The Effect of Exacerbation History on Outcomes in the IMPACT Trial

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Take home message

In COPD patients, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) shows benefits vs FF/VI and UMEC/VI across multiple endpoints irrespective of prior exacerbation history. Exacerbation history and eosinophil counts influenced the comparison between UMEC/VI and FF/VI. Eosinophil counts also influenced the comparison between FF/UMEC/VI and UMEC/VI, albeit to a lesser extent.

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Keywords: COPD, exacerbation history, exacerbation rates, triple therapy, ICS/LABA, LAMA/LABA, eosinophil count

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 chronic obstructive pulmonary disease 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%]). Endpoints included annual on-treatment moderate/severe exacerbation rate (pre-specified), lung function, and health status (both post hoc).

Moderate/severe exacerbation rates were reduced in the FF/UMEC/VI group versus FF/VI (% reduction [95% confidence interval]: 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 chronic obstructive pulmonary disease (COPD) aims to reduce symptoms, improve health status and reduce exacerbations.[1, 2] The ECLIPSE (NCT00292552) and SPIROMICS (NCT01969344) studies have shown that future exacerbation risk is best predicted by history of prior exacerbations.[3-5] In ECLIPSE, patients with 1 or 2 exacerbations in the previous year had a 2-fold or 5-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 corticosteroids (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) suggesting a low probability of treatment benefit and higher counts (>300 eosinophils/µL) suggesting a high probability.[6]

The Informing the Pathway of COPD Treatment (IMPACT) trial evaluated once-daily single-inhaler triple therapy with an ICS, fluticasone furoate (FF), long-acting muscarinic antagonist (LAMA), umeclidinium (UMEC), and 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 (≥2 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; ClinicalTrials.gov number 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). Details of the study

design, including entry criteria and study protocol, have been previously reported.[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 second

(FEV$_1$), St George's Respiratory Questionnaire (SGRQ) Total Score and proportion of SGRQ responders (≥4 units decrease in SGRQ Total Score from baseline) at Week 52.

These endpoints 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 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

Patients enrolled were ≥40 years of age with symptomatic COPD (COPD Assessment Test score ≥10; range 0–40, with higher scores indicating more symptoms; minimal clinically important difference [MCID] 2 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 percent predicted FEV_1 at screening.

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

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 endpoint 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.)

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 (FVC) 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 ≥3 on-treatment moderate or severe exacerbations compared with the other subgroups (Figure 1).

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% vs 6–10%).

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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: 0.80; 95% confidence interval [CI]: 0.71, 0.90) and UMEC/VI (rate ratio: 0.82; 95% CI: 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; 95% CI: 0.92, 1.16) and FF/VI (1.06; 95% CI: 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 (hazard ratio [HR]: 0.81; 95% CI: 0.72, 0.91)(Figure 3A). The risk reduction point estimates favoured FF/UMEC/VI over UMEC/VI (HR: 0.92; 95% CI: 0.79, 1.06) and UMEC/VI over FF/VI but were not significant (HR: 0.88; 95% CI: 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: 0.99; 95% CI: 0.76, 1.28) or UMEC/VI (HR: 1.00; 95% CI: 0.72, 1.38) (Figure 3B).

When modelled according to blood eosinophil counts, exacerbation rates in the three treatment groups were similar at counts below approximately 200 cells per μL (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–<200 cells/µL, 0.76 (0.64, 0.92) for FF/UMEC/VI and 1.03 (0.81, 1.30) for UMEC/VI at 200–<310 cells/µL 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 (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 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).

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: 0.89; 95% CI: 0.81, 0.98) or UMEC/VI (rate ratio: 0.71; 95% CI: 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: 0.80; 95% CI: 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 (rate ratio: 0.45; 95% CI: 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 (rate ratio: 0.79; 95% CI: 0.70, 0.89; HR: 0.87; 95% CI: 0.78, 0.98) and so was the annual rate of severe exacerbations (rate ratio: 0.53; 95% CI: 0.39, 0.75) (Figure 2 and Figure 3A).

