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Original Research

Single-inhaler triple therapy fluticasone furoate/umeclidinium/vilanterol versus dual therapy in current and former smokers with COPD: IMPACT trial post hoc analysis

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ABSTRACT

Background: Smoking is the major risk factor for chronic obstructive pulmonary disease (COPD). In IMPACT, single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) triple therapy significantly reduced moderate/severe exacerbation rates and improved lung function and health status versus FF/VI or UMEC/VI in COPD patients. This post hoc analysis investigated trial outcomes by smoking status.

Methods: IMPACT was a double-blind, 52-week trial. Patients aged ≥40 years with symptomatic COPD and ≥1 moderate/severe exacerbation in the prior year were randomized 2:2:1 to FF/UMEC/VI 100/62.5/25 μg, FF/VI 100/25 μg, or UMEC/VI 62.5/25 μg. Endpoints assessed by smoking status at screening included rate and risk of moderate/severe exacerbations, change from baseline in trough forced expiratory volume in 1 s, and St George's Respiratory Questionnaire total score at Week 52. Safety was also assessed.

Results: Of the 10,355 patients in the intent-to-treat population, 3,587 (35%) were current smokers. FF/UMEC/VI significantly reduced on-treatment moderate/severe exacerbation rates versus FF/VI and UMEC/VI in current

Abbreviations: AEs, adverse events; AESIs, adverse events of special interest; BDI, baseline dyspnea index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FF, fluticasone furoate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HDAC2, histone deacetylase 2 activity; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SAE, serious adverse event; SGRQ, St George's Respiratory Questionnaire; TDI, transition dyspnea index; UMEC, umeclidinium; VI, vilanterol.

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(rate ratio 0.85 [95% confidence interval: 0.77–0.95]; $P = 0.003$ and 0.86 [0.76–0.98]; $P = 0.021$) and former smokers (0.85 [0.78–0.91]; $P < 0.001$ and 0.70 [0.64–0.77]; $P < 0.001$). FF/UMEC/VI significantly reduced time-to-first on-treatment moderate/severe exacerbation versus FF/VI and UMEC/VI in former smokers, and versus FF/VI in current smokers. Similar trends were seen for lung function and health status. Former smokers receiving inhaled corticosteroid-containing therapy had higher pneumonia incidence than current smokers.
Conclusions: FF/UMEC/VI improved clinical outcomes versus dual therapy regardless of smoking status. Benefits of FF/UMEC/VI versus UMEC/VI were greatest in former smokers, potentially due to relative corticosteroid resistance in current smokers.
Clinical trial registration: GSK (CTT116855/NCT02164513).

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, characterized by chronic airflow limitation that causes persistent respiratory symptoms. Smoking is the main risk factor for developing COPD and other comorbidities such as cardiovascular disease. Inhalation of cigarette smoke causes lung inflammation and results in tissue damage and destruction [1,2]. Continued smoking results in worse respiratory symptoms and more severe COPD [3] and is a major contributor to the risk of developing COPD exacerbations [4]. Smoking cessation is recommended for all patients with COPD and has been identified as the most influential factor in altering the disease course.

Based on the frequency or severity of symptoms and exacerbations, COPD treatment regimens can be stepped up 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) [2]. Studies suggest that continued cigarette smoking impairs responses to ICS [5–11]. The mechanism underlying ICS response impairment may include pro-inflammatory effects of smoking and/or reduction in histone deacetylase 2 activity (HDAC2) by oxidative stress generated in the lungs from cigarette smoking [12].

The IMPACT trial demonstrated that once-daily single-inhaler triple therapy with ICS/LAMA/LABA (fluticasone furoate, umeclidinium and vilanterol [FF/UMEC/VI]) significantly reduced the annual rate of moderate/severe exacerbations and improved lung function and health status compared with FF/VI or UMEC/VI in patients ≥40 years of age with symptomatic COPD and a history of exacerbations [13]. A previous post hoc analysis of IMPACT has shown smoking status may modify the relationship between blood eosinophil count and the efficacy of therapy on moderate or severe exacerbations, Transition Dyspnea Index (TDI), and forced expiratory volume in 1 s (FEV_1), with current smokers having a reduced response to ICS at any eosinophil count compared with former smokers [7].

However, the effect of smoking status on the efficacy of triple versus dual therapy on clinical outcomes at multiple time points and safety has yet to be fully reported. Here, we aim to ascertain if smoking status affects treatment outcomes by evaluating the efficacy and safety of FF/UMEC/VI versus FF/VI and UMEC/VI in current and former smokers in a post hoc analysis of the IMPACT trial.

1. Materials and methods

1.1. Study design

IMPACT (GSK Study CTT116855/NCT02164513; N = 10,355) was a Phase III, 52-week randomized, double-blind, multicenter study, which compared the efficacy and safety of once-daily single-inhaler triple therapy with FF/UMEC/VI 100/62.5/25mcg with once-daily dual therapy with FF/VI 100/25 μg or UMEC/VI 62.5/25 μg, all administered via the Ellipta dry-powder inhaler [13,14]. In order to reflect routine clinical practice, patients continued their existing COPD maintenance therapy during a 2-week run-in period prior to being randomized (2:2:1). This post hoc analysis evaluated the efficacy and safety of triple therapy versus dual therapy by smoking status at screening. Patients were classified as former smokers if they had not smoked for >6 months prior to the screening visit in order to minimize recall bias, or as current smokers if they had stopped within the last 6 months or were active smokers at the time of the screening visit. Smoking status was consistent across the 52 weeks during the trial in all treatment arms.

1.2. Study population and endpoints

The inclusion and exclusion criteria have been described previously [13,14]. Briefly, eligible patients were ≥40 years of age with symptomatic COPD (COPD Assessment Test score ≥10) and with either a FEV_1 <50% of predicted normal values and ≥1 moderate or severe exacerbation in the previous year or FEV_1 50–80% of predicted normal values and ≥2 moderate or ≥1 severe exacerbations in the previous year [13]. All patients were required to have a ≥10 pack-year smoking history. Exclusion criteria included a current diagnosis of asthma. However, patients with a history of asthma were eligible to increase the generalizability of the trial [13]. All patients provided written informed consent. The study was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki and received approval by local ethics review boards of the participating sites.

