ORIGINAL ARTICLE
COPD

The effect of exacerbation history on outcomes in the IMPACT trial

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FF/UMEC/VI shows benefits vs FF/VI and UMEC/VI across multiple endpoints irrespective of exacerbation history. Exacerbation history and eosinophils influenced the comparison between UMEC/VI and FF/VI, and eosinophils that between FF/UMEC/VI and UMEC/VI. http://bit.ly/2SHu2ey

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ABSTRACT IMPACT, a 52-week, randomised, double-blind trial, assessed the efficacy and safety of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) triple therapy *versus* FF/VI or UMEC/VI in patients with symptomatic COPD and a history of exacerbations.

Subgroup analyses assessed whether the efficacy of FF/UMEC/VI *versus* FF/VI or UMEC/VI and UMEC/VI *versus* FF/VI varies according to prior exacerbation history, and the combined effects of exacerbation history and blood eosinophil counts. Three subgroups were defined: single moderate (1 moderate/no severe; n=3056 (30%)), frequent moderate (⩾2 moderate/no severe; n=4628 (45%)) and severe (⩾1 severe/any moderate; n=2671 (26%)). End-points included annual on-treatment moderate/severe exacerbation rate (pre-specified), lung function and health status (both post-hoc).

Moderate/severe exacerbation rates (reduction % (95% CI)) were reduced in the FF/UMEC/VI group *versus* FF/VI (single moderate 20% (10–29), frequent moderate 11% (2–19), severe 17% (7–26)) and *versus* UMEC/VI (single moderate 18% (5–29), frequent moderate 29% (21–37), severe 26% (14–35)). Moderate/severe exacerbation rates were reduced in the FF/VI group *versus* UMEC/VI in the frequent moderate subgroup; a numerical reduction was observed in the severe subgroup (single moderate 2% (−12–18), frequent moderate 21% (11–29), severe 11% (−3–22)). Moderate/severe exacerbation rates were lower in the FF/VI group compared with UMEC/VI in patients with higher eosinophil counts. FF/UMEC/VI improved lung function and health status *versus* both dual therapies irrespective of exacerbation subgroup. UMEC/VI improved lung function *versus* FF/VI in all subgroups.

Triple therapy was more effective than dual regardless of exacerbation history, consistent with results in the intent-to-treat population. Comparisons between dual therapies were influenced by prior exacerbation history and eosinophil counts.

Introduction

Pharmacological treatment of patients with COPD aims to reduce symptoms, improve health status and reduce exacerbations [1, 2]. The ECLIPSE (https://clinicaltrials.gov NCT00292552) and SPIROMICS (https://clinicaltrials.gov NCT01969344) studies have shown that future exacerbation risk is best predicted by history of prior exacerbations [3–5]. In ECLIPSE, patients with one or two exacerbations in the previous year had a two- or five-fold increased risk of exacerbation in the subsequent year, respectively [4]. The 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends assessing exacerbation risk based on patients' prior 12-month history of exacerbations, with ⩾2 moderate or 1 severe exacerbation used to predict those at higher risk [1, 6].

Analyses from randomised clinical trials in COPD patients with a history of exacerbations have shown that blood eosinophil counts predict inhaled corticosteroid (ICS) effects on exacerbation prevention [7–10]. GOLD recommends blood eosinophils as a biomarker to help guide ICS use, with lower counts (<100 eosinophils·μL^{-1}) suggesting a low probability of treatment benefit and higher counts (>300 eosinophils·μL^{-1}) suggesting a high probability [6].

The IMPACT (Informing the Pathway of COPD Treatment) trial evaluated once-daily single-inhaler triple therapy with the ICS fluticasone furoate (FF), the long-acting muscarinic antagonist (LAMA) umeclidinium (UMEC), and the long-acting β_2-agonist (LABA) vilanterol (VI), compared with dual therapies FF/VI and UMEC/VI in patients with symptomatic COPD at increased exacerbation risk [11, 12]. The magnitude of benefit of triple therapy and FF/VI in reducing exacerbation rates compared with UMEC/VI increased with higher blood eosinophil counts [13].

Some analyses have reported the effect of prior exacerbation history on exacerbation outcomes following treatment with LAMA/LABA *versus* ICS/LABA [14], or with ICS/LAMA/LABA single-inhaler triple therapy *versus* ICS/LABA or LAMA monotherapy [15–17]. However, these studies included a limited number of patients at high risk of exacerbations (at least two in prior year). Post-hoc analyses have also suggested that there is an interaction between prior exacerbation history and blood eosinophil counts on exacerbation outcomes [18, 19]. IMPACT offers the opportunity to evaluate whether pharmacological treatment effects differ in patients with only one moderate compared with several moderate or severe exacerbations in the previous year and to examine the relationship between blood eosinophil counts and pharmacological treatment by exacerbation history in a large group of patients with COPD. In these analyses, we examined whether exacerbation history influenced the relative effect of FF/UMEC/VI compared with FF/VI and UMEC/VI on moderate and severe exacerbations, lung function and health-related quality of life in patients with symptomatic COPD and at risk of exacerbations.

Methods

Study design

IMPACT (GSK study CTT116855; https://clinicaltrials.gov NCT02164513) was a phase 3, randomised, double-blind, parallel-group multicentre trial. The primary objective was to evaluate the effects of once-daily FF/UMEC/VI (100/62.5/25 μg) *versus* FF/VI (100/25 μg) or UMEC/VI (62.5/25 μg) on the rate of moderate or severe COPD exacerbations over 52 weeks. Each regimen was administered in a single dry-powder inhaler (Ellipta, licensed to the GSK group of companies). Details of the study design, including entry criteria and study protocol, have been reported previously [12].

The primary efficacy outcome was on-treatment annual rate of moderate/severe exacerbations. The two co-primary treatment comparisons were FF/UMEC/VI *versus* UMEC/VI, and FF/UMEC/VI *versus* FF/VI. Secondary outcomes included time-to-first moderate/severe COPD exacerbation, on-treatment annual rate of severe exacerbation, trough forced expiratory volume in 1 s (FEV_1), St George's Respiratory Questionnaire (SGRQ) total score and proportion of SGRQ responders (at least four-unit decrease in SGRQ total score from baseline) at week 52.

