and smoking subgroups, although current smokers were younger and more predominantly female than former smokers (**Table 1**).

Efficacy

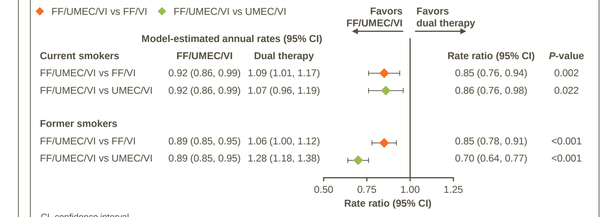
- Over the 52-week treatment period, FF/UMEC/VI demonstrated a statistically significant reduction in the rate of on-treatment moderate/severe COPD exacerbations compared with FF/VI and UMEC/VI in both current and former smokers (**Figure 1**). However, the magnitude of effect for FF/UMEC/VI versus UMEC/VI was greater in former smokers than in current smokers.
- Over the 52-week treatment period, FF/UMEC/VI demonstrated a statistically significant reduction in the risk (time-to-first [TTF]) of on-treatment moderate/severe COPD exacerbations compared with FF/VI in both current and former smokers (**Figure 2**). There was also a statistically significant reduction in the risk (TTF) of moderate/severe exacerbations with FF/UMEC/VI versus UMEC/VI in former smokers. The risk reduction in current smokers favored FF/UMEC/VI over UMEC/VI but was not significant.

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

	Current smoker			Former smoker		
	FF/UMEC/VI (N=1436)	FF/VI (N=1423)	UMEC/VI (N=728)	FF/UMEC/VI (N=2715)	FF/VI (N=2711)	UMEC/VI (N=1342)
Age, years, mean (SD)	62.1 (7.54)	61.9 (7.85)	61.8 (7.64)	67.0 (8.09)	67.0 (7.98)	67.1 (7.99)
Female, n (%)	574 (40)	560 (39)	309 (42)	811 (30)	826 (30)	405 (30)
BMI, kg/m^2, mean (SD)	25.9 (6.22)	26.1 (6.20)	25.8 (5.88)	27.0 (6.19)	26.9 (6.00)	27.0 (5.83)
Lung function (post-bronchodilator)						
FEV_1, % predicted, mean (SD)	45.8 (14.68)	46.0 (15.03)	45.0 (14.43)	45.7 (15.14)	45.2 (14.64)	45.6 (14.82)
Exacerbation history in prior 12 months, n (%)						
≥2 moderate exacerbations	672 (47)	655 (46)	350 (48)	1295 (48)	1266 (47)	639 (48)
≥1 severe exacerbations	356 (25)	356 (25)	169 (23)	731 (27)	713 (26)	346 (26)

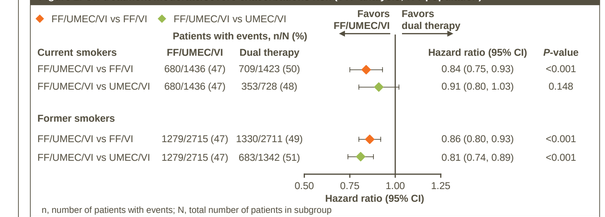
BMI, body mass index; SD, standard deviation

Figure 1. On-treatment moderate/severe exacerbations rates (ITT population)



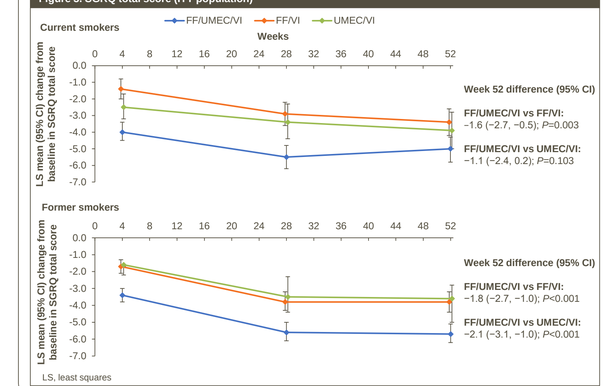
CI, confidence interval

Figure 2. On-treatment moderate/severe exacerbations risk (TTF analysis; ITT population)



n, number of patients with events; N, total number of patients in subgroup

Figure 3. SGRQ total score (ITT population)