The efficacy endpoints assessed in this analysis included rate of on-treatment moderate/severe exacerbations; risk (time-to-first) of on-treatment moderate/severe exacerbation; change from baseline in trough FEV_1 at Weeks 4, 16, 28, 40, and 52; change from baseline in St George's Respiratory Questionnaire (SGRQ) total score and percentage of SGRQ responders (patients with a decrease in SGRQ total score from baseline of ≥4 points) at Weeks 4, 28, and 52; and TDI focal score at Weeks 4, 28, and 52. The safety endpoints included incidences of adverse events (AEs), AEs of special interest (AESIs) and serious AEs (SAEs) from the start of randomization until safety follow-up at Week 52. Moderate exacerbations were defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization or resulting in death). Severe exacerbations were defined as exacerbations that required hospitalization or resulted in death.

1.3. Statistical analyses

Study population characteristics, efficacy and safety endpoints were assessed in the intent-to-treat (ITT) population. The rate of on-treatment moderate/severe COPD exacerbations in current smokers and former smokers was analyzed using a generalized linear model assuming a negative binomial distribution, with covariates of treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), geographical region, post-bronchodilator percent predicted FEV_1 (screening), and treatment group by smoking status (screening) interaction. Interaction testing was performed to determine whether the treatment effect on the primary endpoint was modified by the following factors: gender, exacerbation history (≤1 or ≥2 moderate/severe exacerbations), smoking status at screening, geographical region or post-bronchodilator % predicted FEV_1 at screening. Interactions were deemed significant if $P < 0.1$.

Time-to-first event (risk) analyses for on-treatment moderate/severe COPD exacerbations were conducted using a Cox proportional hazards

Table 1
Baseline characteristics (ITT population).

	Current smokers			Former smokers			
	FF/UMEC/VI N = 1,436	**FF/VI** N = 1,423	**UMEC/VI** N = 728	**FF/UMEC/VI** N = 2,715	**FF/VI** N = 2,711	**UMEC/VI** N = 1,342	**Overall** N = 10,355
Age, mean (SD), years	62.1 (7.5)	61.9 (7.9)	61.8 (7.6)	67.0 (8.1)	67.0 (8.0)	67.1 (8.0)	65.3 (8.3)
Gender, male, n (%)	862 (60)	863 (61)	419 (58)	1,904 (70)	1,885 (70)	937 (70)	6,870 (66)
BMI[a], mean (SD), kg/m^2	25.9 (6.2)	26.1 (6.2)	25.8 (5.9)	27.0 (6.2)	26.9 (6.0)	27.0 (5.8)	26.6 (6.1)
Smoking history (pack years), mean (SD)	46.8 (25.6)	45.8 (23.0)	47.0 (26.1)	46.6 (27.3)	46.8 (27.6)	47.1 (28.1)	46.6 (26.64)
Moderate COPD exacerbations in previous year, n (%)							
0	267 (19)	269 (19)	128 (18)	499 (18)	523 (19)	250 (19)	1,936 (19)
1	497 (35)	499 (35)	250 (34)	921 (34)	922 (34)	453 (34)	3,542 (34)
2	555 (39)	534 (38)	273 (38)	1,067 (39)	1,050 (39)	522 (39)	4,001 (39)
≥3	117 (8)	121 (9)	77 (11)	228 (8)	216 (8)	117 (9)	876 (8)
Moderate or severe COPD exacerbations in previous year, n (%)							
0	1 (<1)	1 (<1)	0	1 (<1)	4 (<1)	2 (<1)	9 (<1)
1	664 (46)	656 (46)	337 (46)	1,189 (44)	1,251 (46)	594 (44)	4,691 (45)
2	619 (43)	613 (43)	300 (41)	1,210 (45)	1,155 (43)	590 (44)	4,487 (43)
≥3	152 (11)	153 (11)	91 (13)	315 (12)	301 (11)	156 (12)	1,168 (11)
Severe COPD exacerbations in previous year, n (%)							
0	1,080 (75)	1,067 (75)	559 (77)	1,984 (73)	1,998 (74)	996 (74)	7,684 (74)
1	310 (22)	298 (21)	151 (21)	630 (23)	623 (23)	288 (21)	2,300 (22)
2	36 (3)	51 (4)	15 (2)	76 (3)	70 (3)	51 (4)	299 (3)
≥3	10 (<1)	7 (<1)	3 (<1)	25 (<1)	20 (<1)	7 (<1)	72 (<1)
Postbronchodilator FEV_1-% predicted[b], mean (SD)	45.8 (14.7)	46.0 (15.0)	45.0 (14.4)	45.7 (15.1)	45.2 (14.6)	45.6 (14.8)	45.5 (14.8)
Baseline eosinophil value (10^9/L)[c], mean (SD)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.3)	0.2 (0.2)	0.2 (0.3)	0.2 (0.2)
GOLD grades[b], n (%)							
1 (mild)	3 (<1)	4 (<1)	2 (<1)	7 (<1)	4 (<1)	2 (<1)	22 (<1)
2 (moderate)	538 (38)	528 (37)	252 (35)	997 (37)	927 (34)	477 (36)	3,719 (36)
3 (severe)	668 (47)	676 (48)	354 (49)	1,266 (47)	1,355 (50)	663 (49)	4,982 (48)
4 (very severe)	224 (16)	215 (15)	120 (16)	442 (16)	424 (16)	199 (15)	1,624 (16)
Baseline COPD medications at screening[d], n (%)							
ICS + LABA + LAMA	492 (34)	522 (37)	280 (38)	1,180 (43)	1,125 (41)	584 (44)	4,183 (40)
ICS + LABA	487 (34)	427 (30)	207 (28)	867 (32)	913 (34)	440 (33)	3,341 (32)
LABA + LAMA	129 (9)	127 (9)	67 (9)	260 (10)	222 (8)	129 (10)	934 (9)
LAMA	115 (8)	153 (11)	80 (11)	189 (7)	212 (8)	82 (6)	831 (8)
SGRQ total score, mean (SD)	52.3 (17.1)	51.9 (17.2)	52.1 (16.6)	50.0 (16.6)	50.1 (16.9)	49.2 (16.7)	50.7 (16.9)

[a]Current smokers receiving FF/UMEC/VI N = 1,435, former smokers receiving FF/UMEC/VI N = 2,713, overall N = 10,352; [b]Current smokers receiving FF/UMEC/VI N = 1,433, former smokers receiving FF/UMEC/VI N = 2,712, former smokers receiving FF/VI N = 2,710, former smokers receiving UMEC/VI N = 1,341, overall N = 10,347; [c]Current smokers receiving FF/UMEC/VI N = 1,430, current smokers receiving FF/VI N = 1,421, current smokers receiving UMEC/VI N = 726, former smokers receiving FF/UMEC/VI N = 2,713, former smokers receiving FF/VI N = 2,704, former smokers receiving UMEC/VI N = 1,339, Overall N = 10,333; [d]Medication taken between date of screening −3 days and date of screening (inclusive).