These end-points were analysed according to patient exacerbation history in the 12 months prior to screening and were classified into three subgroups: single moderate (1 moderate and no severe

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This work is a subanalysis of randomised controlled trial NCT02164513. Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com

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exacerbation), frequent moderate (⩾2 moderate, no severe) and severe (⩾1 severe exacerbation regardless of number of moderate).

Throughout the study, COPD exacerbation severity was categorised as mild, moderate or severe. Mild exacerbations were events not treated with corticosteroids or antibiotics, moderate exacerbations required treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations resulted in hospitalisation or death.

Institutional review boards for human studies at each clinical site approved the protocol and written informed consent was obtained from each patient.

Patients

Enrolled patients were aged ⩾40 years with symptomatic COPD: COPD Assessment Test score ⩾10 (range 0–40) with higher scores indicating more symptoms; minimal clinically important difference (MCID) two units [20]. Patients had to have either a FEV_1 <50% of predicted with ⩾1 moderate or severe exacerbations in the prior year, or FEV_1 of 50 to <80% of predicted and ⩾2 moderate or ⩾1 severe exacerbations in the prior year. Patients continued to take their maintenance medication during a 2-week run-in period before randomisation.

Statistical analyses

Analyses were performed on the intent-to-treat population that comprised all randomised patients (n=10 355), excluding those who were randomised in error who did not receive a dose of study medication (n=12). Patients were randomised in a 2:2:1 ratio to receive FF/UMEC/VI (n=4151), FF/VI (n=4134) or UMEC/VI (n=2070).

The annual rate of on-treatment moderate/severe exacerbations and severe exacerbations was analysed using a generalised linear model assuming a negative binomial distribution with covariates of treatment group, sex, smoking status at screening, geographical region and post-bronchodilator FEV_1 % predicted at screening.

Time-to-first exacerbation end-points were analysed using a Cox proportional hazards model with the same covariates as the annual rate end-points.

Change from baseline in trough FEV_1 and SGRQ total score were analysed using mixed repeated measures models with covariates of treatment group, smoking status at screening, geographical region, visit, relevant end-point at baseline, baseline by visit and treatment group by visit interactions.

Proportions of SGRQ responders were analysed using a generalised linear mixed model with a logit link function and covariates of treatment group, smoking status at screening, geographical region, visit, SGRQ total score at baseline, baseline by visit and treatment group by visit interactions.

We used fractional polynomials to model continuous blood eosinophil counts [13] and plotted the selected best-fitting model as continuous eosinophil count *versus* exacerbation rate in each treatment group for each of the prior exacerbation subgroups. Moderate and severe exacerbation rates on each treatment in each subgroup were also calculated by quintiles of eosinophil counts (<90, 90–<140, 140–<200, 200–<310, ⩾310 cells·μL^{-1}.)

Analyses were performed for each subgroup separately. Analysis of on-treatment moderate/severe exacerbation rates by exacerbation history subgroup was prespecified; all other analyses performed on these subgroups were post-hoc.

Results

Patient population

Baseline demographics were similar across the different subgroups (table 1) and in subgroups by treatment assignment (supplementary table 1). There were differences in the severity of airflow obstruction across the three subgroups. The single moderate subgroup had a lower mean FEV_1 predicted and lower mean FEV_1/forced vital capacity ratio than the other two subgroups, reflecting the inclusion criteria (table 1). More patients in the severe subgroup were on triple therapy at enrolment. There were no meaningful differences in baseline characteristics or prior medication use between treatment arms in each prior exacerbation subgroup.

Association between prior exacerbation history, blood eosinophil count and exacerbation outcomes

There appeared to be a possible association between prior exacerbation history and the number of exacerbations patients experienced during the study. The severe subgroup had a slightly greater proportion of patients having at least three on-treatment moderate or severe exacerbations compared with the other subgroups (figure 1).

TABLE 1 Baseline demographics according to exacerbation history in the year prior to screening

	Subgroup		
	Single moderate	**Frequent moderate**	**Severe**
Subjects	3056 (30)	4628 (45)	2671 (26)
Age years	65.2±7.95	65.3±8.46	65.4±8.29
Male	2069 (68)	2922 (63)	1879 (70)
White	2408 (79)	3604 (78)	1971 (74)
Former smoker	1964 (64)	3014 (65)	1790 (67)
BMI kg·m^{-2}	26.10±6.043	27.03±5.833	26.52±6.532
Lung function post-bronchodilator			
At screening FEV_1 L	1.046±0.3193	1.437±0.5036	1.247±0.5037
FEV_1 % predicted	37.0±8.85	51.9±14.77	44.4±15.25
FEV_1/FVC ratio	0.421±0.1028	0.510±0.1161	0.458±0.1201
Baseline[#] concomitant COPD medication at screening alone or in combination			
LAMA	243 (8)	375 (8)	213 (8)
LABA	84 (3)	166 (4)	41 (2)
LAMA+LABA	327 (11)	392 (8)	215 (8)
ICS+LABA	906 (30)	1694 (37)	741 (28)
ICS+LAMA+LABA	1258 (41)	1651 (36)	1274 (48)
Baseline blood eosinophil counts			
	203±186	230±256	232±242
Patients with count %			
<100	26	25	24
100–300	55	53	52
>300	19	23	23

Date are presented as n (%) or mean±SD, unless otherwise stated. The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (⩾2 moderate/no severe exacerbations in the prior year) and severe (⩾1 severe/any moderate exacerbation in the prior year). BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist. [#]: between day of screening −3 days and date of screening (inclusive).

The proportion of patients having just one moderate exacerbation during the study was similar across all three exacerbation history subgroups (40–46%) and was not affected by treatment (table 2). In contrast, over twice as many patients in the severe subgroup experienced an on-treatment severe exacerbation compared with patients in the single moderate or frequent moderate subgroups (20–23% *versus* 6–10%).

In the frequent moderate subgroup, the proportion of patients who experienced on-treatment severe exacerbations was lower for FF/UMEC/VI and FF/VI (6% and 7%, respectively) *versus* UMEC/VI (10%) (table 2).