Exacerbation rates modelled according to blood eosinophil counts in the three treatment groups were similar at counts below approximately 100 cells per/µL (Figure 4B). Above this level, rates were significantly higher in the UMEC/VI treatment group versus FF/UMEC/VI and FF/VI groups

(Figure 5B) with rates of moderate/severe exacerbations of 0.85 (95% CI: 0.73, 0.98) for

FF/UMEC/VI, 0.93 (0.81, 1.08) for FF/VI and 1.25 (1.04, 1.51) for UMEC/VI at counts 200–<310

cells/µL and 0.87 (0.75, 1.01) for FF/UMEC/VI, 0.91 (0.79, 1.06) for FF/VI and 2.05 (1.70, 2.49) for

UMEC/VI at counts ≥310 cells/µL (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: 0.83; 95%

CI: 0.74, 0.93, HR: 0.81; 95% CI: 0.72, 0.91) and UMEC/VI (rate ratio: 0.74; 95% CI: 0.65, 0.86, HR:

0.81; 95% CI: 0.70, 0.93) and also had a reduced rate of on-treatment severe exacerbations

versus those treated with FF/VI (rate ratio: 0.88; 95% CI: 0.72, 1.08) and UMEC/VI (rate ratio:

0.69; 95% CI: 0.54, 0.88) (Figure 2 and Figure 3A). The FF/VI treatment group had a greater

reduction in the annual rate of severe exacerbations than the UMEC/VI group (rate ratio: 0.78;

95% CI: 0.61, 1.00). The point estimate favoured FF/VI over UMEC/VI for moderate/severe

exacerbation rates (rate ratio: 0.89; 95% CI: 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: 1.00; 95% CI: 0.86, 1.14) (Figure 2 and Figure 3A).

Exacerbation rates modelled according to blood eosinophil counts in the three treatment groups

were similar at counts below approximately 100 cells per/µL (Figure 4C). Above this level, the

FF/UMEC/VI and FF/VI treatment groups had lower rates than the UMEC/VI group (Figure 5C),

with rates of moderate or severe exacerbations of 0.89 (95% CI: 0.73, 1.07) for FF/UMEC/VI, 1.35

(1.14, 1.59) for FF/VI and 1.42 (1.11, 1.80) for UMEC/VI at counts 200–<310 cells/µL and 1.20

(1.01, 1.43) for FF/UMEC/VI, 1.20 (1.00, 1.44) for FF/VI and 2.02 (1.59, 2.58) for UMEC/VI at

counts ≥310 cells/µL (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 (4 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 4-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 on 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 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]

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 endpoints 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 endpoints. 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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Conflict of interest

Contributions

DMG Halpin, MT Dransfield and GJ Criner were involved in acquisition and analysis/interpretation of data. MK Han, CE Jones, S Kilbride, P Lange, DA Lomas, FJ Martinez, D Singh, and R Wise were involved in analysis/interpretation of data. S Pascoe and DA Lipson were involved in the conception/design of the study and analysis/interpretation of data.

Data sharing statement

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

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

	Single moderate subgroup	Frequent moderate subgroup	Severe subgroup
	N=3056 (30%)	N=4628 (45%)	N=2671 (26%)
Age (years), mean (SD)	65.2 (7.95)	65.3 (8.46)	65.4 (8.29)
Sex (male), n (%)	2069 (68)	2922 (63)	1879 (70)
Race (white), n (%)	2408 (79)	3604 (78)	1971 (74)
Former smoker, n (%)	1964 (64)	3014 (65)	1790 (67)
BMI (kg/m^2), mean (SD)	26.10 (6.043)	27.03 (5.833)	26.52 (6.532)
Lung function (post-bronchodilator)			
At screening FEV$_1$ (L), mean (SD)	1.046 (0.3193)	1.437 (0.5036)	1.247 (0.5037)
FEV$_1$ % predicted, mean (SD)	37.0 (8.85)	51.9 (14.77)	44.4 (15.25)
FEV$_1$/FVC ratio, mean (SD)	0.421 (0.1028)	0.510 (0.1161)	0.458 (0.1201)
Baseline* concomitant COPD medication at screening (alone or in combination), n (%)			
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			
Mean (SD)	203 (186)	230 (256)	232 (242)
Percentage of patients with count: <100	26%	25%	24%
100–300	55%	53%	52%
>300	19%	23%	23%

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). *Between day of screening −3 days and date of screening (inclusive). BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β$_2$-agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation.