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FF, fluticasone furoate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

model with covariates of treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), geographical region, post-bronchodilator percent predicted FEV_1 (screening), smoking status (screening), and treatment group by smoking status (screening) interaction. Change from baseline in trough FEV_1, change from baseline in SGRQ total score and TDI focal score were analyzed using a repeated measures model with covariates of treatment group, smoking status (screening), geographical region, visit, treatment group by visit, treatment group by smoking status (screening), visit by smoking status (screening), and treatment group by visit by smoking status (screening) interactions. The analyses of trough FEV_1 and SGRQ total score also included baseline as a covariate and baseline by visit interaction term, and TDI focal score also included Baseline Dyspnea Index (BDI) focal score as a covariate and BDI focal score by visit interaction term. The proportion of responders according to SGRQ total score was assessed for current and former smokers; the analyses did not include an interaction term, instead each subgroup was analyzed separately. Safety endpoints were assessed in the ITT population using descriptive statistics. AESIs were defined as AEs within specified areas of interest for FF, UMEC, and/or VI, or the overall COPD population. All programming for statistical analyses was performed using SAS Version 9.4.

2. Results

2.1. Study population

Baseline characteristics by smoking status at screening and treatment group are displayed in Table 1.

A total of 3,587 of 10,355 (35%) patients were classified as current smokers. A history of ≥2 moderate/severe exacerbations in the previous 12 months was reported for 54% (n = 1,928) of current smokers and 55% (n = 3,727) of former smokers (Table 1). A greater proportion of males were former smokers than current smokers. The former smokers group had a similar proportion of patients with severe COPD across treatment groups compared with current smokers (Global Initiative for Chronic Obstructive Lung Disease [GOLD] grade 3: 47–50% in former smokers compared with 47–49% in current smokers; GOLD grade 4: 15–16% in both former and current smokers) (Table 1). A greater proportion of former smokers were receiving triple therapy at screening (36%) compared with current smokers (29–34%) across all treatment groups. Overall, mean (standard deviation [SD]) SGRQ total score was similar between current and former smokers at baseline (52.1 [17.01] vs 49.9 [16.74]), however, the mean (SD) Symptoms Domain score was slightly higher in current smokers compared with former smoker (71.4 [17.52] vs 63.1 [18.32]).

2.2. Interaction testing

Of the prespecified factors tested in IMPACT, only exacerbation history ($P = 0.010$) and smoking status at screening ($P = 0.023$) demonstrated a significant interaction of treatment on the primary endpoint (Table 2). When examining the primary endpoint by each level of smoking status, FF/UMEC/VI was superior to both FF/VI and UMEC/VI for each level of the subgroup. However, the magnitude of the effect was greater for FF/UMEC/VI compared with UMEC/VI in former smokers compared with current smokers (Fig. 1).

Table 2
Prespecified interactions of treatment (ITT population).

Interaction of Treatment	*P*-value
Sex	0.916
Exacerbation history	0.010
Smoking status at screening	0.023
Geographic region	0.648
% predicted FEV_1 at screening	0.112

Note; Analysis performed using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, sex, exacerbation history (≤1,≥2 moderate/severe), smoking status (screening), geographical region, and post-bronchodilator percent predicted FEV_1 (screening) plus the specified factor by treatment interaction. Each interaction is considered significant if the *P*-value is < 0.10.
FEV_1, forced expiratory volume in 1 s.

2.3. Efficacy endpoints

2.3.1. Exacerbations and lung function

In both current and former smokers, the annual rate of on-treatment moderate/severe COPD exacerbation was significantly lower with FF/UMEC/VI compared with FF/VI and UMEV/VI (Fig. 1). In current smokers, the reduction in annual rate was 15% (95% confidence interval [CI]: 5%, 23%) for FF/UMEC/VI versus FF/VI and 14% (2%, 24%) for FF/UMEC/VI versus UMEC/VI; corresponding values for former smokers were 15% (9%, 22%) and 30% (23%, 36%) (Fig. 1). The risk (time-to-first) of a moderate/severe COPD exacerbation was significantly lower with triple therapy versus either dual therapy in former smokers ($P < 0.001$; Fig. 2). In current smokers, the risk was significantly lower with triple therapy versus FF/VI ($P < 0.001$), and the point estimate favored FF/UMEC/VI versus UMEC/VI but was not statistically significant ($P = 0.135$) (Fig. 2).

For both current and former smokers, the mean improvement from baseline in trough FEV_1 was significantly greater with FF/UMEC/VI versus FF/VI and UMEC/VI at all time points (Fig. 3; Fig. S1). However, in former smokers, the difference in improvement across time points with FF/UMEC/VI versus UMEC/VI was between 58 and 61 mL, whereas in current smokers it was 40–50 mL (Fig. 3; Fig. S1).

2.3.2. Quality of life and symptoms

Improvements in SGRQ total score from baseline at Week 52 were significantly greater with FF/UMEC/VI versus FF/VI regardless of smoking status at baseline; however, improvements with FF/UMEC/VI versus UMEC/VI reached statistical significance only in former smokers. At Week 4 and 28, improvements were significantly greater for FF/UMEC/VI versus both dual therapies in both current and former smokers (Fig. 4; Fig. S2). Improvements in each SGRQ domain from baseline were seen at each time point for FF/UMEC/VI versus both dual therapies, regardless of smoking status. At Week 52, mean (SD) change from baseline in SGRQ Symptoms Domain score was similar between current and former smokers for FF/UMEC/VI (−9.3 [17.24] vs −9.6 [18.50]).

The proportion of responders according to SGRQ total score was higher with FF/UMEC/VI versus FF/VI and UMEC/VI at all time points among both current and former smokers. In the FF/UMEC/VI treatment arm, 42% of both current and former smokers were classed as responders at Week 52 compared with 32% (odds ratio 1.46 [95% CI 1.25, 1.71]; $P < 0.001$) and 36% (1.24 [1.03, 1.50]; $P = 0.023$) of current smokers in the FF/VI and UMEC/VI groups, and 35% (1.39 [1.24, 1.55]; $P < 0.001$) and 33% (1.50 [1.31, 1.73]; $P < 0.001$) of former smokers, respectively, (Fig. 5).

There was no difference in the mean TDI focal score with FF/UMEC/VI versus FF/VI and UMEC/VI at Week 52 in either current or former smokers (Fig. S3). Significantly greater improvements were seen with triple therapy versus either dual therapy at Week 4 in both current and former smokers, while at Week 28, there was only a significantly greater improvement seen with FF/UMEC/VI versus FF/VI in current smokers.