Single moderate subgroup

In the single moderate subgroup, patients treated with FF/UMEC/VI had a significantly lower annual rate of on-treatment moderate/severe exacerbations *versus* those treated with FF/VI (rate ratio (95% CI) 0.80 (0.71–0.90)) and UMEC/VI (rate ratio (95% CI) 0.82 (0.71–0.95)). The model estimated annual rate of on-treatment moderate/severe exacerbations was similar in patients treated with UMEC/VI (1.03 (0.92–1.16)) and FF/VI (1.06 (0.97–1.15)) (figure 2a). Patients treated with FF/UMEC/VI also had a significantly lower risk of a moderate/severe exacerbation compared with those who received FF/VI (HR (95% CI) 0.81 (0.72–0.91)) (figure 3a). The risk reduction point estimates favoured FF/UMEC/VI over UMEC/VI (HR (95% CI) 0.92 (0.79–1.06)) and UMEC/VI over FF/VI but were not significant (HR (95% CI) 0.88 (0.76–1.02)) (figure 3a).

There were no statistically significant differences in annual rate of on-treatment severe exacerbations with patients treated with FF/UMEC/VI *versus* those treated with UMEC/VI or FF/VI (figure 2b). The proportion of patients experiencing a severe exacerbation was 9% for all three treatment arms and there was no difference in the risk when comparing FF/UMEC/VI with FF/VI (HR (95% CI) 0.99 (0.76–1.28)) or UMEC/VI (1.00 (0.72–1.38)) (figure 3b).

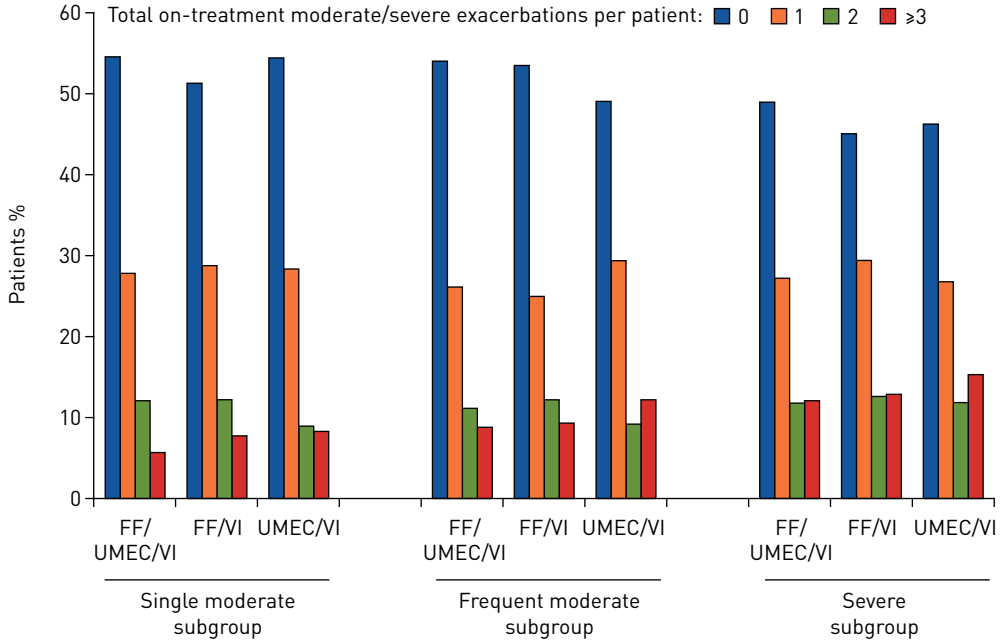


FIGURE 1 Number of combined moderate or severe COPD exacerbations per patient by prior exacerbation subgroup. The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (⩾2 moderate/no severe exacerbations in the prior year) and severe (⩾1 severe/any moderate exacerbation in the prior year). FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

When modelled according to blood eosinophil counts, exacerbation rates in the three treatment groups were similar at counts below ~200 cells·μL^{-1} (figure 4a). Rates were lower in the FF/UMEC/VI treatment group compared with the UMEC/VI treatment group at higher eosinophil counts: the rates of moderate/severe exacerbations were 0.88 (95% CI 0.73–1.05) for FF/UMEC/VI and 0.95 (0.74–1.22) for UMEC/VI at counts 140 to <200 cells·μL^{-1}, 0.76 (0.64–0.92) for FF/UMEC/VI and 1.03 (0.81–1.30) for UMEC/VI at 200 to <310 cells·μL^{-1} and 1.08 (0.89–1.32) for FF/UMEC/VI and 1.21 (0.93–1.57) for UMEC/VI at counts ⩾310 cells·μL^{-1} (supplementary table 2). For FF/VI compared to UMEC/VI, the modelled mean values suggest lower exacerbation rates for patients treated with UMEC/VI at low eosinophil counts, and

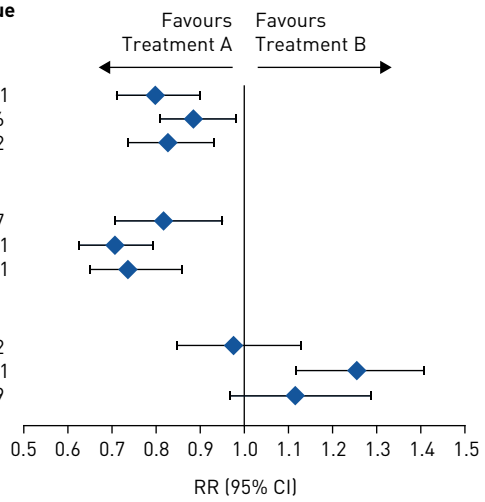
TABLE 2 Patients with ⩾1 moderate, ⩾1 severe and ⩾1 moderate or severe on-treatment exacerbations during the study period by exacerbation history in the year prior to screening

