ORIGINAL ARTICLE

The Effect of Inhaled Corticosteroid Withdrawal and Baseline Inhaled Treatment on Exacerbations in the IMPACT Study
A Randomized, Double-Blind, Multicenter Clinical Trial

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Abstract

Rationale: In the IMPACT (Informing the Pathway of Chronic Obstructive Pulmonary Disease Treatment) trial, fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) significantly reduced exacerbations compared with FF/VI or UMEC/VI in patients with symptomatic chronic obstructive pulmonary disease and a history of exacerbations.

Objectives: To understand whether inhaled corticosteroid (ICS) withdrawal affected IMPACT results, given direct transition from prior maintenance medication to study medication at randomization.

Methods: Exacerbations and change from baseline in trough FEV_1 and St. George's Respiratory Questionnaire results were analyzed by prior ICS use. Exacerbations were also analyzed while excluding data from the first 30 days.

Measurements and Main Results: FF/UMEC/VI significantly reduced the annual moderate/severe exacerbation rate compared with UMEC/VI in prior ICS users (29% reduction; $P < 0.001$), but only a numerical reduction was seen among prior ICS nonusers (12% reduction; $P = 0.115$). To minimize impact from ICS withdrawal, in an analysis excluding the first 30 days, FF/UMEC/VI continued to significantly reduce the annual on-treatment moderate/severe exacerbation rate (19%; $P < 0.001$) compared with UMEC/VI. The benefit of FF/UMEC/VI compared with UMEC/VI was seen for severe exacerbation rates, regardless of prior ICS use (prior ICS users, 35% reduction; $P < 0.001$; non-ICS users, 35% reduction; $P = 0.018$), and overall when excluding the first 30 days (29%; $P < 0.001$). Improvements from baseline with FF/UMEC/VI compared with UMEC/VI were also maintained throughout the study for both trough FEV_1 and St. George's Respiratory Questionnaire, regardless of prior ICS use.

Conclusions: These data support the important treatment effects of FF/UMEC/VI combination therapy on exacerbation reduction, lung function, and quality of life that do not appear to be related to abrupt ICS withdrawal.

Clinical trial registered with www.clinicaltrials.gov (NCT 02164513).

Keywords: chronic obstructive pulmonary disease; triple therapy; step down

At a Glance Commentary

Scientific Knowledge on the Subject: In the IMPACT (Informing the Pathway of Chronic Obstructive Pulmonary Disease [COPD] Treatment) trial, fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) significantly reduced the rate of moderate/severe exacerbations compared with FF/VI or UMEC/VI in patients with symptomatic COPD and a history of exacerbations. However, questions have been raised about the potential effect of prior therapy, in particular inhaled corticosteroid (ICS) withdrawal, on study results.

What This Study Adds to the Field: Here, we demonstrate that FF/UMEC/VI resulted in a 35% reduction in severe exacerbation rates as compared with UMEC/VI for both nonprior ICS users ($P=0.018$) and prior ICS users ($P<0.001$). A numerical but not statistically significant reduction in moderate/severe exacerbations was also seen among prior ICS nonusers. In further analyses removing data from the first 30 days, during which an effect of steroid withdrawal may be more evident, the benefit of FF/UMEC/VI on moderate/severe exacerbation reduction was maintained. Improvements from baseline with FF/UMEC/VI versus UMEC/VI were also manifested throughout the study for both trough FEV_1 and St. George's Respiratory Questionnaire, regardless of prior ICS use. The totality of our data suggests that the treatment effect of FF/UMEC/VI combination therapy on lung function, quality of life, and exacerbation reduction does not appear to be related to abrupt ICS withdrawal.