2.4. Safety

Differences in the incidences and exposure-adjusted rates of pneumonia were seen between current smokers and former smokers across treatment arms. Former smokers had a higher proportion of pneumonia events and higher exposure-adjusted rates of pneumonia per 1,000 patient-years compared with current smokers across all treatment arms,

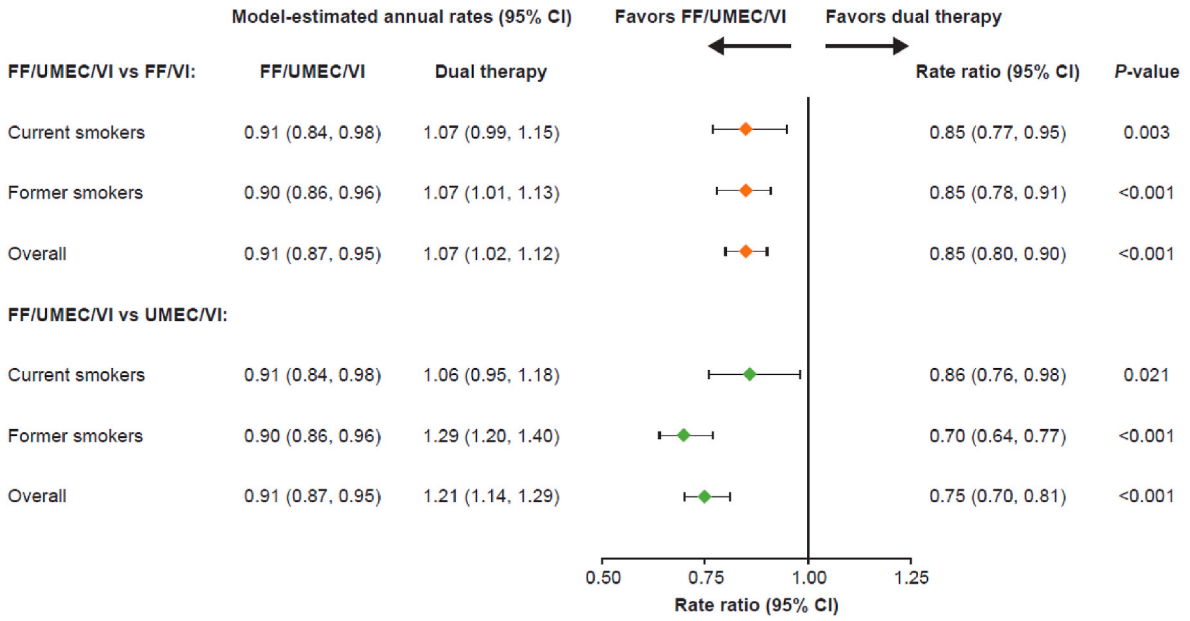

Fig. 1. On-treatment moderate/severe COPD exacerbation rates in current and former smokers and the overall population (ITT population).
Overall: FF/UMEC/VI, N = 4,145; FF/VI, N = 4,133; UMEC/VI, N = 2,069. Current smokers: FF/UMEC/VI, N = 1,433; FF/VI, N = 1,423; UMEC/VI, N = 728. Former smokers: FF/UMEC/VI, N = 2,712; FF/VI, N = 2,710; UMEC/VI, N = 1,341. Note: Analysis performed using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), geographical region, post-bronchodilator percent predicted FEV_1 (screening). Analyses by smoking status included an additional covariate of treatment group by smoking status (screening) interaction.
CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

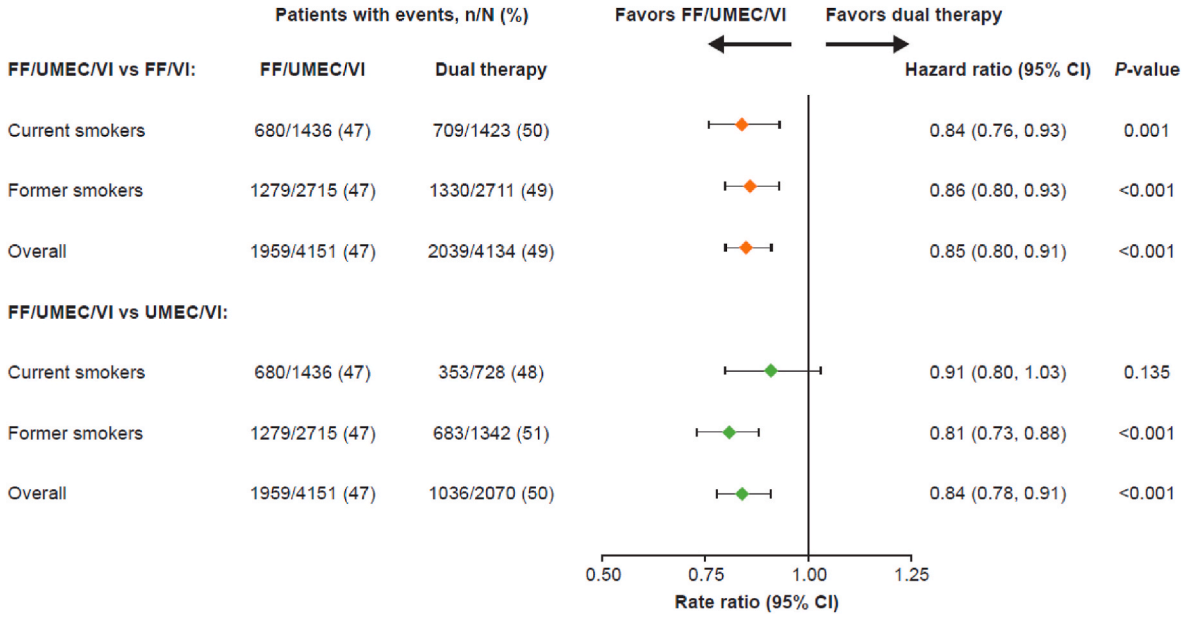

Fig. 2. Risk (time-to-first) of on-treatment moderate/severe COPD exacerbation in current and former smokers and overall population (ITT population). Note: Hazard ratio and 95% CI are from a Cox proportional hazards model with covariates of treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), geographical region, post-bronchodilator percent predicted FEV_1 (screening), smoking status (screening). Analyses by smoking status included an additional covariate of treatment group by smoking status (screening) interaction.
CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

with the greatest differences observed in the ICS treatment arms (8.4%, 107.3 per 1,000 patient-years vs 6.3%, 74.3 per 1,000 patient-years in FF/UMEC/VI; 7.7%, 103.5 per 1,000 patient-years vs 5.8%, 83.4 per 1,000 patient-years in FF/VI; and 4.7%, 63.0 per 1,000 patient-years vs 4.7%, 58.0 per 1,000 patient-years in UMEC/VI, respectively) (Table 3).