Exacerbation history subgroups	On-treatment COPD exacerbations					
	Moderate only		Severe only		Moderate or severe	
FF/UMEC/VI						
Single moderate	486 (41)	708.1 [750]	112 (9)	121.8 [129]	545 (45)	829.9 [879]
Frequent moderate	797 (43)	805.4 [1368]	117 (6)	77.7 [132]	859 (46)	883.1 [1500]
Severe	436 (40)	783.7 [750]	218 (20)	312.4 [299]	555 (51)	1096.1 [1049]
FF/VI						
Single moderate	542 (44)	857.8 [870]	108 (9)	135.1 [137]	605 (49)	992.9 [1007]
Frequent moderate	799 (44)	882.2 [1384]	120 (7)	89.2 [140]	847 (46)	971.4 [1524]
Severe	454 (42)	914.4 [800]	233 (22)	348.6 [305]	587 (55)	1263.0 [1105]
UMEC/VI						
Single moderate	252 (41)	849.1 [429]	55 (9)	120.7 [61]	281 (46)	969.9 [490]
Frequent moderate	430 (46)	1002.1 [790]	96 (10)	145.9 [115]	478 (51)	1147.9 [905]
Severe	205 (40)	958.8 [388]	121 (23)	410.2 [166]	277 (54)	1369.0 [554]

Data are presented as n (%) or rate [number of events]. Rate is reported per 1000 subject-years, calculated as the number of events×1000, divided by the total duration at risk. The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (⩾2 moderate/no severe exacerbations in the prior year) and severe (⩾1 severe/any moderate exacerbation in the prior year). FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

a)

	Treatment A FF/UMEC/VI	Treatment B FF/VI	RR (95% CI)	p-value
FF/UMEC/VI *versus* FF/VI				
Single moderate subgroup	0.85 (0.78–0.92)	1.06 (0.97–1.15)	0.80 (0.71–0.90)	<0.001
Frequent moderate subgroup	0.85 (0.80–0.91)	0.96 (0.90–1.03)	0.89 (0.81–0.98)	0.016
Severe subgroup	1.06 (0.98–1.16)	1.28 (1.18–1.39)	0.83 (0.74–0.93)	0.002
FF/UMEC/VI *versus* UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**		
Single moderate subgroup	0.85 (0.78–0.92)	1.03 (0.92–1.16)	0.82 (0.71–0.95)	0.007
Frequent moderate subgroup	0.85 (0.80–0.91)	1.21 (1.10–1.32)	0.71 (0.63–0.79)	<0.001
Severe subgroup	1.06 (0.98–1.16)	1.43 (1.27–1.61)	0.74 (0.65–0.86)	<0.001
UMEC/VI *versus* FF/VI	**UMEC/VI**	**FF/VI**		
Single moderate subgroup	1.03 (0.92–1.16)	1.06 (0.97–1.15)	0.98 (0.85–1.13)	0.782
Frequent moderate subgroup	1.21 (1.10–1.32)	0.96 (0.90–1.03)	1.26 (1.12–1.41)	<0.001
Severe subgroup	1.43 (1.27–1.61)	1.28 (1.18–1.39)	1.12 (0.97–1.29)	0.129



b)

	Treatment A FF/UMEC/VI	Treatment B FF/VI	RR (95% CI)	p-value
FF/UMEC/VI *versus* FF/VI				
Single moderate subgroup	0.11 (0.09–0.14)	0.13 (0.10–0.16)	0.88 (0.66–1.18)	0.388
Frequent moderate subgroup	0.06 (0.05–0.08)	0.07 (0.06–0.09)	0.84 (0.64–1.10)	0.198
Severe subgroup	0.29 (0.25–0.33)	0.33 (0.28–0.38)	0.88 (0.72–1.08)	0.226
FF/UMEC/VI *versus* UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**		
Single moderate subgroup	0.11 (0.09–0.14)	0.11 (0.08–0.15)	0.99 (0.69–1.43)	0.962
Frequent moderate subgroup	0.06 (0.05–0.08)	0.14 (0.11–0.17)	0.45 (0.33–0.61)	<0.001
Severe subgroup	0.29 (0.25–0.33)	0.42 (0.34–0.51)	0.69 (0.54–0.88)	0.003
UMEC/VI *versus* FF/VI	**UMEC/VI**	**FF/VI**		
Single moderate subgroup	0.11 (0.08–0.15)	0.13 (0.10–0.16)	0.89 (0.62–1.28)	0.519
Frequent moderate subgroup	0.14 (0.11–0.17)	0.07 (0.06–0.09)	1.86 (1.37–2.51)	<0.001
Severe subgroup	0.42 (0.34–0.51)	0.33 (0.28–0.38)	1.28 (1.00–1.64)	0.048

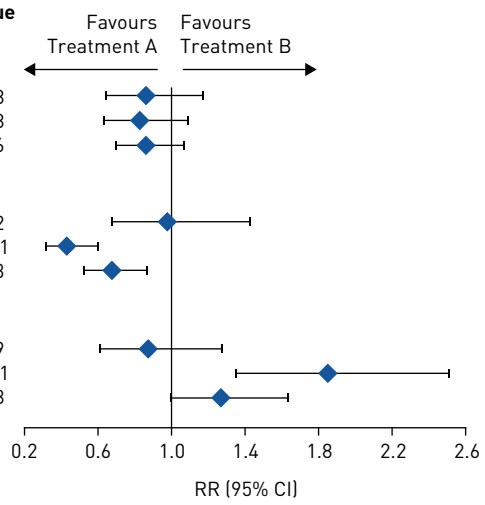


FIGURE 2 Annual rate of on-treatment a) moderate or severe and b) severe exacerbations (post-hoc analysis) according to exacerbation history in the year prior to screening for each treatment comparison. The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (⩾2 moderate/no severe exacerbations in the prior year) and severe (⩾1 severe/any moderate exacerbation in the prior year). Data are presented as model estimated annual rate (95% CI), unless otherwise stated. FF: fluticasone furoate; RR: rate ratio; UMEC: umeclidinium; VI: vilanterol.

lower exacerbation rates for those treated with FF/VI at high eosinophil counts, but the confidence intervals were not significant for these numerical trends (figure 5a and b).