Table 2. Number of 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

| | On-treatment COPD exacerb | |
Exacerbation history subgroups:	Moderate only	Severe only
FF/UMEC/VI, n (%) rate [#]		
Single moderate subgroup	486 (41) 708.1 [750]	112 (9) 121.8 [129]
Frequent moderate subgroup	797 (43) 805.4 [1368]	117 (6) 77.7 [132]
Severe subgroup	436 (40) 783.7 [750]	218 (20) 312.4 [299]
FF/VI, n (%) rate [#]		
Single moderate subgroup	542 (44) 857.8 [870]	108 (9) 135.1 [137]
Frequent moderate subgroup	799 (44) 882.2 [1384]	120 (7) 89.2 [140]
Severe subgroup	454 (42) 914.4 [800]	233 (22) 348.6 [305]
UMEC/VI, n (%) rate [#]		
Single moderate subgroup	252 (41) 849.1 [429]	55 (9) 120.7 [61]
Frequent moderate subgroup	430 (46) 1002.1 [790]	96 (10) 145.9 [115]
Severe subgroup	205 (40) 958.8 [388]	121 (23) 410.2 [166]

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 reported as number of patients (%), and rate (number of events). Rate is reported per 1000 subject-years, calculated as the number of events x 1000, divided by the total duration at risk. #, number of events; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.**Figure legends**

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). COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

Figure 2. Annual rate of on-treatment (A) moderate or severe and (B) severe exacerbations 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). *Post hoc analysis. CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; RR, rate ratio; UMEC, umeclidinium; VI, vilanterol.

Figure 3. Time-to-first combined (A) moderate or severe and (B) severe COPD exacerbation 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). Post hoc analysis. CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; HR, hazard ratio; UMEC, umeclidinium; VI, vilanterol.

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, (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.

Figure 5. Between-treatment differences (FF/UMEC/VI vs UMEC/VI and FF/VI vs UMEC/VI) in rates of moderate or severe exacerbations, by baseline blood eosinophil count and prior exacerbation subgroup: (A) single moderate, (B) frequent moderate, (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.

Figure 6. LS mean (95% CI) change in 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. Numbers below the brackets indicate the between-treatment difference (95% CI) in LS mean change from baseline at Week 52 in SGRQ Total Score for FF/UMEC/VI vs UMEC/VI, FF/UMEC/VI vs FF/VI and UMEC/VI vs FF/VI. *p<0.05. CI, confidence interval; FF, fluticasone furoate; LS, least squares; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

Total on-treatment moderate/severe exacerbations per patient:

A

	Model estimated annual rate (95% CI)		RR (95% CI)	p-value
	Treatment A	**Treatment B**		
FF/UMEC/VI vs FF/VI	**FF/UMEC/VI**	**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 vs 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 vs 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*

	Model estimated annual rate (95% CI)		RR (95% CI)	p-value
	Treatment A	**Treatment B**		
FF/UMEC/VI vs FF/VI	**FF/UMEC/VI**	**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 vs 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 vs 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

A

FF/UMEC/VI vs FF/VI	Patients with event, n/N (%)		HR (95% CI)	p-value
	Treatment A	**Treatment B**		
	FF/UMEC/VI	**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 vs 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 vs 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

Favours Treatment A   Favours Treatment B

HR (95% CI) — 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3

B

FF/UMEC/VI vs FF/VI	Patients with event, n/N (%)		HR (95% CI)	p-value
	Treatment A	**Treatment B**		
	FF/UMEC/VI	**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 vs 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 vs 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