The lowest rate of pneumonia was observed in current smokers treated with UMEC/VI (58.0 per 1,000 patient-years). Differences in the occurrence of local corticosteroid effects were also observed between current smokers (6–10%) and former smokers (5–7%) across treatment arms. Current smokers had higher exposure-adjusted rates of local corticosteroid effects compared with former smokers across all

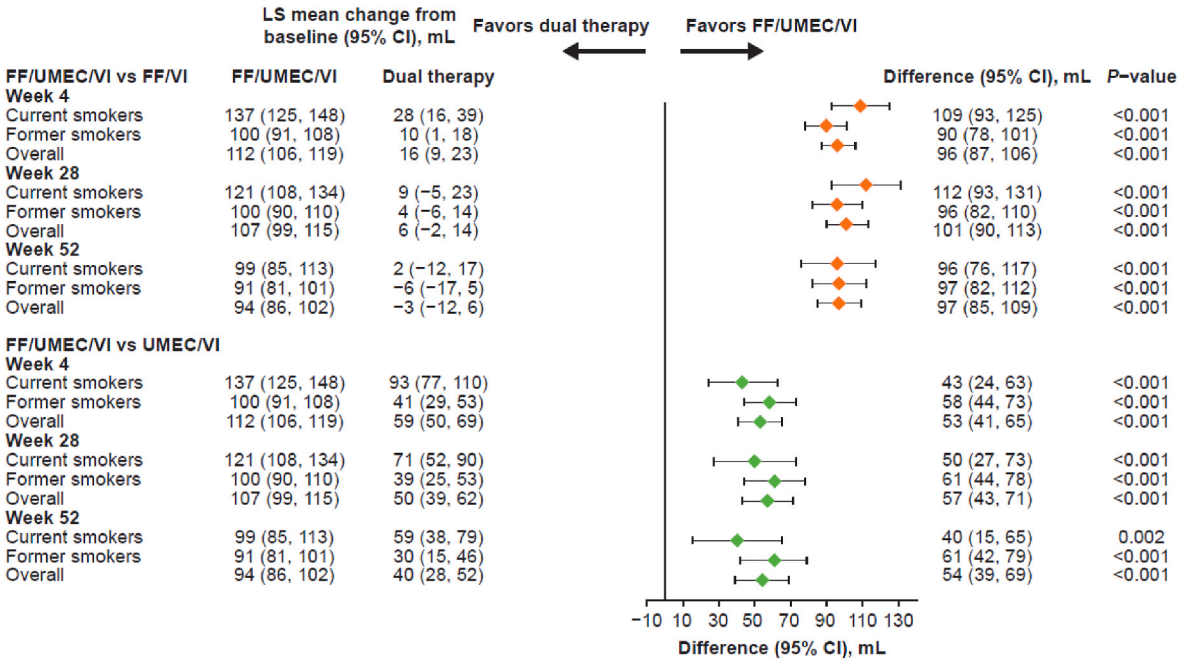

Fig. 3. Change from baseline in trough FEV_1 in current and former smokers and overall population (ITT population).
Overall: FF/UMEC/VI, N = 3,999 (week 4), N = 3,609 (week 28), N = 3,366 (week 52); FF/VI, N = 3,880 (week 4), N = 3,322 (week 28), N = 3,060 (week 52); UMEC/VI, N = 1,946 (week 4), N = 1,624 (week 28), N = 1,490 (week 52). Current smokers: FF/UMEC/VI, N = 1,392 (week 4), N = 1,265 (week 28), N = 1,162 (week 52); FF/VI, N = 1,333 (week 4), N = 1,142 (week 28), N = 1,039 (week 52); UMEC/VI, N = 685 (week 4), N = 573 (week 28), N = 538 (week 52). Former smokers: FF/UMEC/VI, N = 2,607 (week 4), N = 2,344 (week 28), N = 2,204 (week 52); FF/VI, N = 2,547 (week 4), N = 2,180 (week 28), N = 2,021 (week 52); UMEC/VI, N = 1,261 (week 4), N = 1,051 (week 28), N = 952 (week 52). Note: Analysis performed using a repeated measures model with covariates of treatment group, smoking status (screening), geographical region, visit, baseline, baseline by visit and treatment group by visit interactions. Analyses by smoking status included additional interactions of treatment group by smoking status (screening), visit by smoking status (screening) and treatment group by visit by smoking status (screening).
CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FF, fluticasone furoate; LS, least squares; UMEC, umeclidinium; VI, vilanterol.

treatment arms (Table 2).

The most common on-treatment AESIs were cardiovascular effects, occurring with a similar incidence and rate across all treatment groups among both current smokers and former smokers (10–11% and 155.0–169.1 per 1,000 patient-years) (Table 2).

3. Discussion

This post hoc analysis of data from the IMPACT trial demonstrates that single-inhaler triple therapy with FF/UMEC/VI significantly reduces the rate of on-treatment moderate/severe exacerbations and improves trough FEV_1 and SGRQ total score compared with FF/VI and UMEC/VI in both current and former smokers. A significant interaction of smoking status at screening with treatment was observed for the primary analysis; in line with this finding, subgroup analysis showed that the benefit of FF/UMEC/VI versus UMEC/VI on rate of on-treatment moderate/severe exacerbations was seen among both current and former smokers, however the benefit was greater in former versus current smokers, potentially due to a relative corticosteroid resistance in current smokers [5]. Similar trends were seen for both lung function and health status. These findings emphasize the importance of smoking cessation in the moderate-to-severe COPD population, to enable optimal response to treatment.

These differences in treatment effects by smoking status may be related to patients being more likely to stop smoking if they have more severe disease and worse health status at the time of COPD diagnosis [15]. Although in our study, current and former smokers had similar symptoms and exacerbation rates at baseline, a higher proportion of former smokers were receiving triple therapy prior to the study in line with previous studies which have shown former smokers are more symptomatic [15] and have a greater number of comorbid conditions [16]. In former smokers, triple therapy demonstrated greater effects compared with UMEC/VI for the rate and risk of exacerbations and health status (as measured by SGRQ); however, for lung function, the added benefit of triple therapy was more pronounced versus FF/VI. In current smokers, the added benefit of triple therapy versus FF/VI was greater than versus UMEC/VI for all endpoints. These findings illustrate the utility of the ICS in the treatment regimen for former smokers. In current smokers, however, concomitant use appears to blunt the clinical response to ICS. Impairment of the response to ICS in smokers has been reported for both asthma and COPD [5,7–10,17,18]. Whilst this effect could be a result of increased mucus production impairing the absorption of ICS [19], several possible mechanisms have been proposed for this finding, including a decrease in the enzyme HDAC2 or of the anti-oxidative transcription factor nuclear factor erythroid 2-related factor 2 [20]. Additionally, reduced glucocorticoid receptor nuclear translocation due to receptor phosphorylation at Ser226 by p38 mitogen-activated protein kinase can confer corticosteroid insensitivity [21,22]. Alternatively, a less likely explanation may be that acute anti-inflammatory effects associated with substances present in cigarette smoke such as carbon monoxide may result in ICS being superfluous [23].