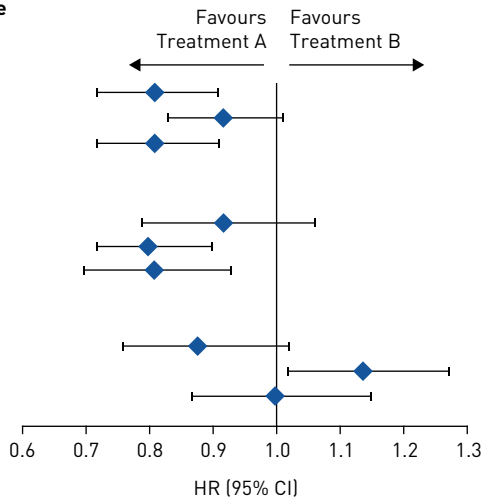
Frequent moderate subgroup

In the frequent moderate subgroup, the annual rate of on-treatment moderate/severe exacerbations was significantly lower for patients receiving FF/UMEC/VI *versus* FF/VI (rate ratio (95% CI) 0.89 (0.81–0.98)) or UMEC/VI (0.71 (0.63–0.79)) (figure 2a), and the risk of a moderate/severe exacerbation was significantly lower for patients receiving FF/UMEC/VI compared with UMEC/VI (HR (95% CI) 0.80 (0.72–0.90)) (figure 3a). The FF/UMEC/VI treatment group also had a lower annual rate of on-treatment severe exacerbations compared with the UMEC/VI group (0.45 (0.33–0.61)) (figure 2b). The annual rate and the risk of on-treatment moderate/severe exacerbations was significantly lower in the FF/VI than the UMEC/VI treatment group (0.79 (0.70–0.89), HR (95% CI) 0.87 (0.78–0.98)) and so was the annual rate of severe exacerbations (0.53 (0.39–0.75)) (figures 2 and 3a).

Exacerbation rates modelled according to blood eosinophil counts in the three treatment groups were similar at counts below approximately 100 cells·μL^{-1} (figure 4b). Above this level, rates were significantly higher in the UMEC/VI treatment group *versus* FF/UMEC/VI and FF/VI groups (figure 5d) with rates of moderate/severe exacerbations of 0.85 (95% CI 0.73–0.98), 0.93 (0.81–1.08) and 1.25 (1.04–1.51) for FF/UMEC/VI, FF/VI and UMEC/VI, respectively, at counts of 200 to <310 cells·μL^{-1} and 0.87 (0.75–1.01),

a)

	Treatment A FF/UMEC/VI	Treatment B FF/VI	HR (95% CI)	p-value
FF/UMEC/VI *versus* FF/VI				
Single moderate subgroup	545/1198 (45)	605/1242 (49)	0.81 (0.72–0.91)	<0.001
Frequent moderate subgroup	859/1866 (46)	847/1823 (46)	0.92 (0.83–1.01)	0.069
Severe subgroup	555/1087 (51)	587/1069 (55)	0.81 (0.72–0.91)	<0.001
FF/UMEC/VI *versus* UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**		
Single moderate subgroup	545/1198 (45)	281/616 (46)	0.92 (0.79–1.06)	0.246
Frequent moderate subgroup	859/1866 (46)	478/939 (51)	0.80 (0.72–0.90)	<0.001
Severe subgroup	555/1087 (51)	277/515 (54)	0.81 (0.70–0.93)	0.003
UMEC/VI *versus* FF/VI	**UMEC/VI**	**FF/VI**		
Single moderate subgroup	281/616 (46)	605/1242 (49)	0.88 (0.76–1.02)	0.080
Frequent moderate subgroup	478/939 (51)	847/1823 (46)	1.14 (1.02–1.27)	0.023
Severe subgroup	277/515 (54)	587/1069 (55)	1.00 (0.87–1.15)	0.991



b)

	Treatment A FF/UMEC/VI	Treatment B FF/VI	HR (95% CI)	p-value
FF/UMEC/VI *versus* FF/VI				
Single moderate subgroup	112/1198 (9)	108/1242 (9)	0.99 (0.76–1.28)	0.914
Frequent moderate subgroup	117/1866 (6)	120/1823 (7)	0.88 (0.69–1.14)	0.347
Severe subgroup	218/1087 (20)	233/1069 (22)	0.83 (0.69–1.00)	0.050
FF/UMEC/VI *versus* UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**		
Single moderate subgroup	112/1198 (9)	55/616 (9)	1.00 (0.72–1.38)	0.978
Frequent moderate subgroup	117/1866 (6)	96/939 (10)	0.55 (0.42–0.72)	<0.001
Severe subgroup	218/1087 (20)	121/515 (23)	0.77 (0.62–0.96)	0.021
UMEC/VI *versus* FF/VI	**UMEC/VI**	**FF/VI**		
Single moderate subgroup	55/616 (9)	108/1242 (9)	0.99 (0.72–1.37)	0.952
Frequent moderate subgroup	96/939 (10)	120/1823 (7)	1.62 (1.24–2.12)	<0.001
Severe subgroup	121/515 (23)	233/1069 (22)	1.08 (0.87–1.34)	0.498

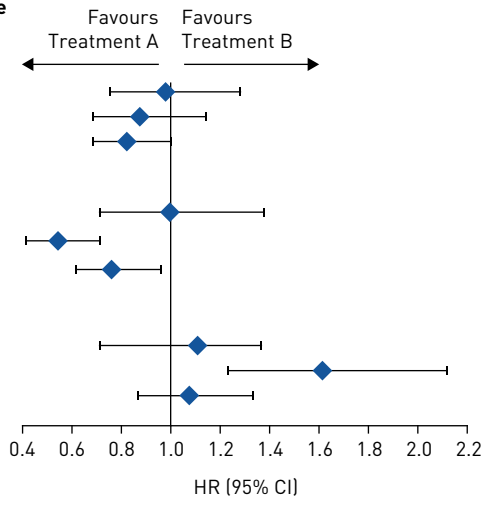


FIGURE 3 Time-to-first combined a) moderate or severe and b) severe COPD exacerbations (post-hoc analysis) by treatment by prior exacerbation subgroup for each treatment comparison. The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (⩾2 moderate/no severe exacerbations in the prior year) and severe (⩾1 severe/any moderate exacerbation in the prior year). Data are presented as patients with events n/N (%), unless otherwise stated. FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

0.91 (0.79–1.06) and 2.05 (1.70–2.49) for FF/UMEC/VI, FF/VI and UMEC/VI, respectively, at counts ⩾310 cells·μL^{-1} (supplementary table 2).