LS, least squares

Figure 4. Trough FEV_1 (ITT population)

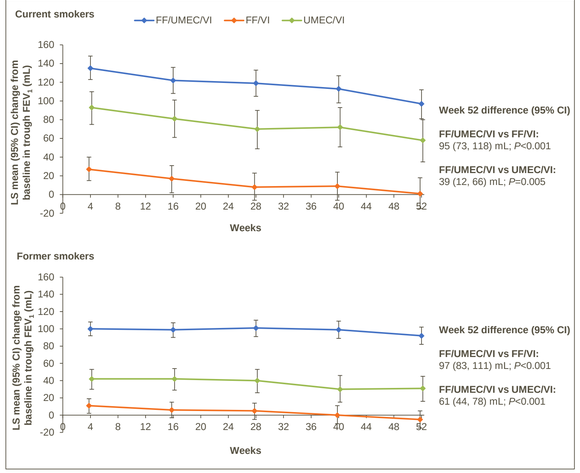
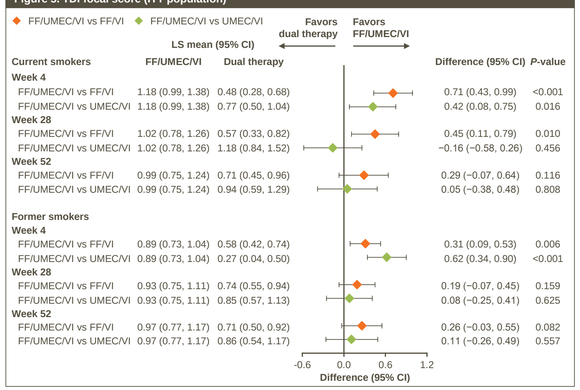


Figure 5. TDI focal score (ITT population)



- FF/UMEC/VI significantly improved SGRQ total score from baseline at Week 4 and 28 versus both FF/VI and UMEC/VI, irrespective of smoking status. At Week 52, statistically significant improvements were seen with FF/UMEC/VI versus FF/VI in both current and former smokers, and with FF/UMEC/VI versus UMEC/VI in former smokers. In current smokers, the point estimate favored FF/UMEC/VI over UMEC/VI but was not significant (**Figure 3**).
- Statistically significant improvements from baseline in trough FEV_1 were shown with FF/UMEC/VI versus FF/VI and UMEC/VI in both former and current smokers at all time points analyzed (P≤0.005; **Figure 4**).
- All treatments improved TDI focal score at Week 52 in both current and former smokers. FF/UMEC/VI significantly improved TDI focal score versus both dual therapies at Week 4 irrespective of smoking status. Differences in TDI focal score at Week 52 favored triple therapy over both dual therapies in both smoking status subgroups, although they were not significant (**Figure 5**).

Safety

- The safety profile for FF/UMEC/VI, FF/VI, and UMEC/VI was similar and consistent between the smoking status subgroups over the 52-week study period (**Table 2**).
  - In current smokers, incidence of pneumonia AESIs was comparable between treatment arms. In former smokers, incidence of pneumonia AESIs was slightly higher in ICS-containing treatment arms compared with UMEC/VI (**Table 2**).