Our findings complement previous analyses and published data. In an earlier analysis of the IMPACT trial investigating the effect of smoking status and blood eosinophil counts, former smokers had a greater ICS treatment effect at all blood eosinophil counts compared with current smokers. Furthermore, when comparing FF/UMEC/VI versus UMEC/VI, no benefit of ICS was seen in current smokers with blood eosinophil levels below 200 eosinophils/μL [7]. In the SUMMIT trial, current smokers were shown to have a blunted FEV_1 response with FF and a smaller reduction in exacerbation frequency with FF/VI compared with former smokers. The study authors inferred that

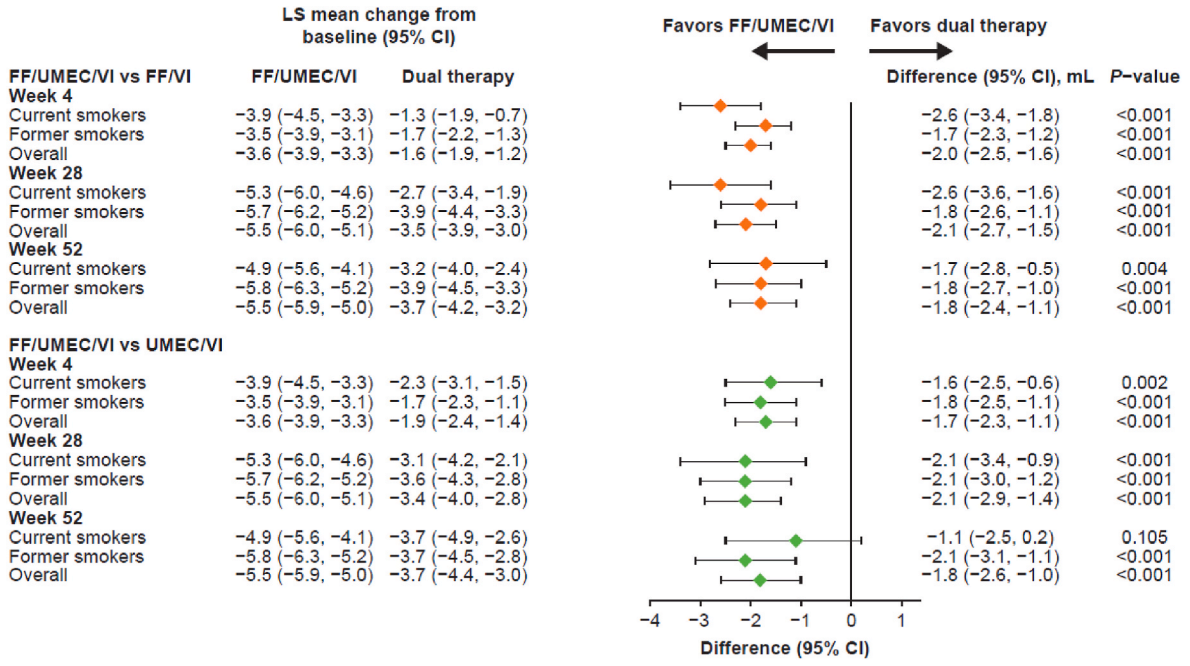

Fig. 4. Change from baseline in SGRQ total score in current and former smokers and overall population (ITT population).
Overall: FF/UMEC/VI, N = 3,967 (week 4), N = 3,573 (week 28), N = 3,318 (week 52); FF/VI, N = 3,855 (week 4), N = 3,276 (week 28), N = 3,026 (week 52); UMEC/VI, N = 1,924 (week 4), N = 1,598 (week 28), N = 1,470 (week 52). Current smokers: FF/UMEC/VI, N = 1,383 (week 4), N = 1,250 (week 28), N = 1,146 (week 52); FF/VI, N = 1,322 (week 4), N = 1,124 (week 28), N = 1,020 (week 52); UMEC/VI, N = 680 (week 4), N = 569 (week 28), N = 529 (week 52). Former smokers: FF/UMEC/VI, N = 2,584 (week 4), N = 2,323 (week 28), N = 2,172 (week 52); FF/VI, N = 2,533 (week 4), N = 2,152 (week 28), N = 2,006 (week 52); UMEC/VI, N = 1,244 (week 4), N = 1,029 (week 28), N = 941 (week 52). Note: Analysis performed using a repeated measures model with covariates of treatment group, smoking status (screening), geographical region, visit, baseline, baseline by visit and treatment group by visit interactions. Analyses by smoking status included additional interactions of treatment group by smoking status (screening), visit by smoking status (screening) and treatment group by visit by smoking status (screening).
CI, confidence interval; FF, fluticasone furoate; LS, least squares; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