Severe subgroup

In the severe subgroup, patients treated with FF/UMEC/VI had a reduced rate and risk of on-treatment moderate/severe exacerbations *versus* those treated with FF/VI (rate ratio (95% CI) 0.83 (0.74–0.93), HR (95% CI) 0.81 (0.72–0.91)) and UMEC/VI (rate ratio (95% CI) 0.74 (0.65–0.86), HR (95% CI) 0.81 (0.70–0.93)) and also had a reduced rate of on-treatment severe exacerbations *versus* those treated with FF/VI (rate ratio (95% CI) 0.88 (0.72–1.08)) and UMEC/VI (rate ratio (95% CI) 0.69 (0.54–0.88)) (figures 2 and 3a). The FF/VI treatment group had a greater reduction in the annual rate of severe exacerbations than the UMEC/VI group (rate ratio (95% CI) 0.78 (0.61–1.00)). The point estimate favoured FF/VI over UMEC/VI for moderate/severe exacerbation rates (rate ratio (95% CI) 0.89 (0.77–1.03)), but there were no differences observed between patients treated with FF/VI and those treated with UMEC/VI on the time-to-first moderate/severe exacerbation (HR (95% CI) 1.00 (0.86–1.14)) (figures 2 and 3a).

Exacerbation rates modelled according to blood eosinophil counts in the three treatment groups were similar at counts below ~100 cells·μL^{-1} (figure 4c). Above this level, the FF/UMEC/VI and FF/VI treatment groups had lower rates than the UMEC/VI group (figure 5e and 5f), with rates of moderate or severe exacerbations of 0.89 (95% CI 0.73–1.07), 1.35 (1.14–1.59) and 1.42 (1.11–1.80) for FF/UMEC/VI,

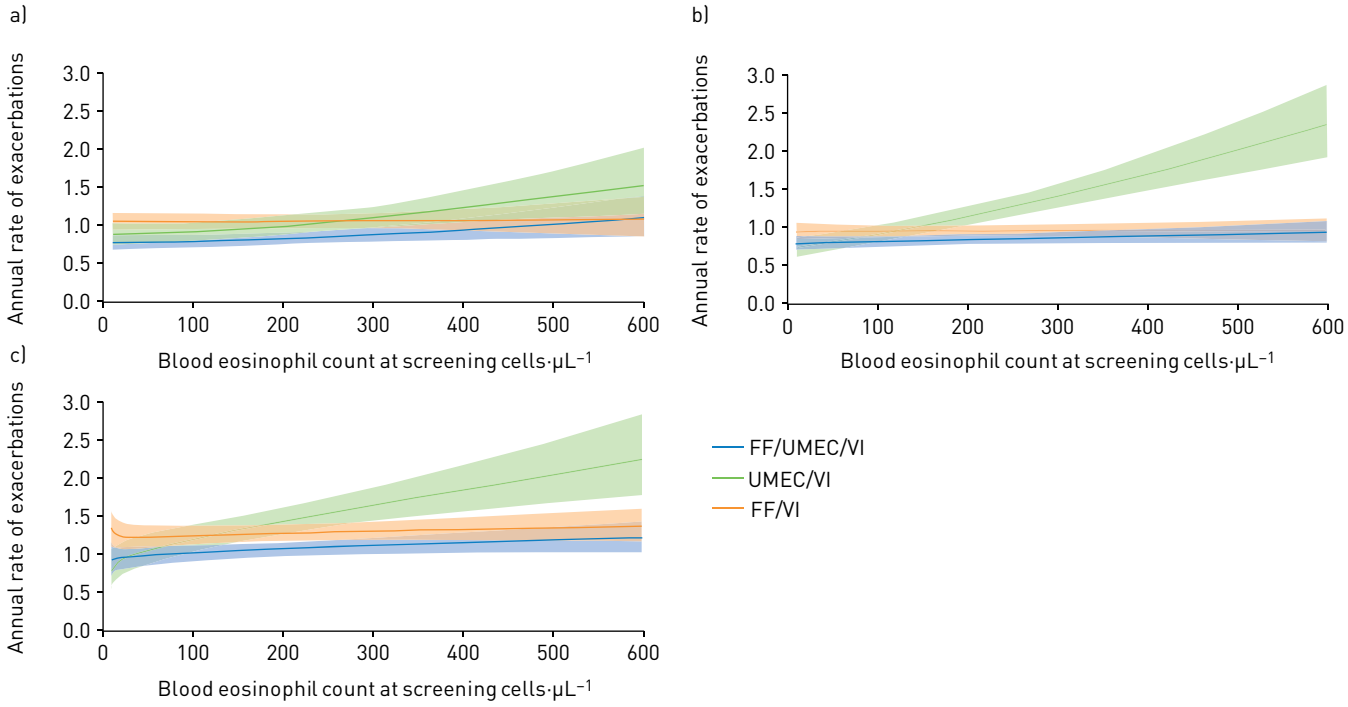


FIGURE 4 Annual rate of moderate or severe exacerbations, by baseline blood eosinophil count and individual treatment group by prior exacerbation subgroup: a) single moderate, b) frequent moderate and c) severe. The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (⩾2 moderate/no severe exacerbations in the prior year) and severe (⩾1 severe/any moderate exacerbation in the prior year). FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

FF/VI and UMEC/VI, respectively, at counts of 200 to <310 cells·μL^{-1} and 1.20 (1.01–1.43), 1.20 (1.00–1.44) and 2.02 (1.59–2.58) for FF/UMEC/VI, FF/VI and UMEC/VI, respectively, at counts ⩾310 cells·μL^{-1} (supplementary table 2).

Association between prior exacerbation history and health status

In all subgroups, the mean change from baseline in SGRQ total score at week 52 for the FF/UMEC/VI treatment group was greater than the MCID (four units) [21], and in each subgroup the improvement in SGRQ total score from baseline was greater in the FF/UMEC/VI treatment group (single: −4.8, frequent: −6.3, severe: −4.6), than the FF/VI (single: −2.4, frequent: −4.9, severe: −2.9) and UMEC/VI treatment groups (single: −3.0, frequent: −4.5, severe: −3.0), both of which showed similar effects (figure 6). The mean changes from baseline in SGRQ total score at week 52 for all treatments were greater in the frequent moderate subgroup than the other subgroups. A larger proportion of patients on FF/UMEC/VI had a four-unit change in SGRQ total score at week 52 compared with FF/VI or UMEC/VI, regardless of exacerbation history (supplementary figure 1).