The IMPACT (Informing the Pathway of Chronic Obstructive Pulmonary Disease [COPD] Treatment) trial was a 52-week, randomized, double-blind, multicenter trial that showed a greater effect of a once-daily single triple therapy that included the inhaled corticosteroid (ICS) fluticasone furoate (FF) combined with the long-acting muscarinic antagonist (LAMA) umeclidinium (UMEC) and the long-acting β_2-agonist (LABA) vilanterol (VI) at 100, 62.5, and 25 μg, respectively, compared with treatment with the dual combinations FF/VI at 100 and 25 μg and UMEC/VI at 62.5 and 25 μg on the annual rate of moderate/severe exacerbations, lung function, and quality of life in patients with symptomatic COPD and a history of exacerbations (1). FF/UMEC/VI also reduced severe exacerbations and risk of all-cause mortality compared with LAMA/LABA (UMEC/VI) with a safety profile, including pneumonia, that is consistent with previous data regarding the ICS class (1–4).

The IMPACT trial allowed patients to run-in on their current COPD medications, which more closely reflects clinical practice than using a run-in period in which the treatment is artificially changed (1). The nature of the IMPACT run-in period means that patients were allowed to receive different classes of treatment (e.g., multiple-inhaler triple therapy, ICS/LABA, LABA/LAMA, and LAMA) up until randomization. It has been suggested that the outcomes observed with triple therapy compared with UMEC/VI in the IMPACT trial arose mainly because of abrupt ICS withdrawal among patients receiving a prior ICS-containing maintenance treatment who were then randomly assigned to UMEC/VI (5). Suissa and Drazen (5) have suggested that a "rapid surge in exacerbations" occurred in the IMPACT trial during the first month after

randomization in the UMEC/VI group, which was followed by an identical incidence of exacerbations in the FF/UMEC/VI and UMEC/VI groups in Months 2–12. In these *post hoc* analyses of the IMPACT trial, we address whether the efficacy of FF/UMEC/VI compared with UMEC/VI is related to ICS withdrawal.

Methods

The IMPACT trial was a randomized, double-blind, parallel-group, 52-week study comparing the efficacy and safety of the fixed-dose triple combination of FF/UMEC/VI with the fixed-dose dual combinations of FF/VI and UMEC/VI, all administered once daily in the morning via a dry-powder ELLIPTA inhaler (GlaxoSmithKline) in patients with symptomatic COPD and a history of exacerbations. The primary endpoint was the annual rate of on-treatment moderate/severe COPD exacerbations. Details of the overall trial design and primary results have been previously published (1). The study was performed in 37 countries between June 2014 and July 2017 and in accordance with Good Clinical Practice and the Declaration of Helsinki. Local institutional review board/independent ethics committee approval was received at all enrolling sites, and all patients provided signed informed consent.

Patients were required to be ≥40 years of age, symptomatic (defined as a COPD Assessment Test score ≥10) and to have either *1*) a FEV_1 <50% of the predicted normal values and a history of at least one moderate or severe (hospitalized) exacerbation or *2*) a FEV_1 of 50% to <80% of the predicted values and at least two moderate or one severe exacerbation in the previous year.

Relevant to these analyses, patients remained on their own medication during a

2-week run-in before being randomly assigned (2:2:1) to one of the following double-blind treatment groups: FF/UMEC/VI (100/62.5/25 μg), FF/VI (100/25 μg), or UMEC/VI (62.5/25 μg). Here, we conducted the following *post hoc* analyses: *1)* cumulative-event curves for moderate/severe exacerbations overall and by ICS use at screening; *2)* on-treatment moderate/severe and severe exacerbation rates by ICS use at screening and repeated for the different previous medication-class categories for greater granularity; *3)* on-treatment moderate/severe and severe exacerbation rates with FF/UMEC/VI compared with UMEC/VI, excluding data before Day 30 (i.e., within the first 4 wk of the study) and only including time after Day 30 as being at risk (analysis after Day 30); *4)* on-treatment moderate/severe exacerbations with FF/UMEC/VI compared with UMEC/VI excluding data before Day 30 for those patients on a prior ICS-containing maintenance treatment; *5)* change from baseline in trough FEV_1 and St. George's Respiratory Questionnaire (SGRQ) by ICS use at screening; and *6)* the incidence of adverse events of special interest (AESI) by ICS use and study treatment assignment.