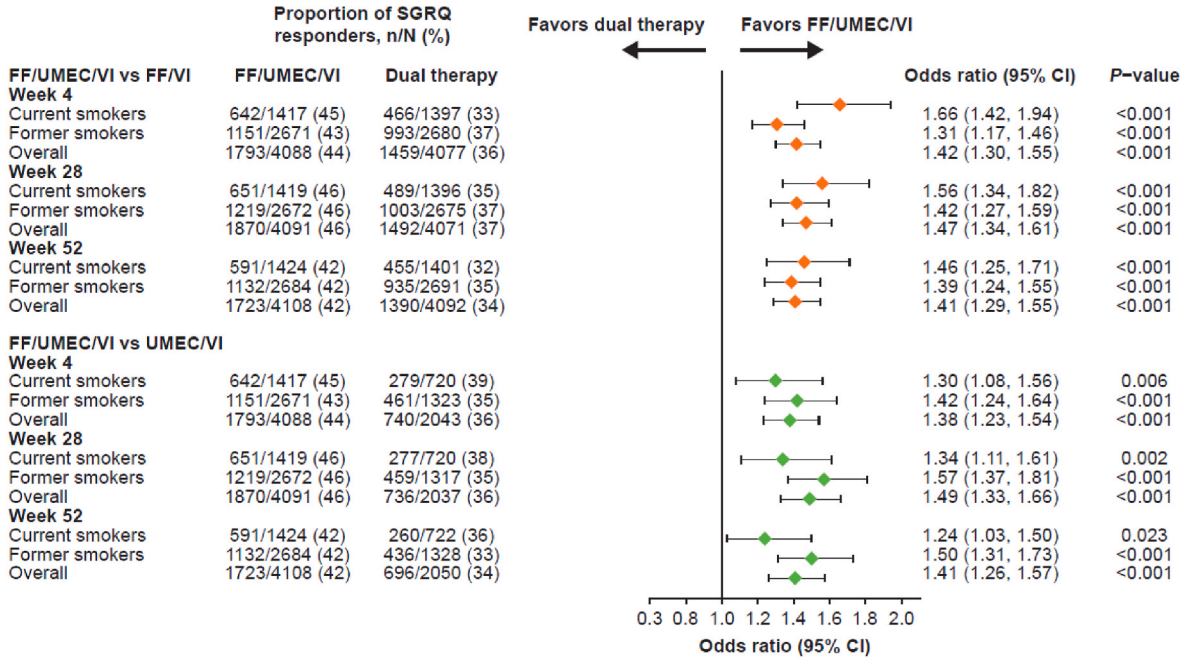

Fig. 5. Proportion of patients achieving SGRQ response (≥4 unit change from baseline) in current and former smokers and overall population (ITT population). Note: Analysis performed using a generalized linear mixed model with a logit link function and covariates of treatment group, geographical region, visit, baseline, baseline by visit and treatment group by visit interactions; each subgroup was analyzed separately.
CI, confidence interval; FF, fluticasone furoate; LS, least squares; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

Table 3
Incidence of on-treatment AEs (ITT population).

	Current smokers			Former smokers		
	FF/UMEC/VI N = 1,436	FF/VI N = 1,423	UMEC/VI N = 728	FF/UMEC/VI N = 2,715	FF/VI N = 2,711	UMEC/VI N = 1,342
Total duration at risk (patient-years)	1,291.3	1,187.2	603.2	2,423.6	2,270.8	1,095.0
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
	Rate [#]	**Rate [#]**	**Rate [#]**	**Rate [#]**	**Rate [#]**	**Rate [#]**
AEs						
Any	997 (69)	968 (68)	503 (69)	1,900 (70)	1,832 (68)	926 (69)
	2,727.5 [3,522]	2,810.8 [3,337]	2,730.3 [1,647]	2,575.9 [6,243]	2,480.2 [5,632]	2,497.6 [2,735]
Leading to permanent discontinuation or study withdrawal	88 (6)	121 (9)	61 (8)	164 (6)	206 (8)	126 (9)
	85.2 [110]	131.4 [156]	137.6 [83]	95.7 [232]	127.3 [289]	147.9 [162]
SAEs						
Any	330 (23)	311 (22)	167 (23)	565 (21)	539 (20)	303 (23)
	460.0 [594]	436.3 [518]	434.3 [262]	416.7 [1010]	417.0 [947]	448.4 [491]
Fatal	25 (2)	23 (2)	12 (2)	43 (2)	53 (2)	37 (3)
	24.8 [32]	23.6 [28]	19.9 [12]	27.2 [66]	29.9 [68]	48.4 [53]
AESIs						
Anticholinergic syndrome (SMQ)	58 (4)	52 (4)	25 (3)	126 (5)	88 (3)	45 (3)
	49.6 [64]	53.9 [64]	49.7 [30]	66.8 [162]	43.6 [99]	46.6 [51]
Asthma/bronchospasm (SMQ)	14 (<1)	13 (<1)	6 (<1)	13 < 1)	21 (<1)	10 (<1)
	10.8 [14]	11.0 [13]	9.9 [6]	5.8 [14]	9.7 [22]	9.1 [10]
Cardiovascular effects	155 (11)	147 (10)	82 (11)	295 (11)	283 (10)	142 (11)
	167.3 [216]	155.0 [184]	169.1 [102]	167.1 [405]	158.1 [359]	165.3 [181]
LRTI excluding pneumonia	73 (5)	58 (4)	45 (6)	127 (5)	141 (5)	63 (5)
	6.5 [82]	57.3 [68]	92.8 [56]	62.7 [152]	76.2 [173]	66.7 [73]
Local corticosteroid effects	143 (10)	131 (9)	42 (6)	194 (7)	170 (6)	66 (5)
	149.5 [193]	138.1 [164]	91.2 [55]	95.7 [232]	91.2 [207]	74.0 [81]
Pneumonia	90 (6)	82 (6)	34 (5)	227 (8)	210 (8)	63 (5)
	74.3 [96]	83.4 [99]	58.0 [35]	107.3 [260]	103.5 [235]	63.0 [69]
Urinary retention	0 (0)	5 (<1)	2 (<1)	8 (<1)	7 (<1)	7 (<1)
	0 [0]	4.2 [5]	3.3 [2]	4.1 [10]	3.1 [7]	6.4 [7]

Note: n = Number of subjects, # = Number of events. Note: Rate is event rate per 1,000 subject-years, calculated as the number of events x 1,000, divided by the total duration at risk.
AEs, adverse events; AESIs, adverse events of special interest; FF, fluticasone furoate; ITT, intent-to-treat; LRTI, lower respiratory tract infections; SAEs, serious adverse events; SMQ, standard Medical Dictionary for Regulatory Activities (MedDRA) queries; UMEC, umeclidinium; VI, vilanterol.

continued smoking is associated with an impaired response to ICS in patients with COPD [5]. In a pooled analysis, glycopyrrolate (a LAMA) versus placebo was associated with a non-significant improvement in trough FEV_1 in current smokers receiving background ICS but with significant improvements in trough FEV_1 in former smokers regardless of ICS use [17]. In a systematic review examining the impact of smoking status on the efficacy of ICS use in patients with COPD, the majority of participants who were ex-smokers demonstrated a greater increase in lung function and decrease in exacerbations over current smokers [6]. In addition, a greater decline in lung function in patients with a smoking pack-year history ≥36 years compared with those with a history <36 years has been reported for patients receiving fluticasone or budesonide treatment [9,10].