Association between prior exacerbation history and trough FEV_1 during the study

Mean change from baseline in trough FEV_1 at week 52 according to exacerbation history is shown in supplementary figure 2. In all three subgroups, patients treated with FF/UMEC/VI had a significantly improved trough FEV_1 compared with those treated with FF/VI (by ~100 mL) and UMEC/VI (by 30 to ~70 mL). The UMEC/VI treatment group had a greater improvement in trough FEV_1 than the FF/VI treatment group (by 27–63 mL).

Safety data have been previously published [11]. The safety profile of FF/UMEC/VI was similar to that of FF/VI and UMEC/VI, with no new identified safety signals [11].

Discussion

These analyses, based on prior exacerbation history, show that in patients with symptomatic COPD and at risk of exacerbations, triple therapy (FF/UMEC/VI) was superior to dual therapy for preventing exacerbations and improving health status and FEV_1, regardless of exacerbation history. Analysis based on both prior exacerbation history and blood eosinophil counts showed no significant difference in

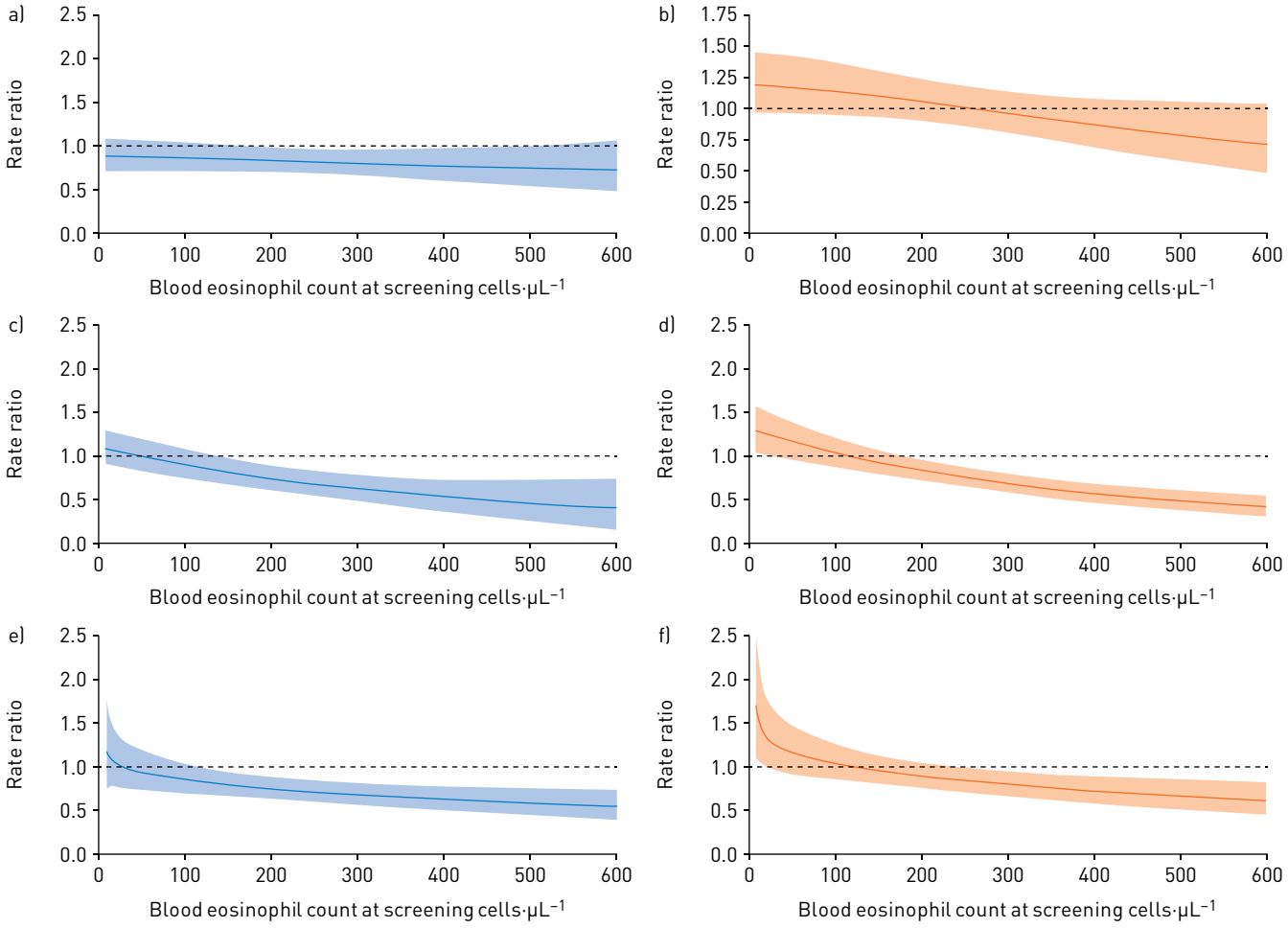


FIGURE 5 Between-treatment differences of a, c, e) FF/UMEC/VI *versus* UMEC/VI and b, d, f) FF/VI *versus* UMEC/VI in rates of moderate or severe exacerbations, by baseline blood eosinophil count and prior exacerbation subgroup: a, b) single moderate, c, d) frequent moderate, e, f) severe. The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (≥2 moderate/no severe exacerbations in the prior year) and severe (≥1 severe/any moderate exacerbation in the prior year). FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

exacerbation rates with triple therapy compared with dual therapy in patients with lower eosinophil counts irrespective of prior exacerbation history. The comparative effects of LAMA/LABA *versus* ICS/LABA varied according to previous exacerbation history and were different for different outcomes; importantly, the effects of FF/VI were greater than UMEC/VI only in patients with higher blood eosinophil counts together with either frequent moderate exacerbations or a severe exacerbation in the previous year.

Patients with a history of severe exacerbations in the previous year were more likely to have a severe exacerbation whilst on treatment than patients who only had moderate exacerbations. In the severe subgroup, FF/UMEC/VI was significantly more effective overall than FF/VI and UMEC/VI at reducing the rate of severe exacerbations.