The time-to-first-exacerbation analyses only describe the first moderate/severe exacerbation experienced by patients; all subsequent events are not included. Conversely, the rate analyses and cumulative-event figures include all moderate/severe exacerbations over the duration of the trial. Analyses of the annual rate of exacerbations were performed using a generalized linear model, assuming a negative binomial distribution and covariates of treatment group, sex, exacerbation history (≤ 1 or ≥ 2 moderate/severe exacerbations), smoking status (at screening), geographical region, and post-bronchodilator FEV_1% predicted (at screening). Analyses of time-to-first moderate/severe exacerbation were performed using a Cox proportional-hazards model with the same covariates used for the annual rate of exacerbations.

Analyses of SGRQ and FEV_1 were performed using a repeated-measures model with covariates of treatment group, smoking status (at screening), geographical region, visit, relevant measure at baseline, and baseline by visit and treatment group by visit interactions.

Results

Patient Disposition
At baseline, 71% ($n = 7,360$) of patients were on an ICS-containing treatment. Patients were required to be on maintenance therapy for at least 3 months before study entry and to continue these medicines during the 2-week run-in period; 29% ($n = 2,995$) were not on an ICS-containing regimen at baseline (1) (*see* Figure E1 in the online supplement). As expected, patients entering the trial with prior ICS use had slightly more severe COPD according to their baseline characteristics than those without ICS use (Table 1). Despite treatment with ICS, this subgroup still had more severe airflow limitation, as indicated by the proportion of patients with a FEV_1% predicted of <50% (66% vs. 58%), a higher mean SGRQ total score (51.5 vs. 48.6), and greater percentage of patients with one or more severe exacerbations (27% vs. 22%) compared with the no-prior-ICS subgroup at study entry. Table E1 provides baseline characteristics stratified by treatment and includes all covariates considered in the analyses.

Impact of ICS Withdrawal on Exacerbations
To assess the potential effect of abrupt ICS withdrawal on exacerbations, one could examine the time-to-event curves. However, these time-to-event curves (Figures 1D–1F) only use the first exacerbation experienced by a subject and ignore all subsequent exacerbations. Hence, examination of the cumulative number of events provides greater insights into the potential effects of abrupt ICS withdrawal. In Figure 1A, all moderate and severe exacerbations for the three treatment arms throughout the 12-month treatment period are compared (adjusted for exposure). No obvious

Table 1. Baseline Characteristics by ICS Use at Screening

	Prior ICS Use (*n = 7,360*)	No Prior ICS Use (*n = 2,995*)
Age, mean (SD), yr	65.3 (8.2)	65.2 (8.4)
Sex, M, *n* (%)	4,813 (65)	2,057 (69)
BMI, mean (SD), kg/m^2	26.7 (6.1)	26.5 (6.1)
Current smoker, *n* (%)	2,408 (33)	1,179 (39)
Former smoker, *n* (%)	4,952 (67)	1,816 (61)
SGRQ total score, mean (SD)	51.5 (16.84)	48.6 (16.76)
Prebronchodilator FEV_1, mean (SD), L	1.14 (0.46)	1.24 (0.49)
Prebronchodilator FEV_1, mean (SD), % predicted	40.9 (14.2)	43.9 (14.8)
Post-bronchodilator FEV_1, mean (SD), L	1.24 (0.47)	1.35 (0.50)
Post-bronchodilator FEV_1, mean (SD), % predicted	44.7 (14.7)	47.7 (15.1)
Post-bronchodilator FEV_1% predicted < 50%, *n* (%)	4,861 (66)	1,745 (58)
Reversibility, mean (SD), %	10.6 (12.3)	10.0 (12.6)
Moderate/severe exacerbations in the prior year, *n* (%)		
0	5 (<1)	4 (<1)
1	3,360 (46)	1,331 (44)
≥ 2	3,995 (54)	1,660 (55)
Severe exacerbations in the prior year, *n* (%)		
0	5,343 (73)	2,341 (78)
1	1,725 (23)	575 (19)
≥ 2	292 (4)	79 (3)