Favours Treatment A   Favours Treatment B
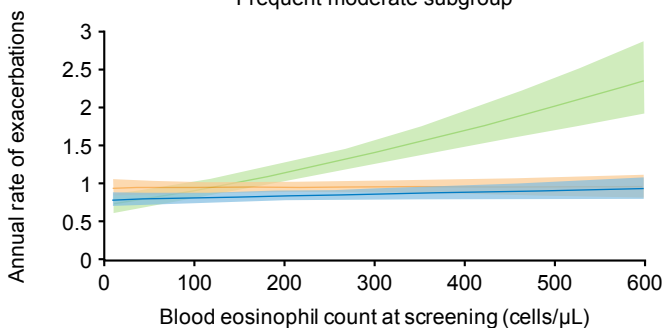
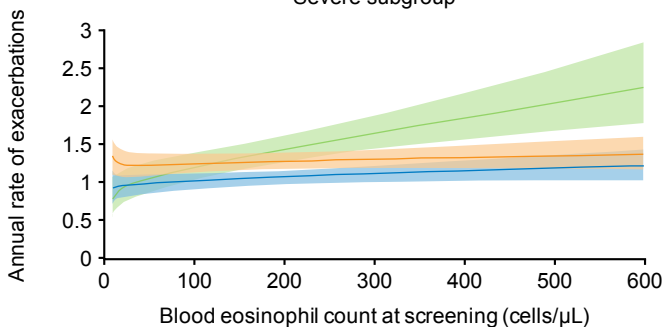HR (95% CI) — 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2
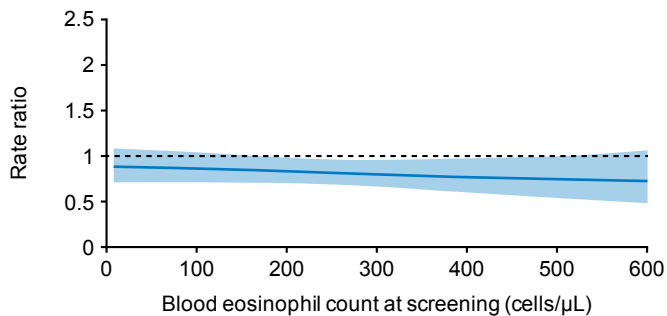
Single moderate subgroup

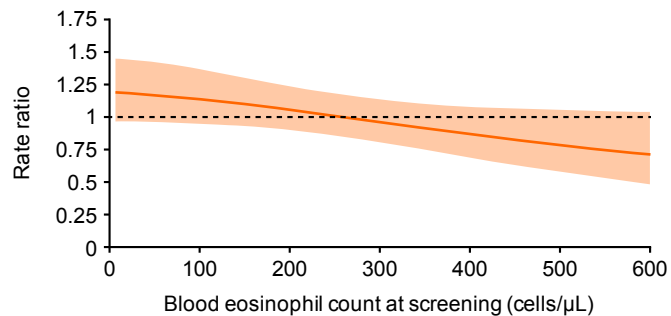Frequent moderate subgroup

Severe subgroup

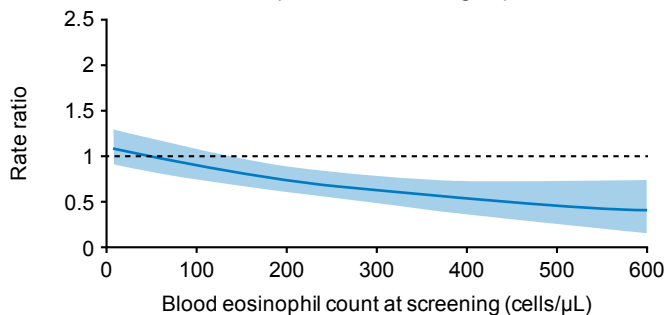FF/UMEC/VI — UMEC/VI — FF/VI

A

FF/UMEC/VI vs UMEC/VI

Single moderate subgroup

FF/VI vs UMEC/VI
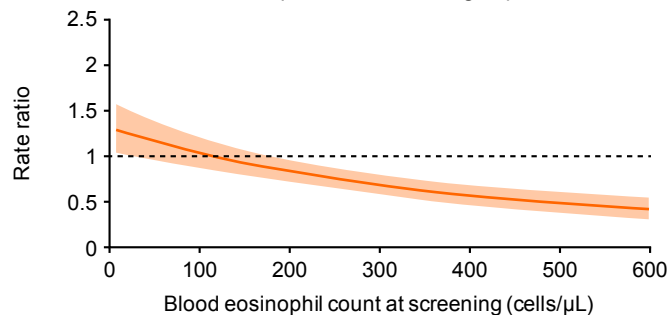
Single moderate subgroup