In the subgroup who had a single moderate exacerbation in the previous year, the overall rate of exacerbations with UMEC/VI was lower than with FF/VI, although the difference was not statistically significant. When blood eosinophil counts were considered, there was a trend for patients on UMEC/VI to have higher rates of exacerbations compared with those on FF/VI at higher eosinophil counts, although the differences were not statistically significant, possibly because of lack of power owing to the small size of this subgroup. The patients in this subgroup are similar to those recruited to the FLAME study (NCT01782326), as approximately 80% had just one exacerbation in the year prior to the study. The effect of LAMA/LABA on exacerbation rates in these patients is in line with the FLAME study results [22]. Indeed, these findings comparing dual combinations in patients with one moderate exacerbation, coupled with the greater effect of ICS/LABA in patients with higher exacerbation risk, are compatible with the GOLD 2019 follow-up recommendations for the prevention of exacerbations. Greater exacerbation risk along with higher blood eosinophil counts favour ICS/LABA rather than LAMA/LABA use [1, 6].

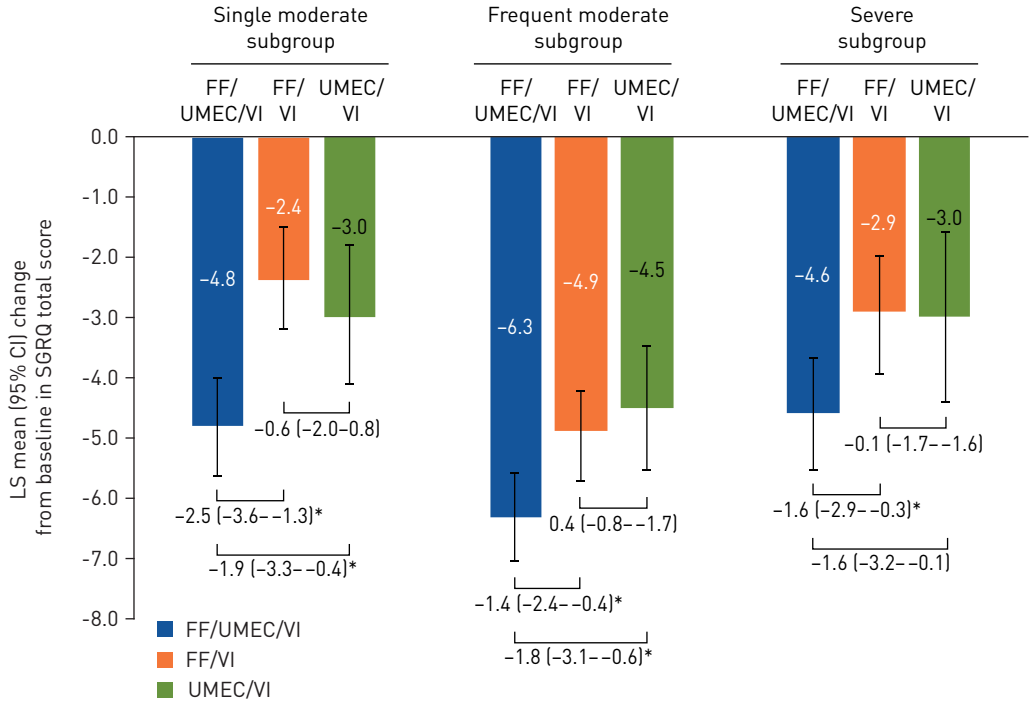


FIGURE 6 LS mean (95% CI) change in St George's Respiratory Questionnaire (SGRQ) at week 52 by prior exacerbation subgroup. The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (≥2 moderate/no severe exacerbations in the prior year) and severe (≥1 severe/any moderate exacerbation in the prior year). Post hoc analysis. Data presented as between-treatment difference (95% CI) in LS mean change from baseline at week 52 in SGRQ total score for FF/UMEC/VI *versus* UMEC/VI, FF/UMEC/VI *versus* FF/VI and UMEC/VI *versus* FF/VI. FF: fluticasone furoate; LS: least squares; UMEC: umeclidinium; VI: vilanterol. *: p<0.05.

The analysis shows differences in both the annual rate of exacerbations and the time-to-first exacerbation. The latter is important clinically because reducing exacerbation risk is an important goal for clinicians and patients. The effect on exacerbation rates reflects reductions in repeated exacerbations during the study and is likely to have contributed to the positive effects seen on health status.

Health status, as measured by SGRQ total score, did not show differential treatment effects by prior exacerbation history; FF/UMEC/VI was the most effective therapy and produced changes in health status greater than the MCID in all three subgroups. The greatest effect was seen in patients with frequent moderate but no severe exacerbations. UMEC/VI had similar effects to FF/VI.

The strengths of the analyses are the study population size, the prospective double-blinded study design comparing FF/UMEC/VI with FF/VI and UMEC/VI, the 52-week study duration, and the completeness and rigor of study end-points collection.

Limitations include the retrospective nature of the subgroup classification and that entry criteria based on exacerbation frequency were confounded by percent predicted FEV_1, mirroring GOLD recommendations at the time of study set-up. Therefore, patients with worse airflow obstruction had lower frequencies of historically reported moderate or severe exacerbations compared with those with less airflow limitation. Assessing treatment effects by prior exacerbation history subgroups gives insights into the relative effectiveness of ICS/LAMA/LABA, LAMA/LABA and ICS/LABA in these subgroups, but the interpretation of these results could be confounded by additional factors such as blood eosinophil counts. The analysis by blood eosinophil counts relies on the statistical models fitted to this dataset but the thresholds we report for differential effects of therapy are similar to those reported in other studies comparing ICS/LAMA/LABA, ICS/LABA and LAMA/LABA [7, 23].

In summary, these analyses show that FF/UMEC/VI was more effective than both FF/VI and UMEC/VI across multiple COPD end-points. A more complex pattern was apparent for the comparison of FF/VI *versus* UMEC/VI that varied according to previous exacerbation history. The blood eosinophil count helps discriminate different treatment effects in patients at greater risk of exacerbations (*i.e.* the frequent moderate and severe subgroups) but had less influence in the single moderate subgroup. These results have

relevance to clinical practice, as a higher exacerbation risk (based on previous history) and higher blood eosinophil counts favour the use of ICS/LAMA/LABA or ICS/LABA over LAMA/LABA.

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