This reduced response to ICS in current smokers may have resulted in a greater relative treatment effect among current smokers in the IMPACT UMEC/VI treatment arm, and therefore a smaller benefit of triple therapy versus UMEC/VI in this patient subgroup. This is particularly evident from the difference in the rate ratio for moderate/severe exacerbation rate with FF/UMEC/VI versus UMEC/VI in current smokers compared with former smokers (0.86 vs 0.70). Reduced corticosteroid sensitivity in smokers, however, might not fully explain these results. In contrast to the SUMMIT and Glycopyrrolate Effect on syMptoms and lung function 1 and 2 (GEM1 and GEM2) studies, the IMPACT trial compared triple therapy versus both dual ICS/LABA and LAMA/LABA therapy, allowing the effects of dual bronchodilation to be investigated in current and former smokers. The lung function results in this analysis suggest that the benefits of dual bronchodilation with UMEC/VI might be more important than use of an ICS in current smokers as a result of neutrophilic inflammation that increases airflow obstruction and leads to more air trapping [2,24], as well as the anticholinergic effect of LAMA that may offset the airway cholinergic drive of smoking [25]. However, improvements in lung function and exacerbations were greatest with FF/UMEC/VI versus FF/VI regardless of smoking status, emphasizing the importance of treatment with the combination of ICS and two bronchodilators.

The incidence of AESIs were similar between current and former smokers, except for pneumonia and local corticosteroid effects. Pneumonia incidence was higher in former smokers compared with current smokers, particularly in the ICS treatment arms (6.3% and 5.8% among current smokers vs 8.4% and 7.7% among former smokers in the FF/UMEC/VI and FF/VI treatment arms). Former smokers with COPD may have ceased smoking due to necessity from ill health, symptoms or frequent COPD exacerbations [15]. Local corticosteroid effects were higher in current smokers; however, local corticosteroid effects are also common side effects of smoking, notably increasing dysphonia [26], and oral candidiasis in those with immune dysfunction such as HIV [27].

Some limitations should be considered in the interpretation of the findings of this study. Analyses were conducted post hoc and the IMPACT trial, whilst extensive with a large sample size, was not powered to analyze endpoints by smoking status. Smoking status was measured at screening via self-reporting, which may have led to an underestimation of current smoking. Without cotinine levels being checked, it is possible some patients self-reported as former smokers when they were still actively smoking. As stated earlier, the baseline characteristics between the current and former smoker populations were not balanced, with former smokers more likely to be older, male and receiving triple therapy at baseline. As such, formal statistical comparisons between current and former smokers were not conducted as these differences may confound the results of any formal comparison between the groups. Strengths of the study include that IMPACT was a large, prospective COPD clinical trial and was designed to be generalizable to clinical practice [13].

4. Conclusion

FF/UMEC/VI improved the exacerbation rate, lung function, and health status compared with FF/VI and UMEC/VI in patients with symptomatic COPD and a history of exacerbations, regardless of smoking status. The optimal benefit for triple versus LAMA/LABA dual therapy was observed in former smokers, potentially due to relative corticosteroid resistance in current smokers. This emphasizes the importance of smoking cessation in this symptomatic COPD population at risk of exacerbations, as amongst its many advantages, it leads to greater benefits from corticosteroid-containing therapy such as once-daily FF/UMEC/VI versus dual therapies across a range of COPD endpoints.

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Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. All authors had full access to the data in this study, note adherence of the study to the protocol, and take complete responsibility for the integrity of the data and accuracy of the data analysis, and responsibility for the integrity of the work as a whole. All authors discussed and interpreted the results, contributed to the data analyses, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published.

DAL was involved in the conception/design of the study and analysis/interpretation of data. SB, MKH, DM, DH, FJM, DS, RAW, PL, RNvZS, NB, NAH and TMS were involved in analysis/interpretation of data. DMGH and GJC were involved in acquisition and analysis/interpretation of data.

Data sharing

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Declaration of competing interest

DM and DAL are GSK employees and hold GSK stocks/shares. SB is a former GSK employee and holds GSK stocks/shares. GJC has received personal fees from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Broncus Medical, Chiesi, CSA Medical, Eolo, Gala Therapeutics, GSK, Helios Medical, HGE Technologies, Merck, Medtronic, Mereo BioPharma, NGM Biopharmaceuticals, Novartis, Nuvaira, Olympus, Philips, Pulmonx, Respironics, Respivant Sciences, The Implementation Group and Verona. DMGH has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer and Sanofi, and non-financial support from Boehringer Ingelheim and GSK. MKH reports personal fees from Medscape and Integrity, as well as consulting fees from GSK, AstraZeneca, Boehringer Ingelheim, Novartis, Pulmonx, Teva, Verona, Merck, Mylan, Sanofi, DevPro, Aerogen, Polarian, Regeneron, Altesa Biopharma and United Therapeutics. She has received royalties from UpToDate, WW Norton and Penguin Random House. She has received payment or honoraria for consultancy from Cipla, Chiesi, AstraZeneca, Boehringer Ingelheim, GSK, Medscape and Integrity. She has served roles on boards or scientific committees for COPD foundation, ALA, Emerson School and GOLD, and has been a volunteer spokesperson for ALA and deputy editor of the ATS journal. She has received either in-kind research support or funds paid to the institution from the NIH, Novartis, Sunovion, Nuvaira, Sanofi, AstraZeneca, Boehringer Ingelheim, Gala Therapeutics, Biodesix, the COPD Foundation and the American Lung Association. She has participated in Data Safety Monitoring Boards for Novartis and Medtronic with funds paid to the institution. She holds stock options from Meissa Vaccines and Altesa Biopharma. NAH is the Editor-in-Chief for Respiratory Medicine and was an investigator on the IMPACT study. He reports receiving personal fees from GSK, AstraZeneca, Boehringer Ingelheim, Sanofi Genzyme, Novartis, Regeneron, Genentech, Sunovion, and Mylan for serving as an advisor or consultant. He also received research support from GSK, Boehringer Ingelheim and AstraZeneca. DH has received personal fees from GSK, Boehringer Ingelheim, AstraZeneca, Mylan, Novartis, and Sunovion. Research support from GSK, Boehringer Ingelheim and Mylan. He is a National Board of Directors member for the American Lung Association. PL has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi and GSK. FJM has received consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Gala, GSK, Novartis, Polarean, Pulmonx, Sanofi/Regeneron, Sunovion, Teva, Theravance/Viatris and Verona; grant support from AstraZeneca, Chiesi, GSK and Sanofi/Regeneron; payment or honoraria from UpToDate for participation in COPD CME activities; and participated in an event adjudication committee for MedTronic. FJM states that AstraZeneca, Boehringer Ingelheim and GSK are partners of the SPIROMICS program and partners in the NHLBI CAPTURE validation study; Novartis, Sanofi/Regeneron, Sunovion and Teva are partners of the SPIROMICS program; Theravance/Viatris are partners in the NHLBI CAPTURE validation study. 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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.107040.

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