Definition of abbreviations: BMI = body mass index; ICS = inhaled corticosteroid; SGRQ = St. George's Respiratory Questionnaire.
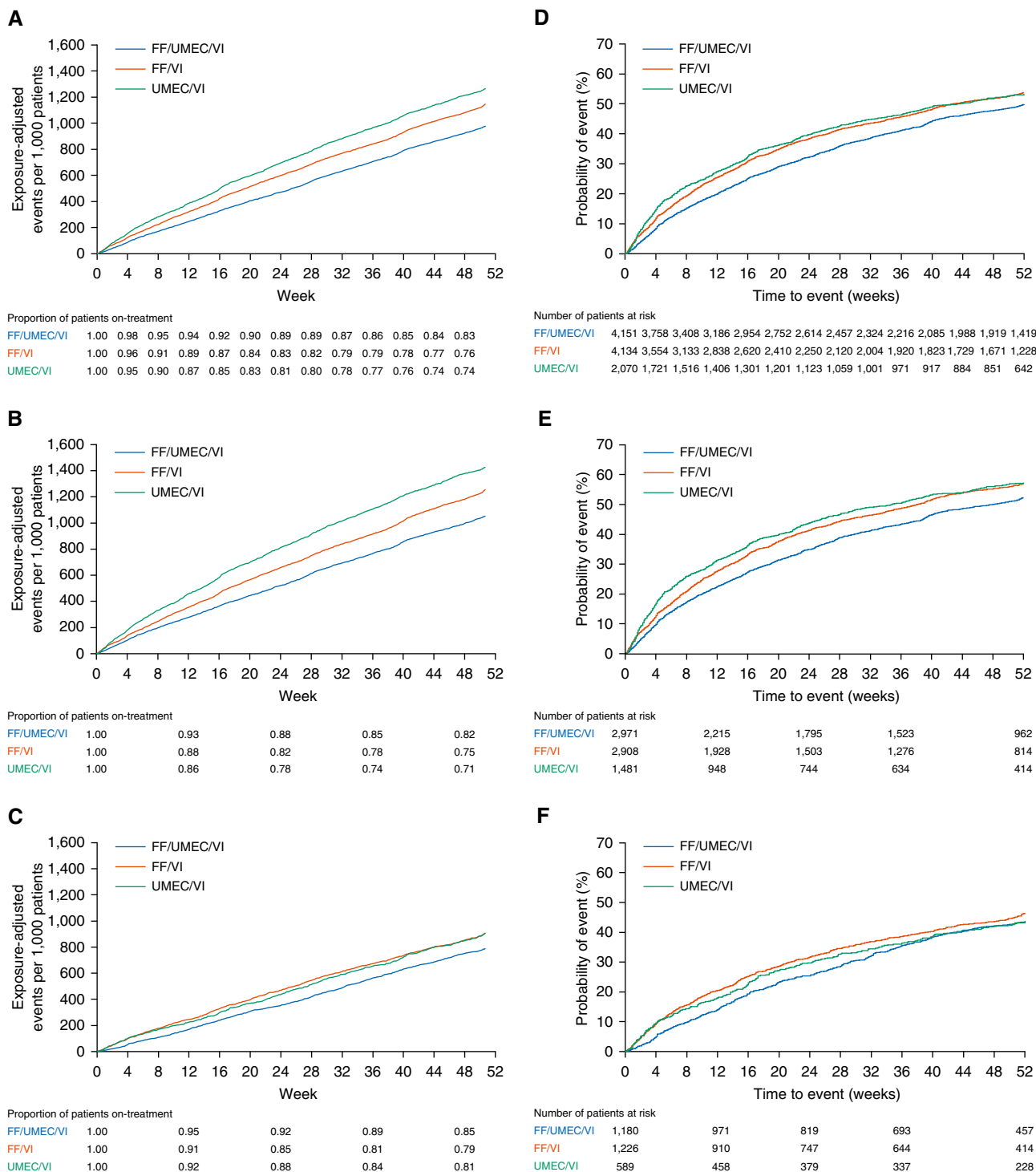
A