B
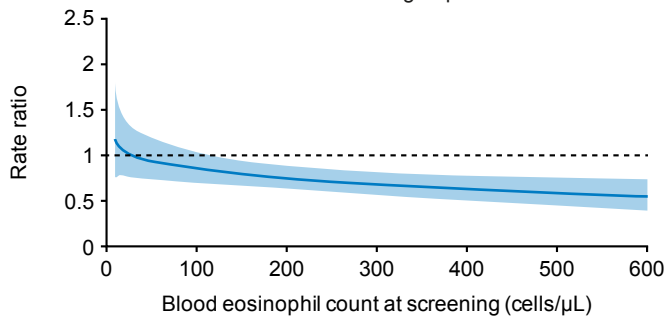
Frequent moderate subgroup

Frequent moderate subgroup

C
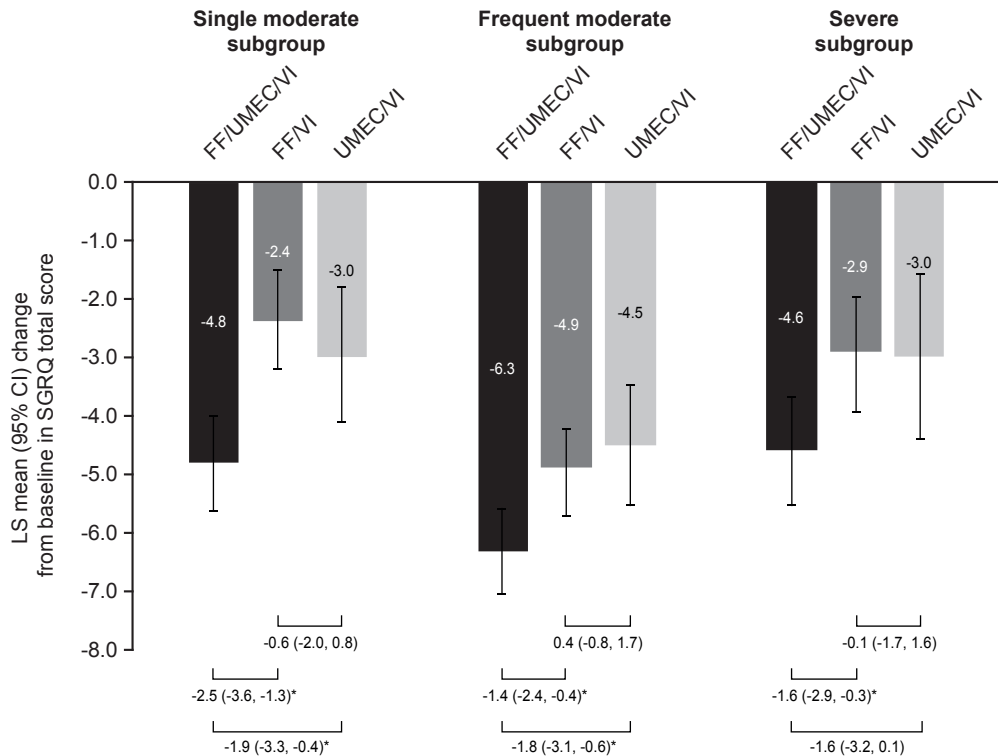
Severe subgroup

Severe subgroup

Rate ratio

Blood eosinophil count at screening (cells/μL)

Legend: FF/UMEC/VI ■ FF/VI ■ UMEC/VI

Y-axis: Proportion of responders: SGRQ total score at week 52 (%)

Single moderate subgroup
- FF/UMEC/VI: 39
- FF/VI: 29
- UMEC/VI: 33
- 1.29 (1.05, 1.59)*
- 1.54 (1.30, 1.83)*
- 1.19 (0.97, 1.48)

Frequent moderate subgroup
- FF/UMEC/VI: 45
- FF/VI: 38
- UMEC/VI: 37
- 1.43 (1.22, 1.69)*
- 1.36 (1.19, 1.55)*
- 0.95 (0.80, 1.12)

Severe subgroup
- FF/UMEC/VI: 40
- FF/VI: 33
- UMEC/VI: 30
- 1.52 (1.21, 1.91)*
- 1.38 (1.15, 1.64)*
- 0.90 (0.72, 1.14)

Legend: ■ FF/UMEC/VI ■ FF/VI □ UMEC/VI

Y-axis: LS mean (95% CI) change from baseline in trough FEV_1 (mL)

Single moderate subgroup:
- FF/UMEC/VI: 83
- FF/VI: -9
- UMEC/VI: 54
- 30 (5, 54)*
- 93 (73, 113)*
- 63 (38, 88)*

Frequent moderate subgroup:
- FF/UMEC/VI: 109
- FF/VI: 15
- UMEC/VI: 42
- 67 (44, 91)*
- 95 (76, 113)*
- 27 (4, 51)*

Severe subgroup:
- FF/UMEC/VI: 77
- FF/VI: -25
- UMEC/VI: 21
- 56 (26, 85)*
- 102 (79, 125)*
- 46 (17, 76)*