Table 2. On-treatment AESI incidence (ITT population)

	Current smokers			Former smokers		
	FF/UMEC/VI (N=1436)	FF/VI (N=1423)	UMEC/VI (N=728)	FF/UMEC/VI (N=2715)	FF/VI (N=2711)	UMEC/VI (N=1342)
Any on-treatment AESI						
Anticholinergic syndrome (SMQ)	58 (4)	52 (4)	25 (3)	126 (5)	88 (3)	45 (3)
Asthma/bronchospasm (SMQ)	14 (<1)	13 (<1)	6 (<1)	13 (<1)	21 (<1)	10 (<1)
Cardiovascular effects	155 (11)	147 (10)	82 (11)	295 (11)	283 (10)	142 (11)
LRTI excluding pneumonia	73 (5)	58 (4)	45 (6)	127 (5)	141 (5)	63 (5)
Local steroid effects	143 (10)	131 (9)	42 (6)	194 (7)	170 (6)	66 (5)
Pneumonia	90 (6)	82 (6)	34 (5)	227 (8)	210 (8)	63 (5)
Urinary retention	0 (0)	5 (<1)	2 (<1)	8 (<1)	7 (<1)	7 (<1)

AESIs (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; SMQ, Standardized MedDRA Query

Conclusions

- Improvements in exacerbation rate, lung function, and SGRQ total score were demonstrated with FF/UMEC/VI versus FF/VI and UMEC/VI in both former and current smokers with symptomatic COPD and a history of exacerbations, underscoring a beneficial efficacy profile with once-daily FF/UMEC/VI across a multitude of COPD endpoints, regardless of smoking status.
- There appeared to be increased clinical benefit with FF/UMEC/VI compared with UMEC/VI in former smokers. These findings may be related to relative steroid resistance in current smokers and highlight that smoking cessation advice remains appropriate to maximize the add-on benefits of ICS.

References

1. Global Initiative for Chronic Obstructive Lung Disease. 2019 Report. Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf [last accessed January 2019]; 2. Liang J, et al. *Med J Aust* 2018;208(1):29–34; 3. Riesco JA, et al. *Int J COPD* 2017;12:1989–99; 4. Vozoris NT, et al. *Resp Med* 2011;105:477–84; 5. Bhatt SP, et al. *Eur Respir J* 2018;51(1); 6. Bafadhel M, et al. *Lancet Respir Med* 2018;6:117–26; 7. Hinds DR, et al. *BMJ Open* 2016;6(6):e010099; 8. Lipson DA, et al. *N Engl J Med* 2018;378:1671–80.

Disclosures

- 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 Chrystelle Rasamison, of Fishawack Indicia Ltd, UK, and was funded by GlaxoSmithKline (GSK).
- This study was funded by GSK (CTT116855; NCT02164513).

- SB, CEJ, SK, and DALi are employees of GSK and hold stocks/shares in GSK. SJP was an employee of GSK at the time of the study and hold stocks/shares in GSK. DMGH has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, and Pfizer. GJC has received personal fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, CSA Medical, Eolo, GSK, HGE Technologies, Novartis, Nuvaira, Olympus, Pulmonx, and Verona. MTD has received personal fees from AstraZeneca and GSK and contracted clinical trial support from AstraZeneca, Boehringer Ingelheim and GSK. MKH has received personal fees from AstraZeneca, Boehringer Ingelheim, and GSK and research support from Novartis and Sunovion. DALo has received personal fees from GSK. FJM has taken part in advisory boards for AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Sunovion, and Teva, steering committees for AstraZeneca and GSK, DSMB for Genentech/Roche and GSK and has been an advisor for ProTerrix Bio. DS has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, Glenmark, GSK, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Theravance, and Verona. RAW has been a consultant for AstraZeneca, Boehringer Ingelheim, Contrafect, GSK, Novartis, and Merck, has received research grants from AstraZeneca, Boehringer Ingelheim, and GSK and has taken part in advisory boards for Mylan/Theravance, Propeller Health, Sunovion, and Verona. PL has received personal fees from GSK.

Presented at the American Thoracic Society International Conference, Dallas, TX, USA, May 17–22, 2019

Please find the online version of this poster by scanning the QR code or via http://tago.ca/ATS_9