Proportion of patients on-treatment

FF/UMEC/VI	1.00	0.98	0.95	0.94	0.92	0.90	0.89	0.89	0.87	0.86	0.85	0.84	0.83
FF/VI	1.00	0.96	0.91	0.89	0.87	0.84	0.83	0.82	0.79	0.79	0.78	0.77	0.76
UMEC/VI	1.00	0.95	0.90	0.87	0.85	0.83	0.81	0.80	0.78	0.77	0.76	0.74	0.74

D

Number of patients at risk

FF/UMEC/VI	4,151	3,758	3,408	3,186	2,954	2,752	2,614	2,457	2,324	2,216	2,085	1,988	1,919	1,419
FF/VI	4,134	3,554	3,133	2,838	2,620	2,410	2,250	2,120	2,004	1,920	1,823	1,729	1,671	1,228
UMEC/VI	2,070	1,721	1,516	1,406	1,301	1,201	1,123	1,059	1,001	971	917	884	851	642

B

Proportion of patients on-treatment

FF/UMEC/VI	1.00	0.93	0.88	0.85	0.82
FF/VI	1.00	0.88	0.82	0.78	0.75
UMEC/VI	1.00	0.86	0.78	0.74	0.71

E

Number of patients at risk

FF/UMEC/VI	2,971	2,215	1,795	1,523	962
FF/VI	2,908	1,928	1,503	1,276	814
UMEC/VI	1,481	948	744	634	414

C

Proportion of patients on-treatment

FF/UMEC/VI	1.00	0.95	0.92	0.89	0.85
FF/VI	1.00	0.91	0.85	0.81	0.79
UMEC/VI	1.00	0.92	0.88	0.84	0.81

F

Number of patients at risk

FF/UMEC/VI	1,180	971	819	693	457
FF/VI	1,226	910	747	644	414
UMEC/VI	589	458	379	337	228

Figure 1. Cumulative number of moderate/severe exacerbations (*A*) overall, for (*B*) inhaled corticosteroid (ICS) use at screening, and for (*C*) no ICS use at screening and time to the first moderate/severe exacerbations (*D*) overall, for (*E*) ICS use at screening, and for (*F*) no ICS use at screening. (*A*) In this study, 4,151 subjects were randomly assigned to fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI), 4,134 were randomly assigned to FF/VI, and 2,070 were randomly assigned to UMEC/VI. (*B*) As shown, 2,971 and 1,180 subjects were randomly assigned to FF/UMEC/VI in the ICS-use and no-ICS-use groups, respectively; 2,908 and 1,226 were randomly assigned to FF/VI; and 1,481 and 589 were randomly assigned to UMEC/VI. In the cumulative plots (*A–C*), events have been adjusted to account for the different randomized population sizes and withdrawal from treatment by scaling the plot on all three arms to represent the number of events per 1,000 patients on each arm and by further adjusting to account for the proportion of patients left on treatment. The figure in *D* was reprinted by permission from Reference 1.

inflection in the curve is seen at any point that might indicate an ICS withdrawal effect. Furthermore, exacerbation events continued to occur throughout the treatment period. Findings were consistent when stratified by ICS use at screening for both the cumulative-event curves (Figures 1B and 1C) and the time-to-first-event curves (Figures 1E and 1F).

We then examined event rates for moderate/severe and severe exacerbations among individuals by ICS use at screening. For moderate and severe exacerbation events combined, the annual event rate was reduced by 29% (95% confidence interval [CI], 23 to 35; $P < 0.001$) with FF/UMEC/VI compared with UMEC/VI among patients using ICS at screening and by 12% among non-ICS users at screening, although this did not achieve statistical significance (95% CI, −3 to 24; $P = 0.115$) in this relatively smaller subgroup. From Figure 2, it should also be noted that the overall rate of moderate/severe exacerbations during the trial among non-ICS users at screening was much lower (0.73 in the FF/UMEC/VI arm and 0.83 in the UMEC/VI arm) compared with prior ICS users (0.98 in the FF/UMEC/VI arm and 1.38 in the UMEC/VI arm). FF/UMEC/VI reduced severe exacerbations compared with UMEC/VI regardless of prior ICS use; there was a 35% annual rate reduction (95% CI, 20 to 46; $P < 0.001$) among prior ICS users and a 35% rate reduction (95% CI, 7 to 55; $P = 0.018$) among non-ICS users (Figure 2).

We then performed additional analyses by medication class at screening. The forest plot in Figure 3 demonstrates that FF/UMEC/VI significantly reduced annual moderate/severe exacerbation rates by 30% (95% CI, 23–37) compared with UMEC/VI among the 2,406 patients who were on a multiple-inhaler ICS + LAMA + LABA triple therapy at screening. Similarly, FF/UMEC/VI significantly reduced moderate/severe exacerbation rates compared with UMEC/VI in patients who were on ICS + LABA at screening (exacerbation rate reduction, 24%; 95% CI, 11–35).

Significantly fewer patients were on LAMA + LABA or LAMA at screening than on an ICS-containing regimen. Among patients randomly assigned to FF/UMEC/VI or UMEC/VI, 545 were receiving LAMA + LABA at screening. Among these individuals, FF/UMEC/VI numerically reduced annual moderate/severe exacerbation rates compared with UMEC/VI (18% rate reduction; 95% CI, −6 to 36). However, there was no detectable difference in annual moderate/severe exacerbation rates with FF/UMEC/VI compared with UMEC/VI in patients on LAMA ($n = 434$ randomly assigned to FF/UMEC/VI or UMEC/VI) at screening (1% rate reduction; 95% CI, −39 to 29). Notably, exacerbation rates during the trial were highest for those entering on ICS/LABA/LAMA (1.22 and 1.76 events/yr in the FF/UMEC/VI and UMEC/VI arms, respectively) and lowest for those entering the trial on LAMA alone (0.62 events/yr

for both FF/UMEC/VI and UMEC/VI treatment arms).

Next, we conducted an analysis of moderate/severe and severe exacerbations excluding data from the first 30 days, when the effect of ICS withdrawal would be expected to be greatest (Figures 4 and E2). Without inclusion of the data from the first 30 days of the trial, FF/UMEC/VI reduced the rate of moderate/severe exacerbations by 19% (95% CI, 12–25; $P < 0.001$) compared with UMEC/VI, as compared with the 25% reduction from the original analysis (95% CI, 19–30; $P < 0.001$) (1). Narrowing further to only patients at risk for ICS withdrawal (those on ICS use at screening), FF/UMEC/VI reduced moderate/severe exacerbation rates by 23% (95% CI, 16–30; $P < 0.001$) compared with UMEC/VI. Furthermore, similar results were seen for severe exacerbations.

Impact of ICS Withdrawal on Lung Function and Quality of Life

We examined the change from baseline in trough FEV_1 by ICS use at screening. Examining 4-, 16-, 28-, 40-, and 52-week time points (Figure E3; Week 52 data in Table E2), all three treatment arms demonstrated a change from baseline in trough FEV_1 with FF/UMEC/VI that was similar across all time points in both prior ICS users and nonusers. The magnitude of the change from baseline in trough FEV_1 was greatest with FF/UMEC/VI, followed by UMEC/VI and FF/VI. Overall FEV_1 improvements

	FF/UMEC/VI	UMEC/VI	Favors FF/UMEC/VI ← / → Favors UMEC/VI	Rate ratio (95% CI); p-value	Annual rate reduction, % (95% CI)
On-treatment moderate/severe exacerbation					
Overall (n=6,214)	0.91 (0.87, 0.95)	1.21 (1.14, 1.29)		0.75 (0.70, 0.81); p<0.001	25 (19, 30)
ICS use at screening (n=4,448)	0.98 (0.93, 1.03)	1.38 (1.29, 1.48)		0.71 (0.65, 0.77); p<0.001	29 (23, 35)
No ICS use at screening (n=1,766)	0.73 (0.67, 0.80)	0.83 (0.73, 0.94)		0.88 (0.76, 1.03); p=0.115	12 (−3, 24)
On-treatment severe exacerbation					
Overall (n=6,214)	0.13 (0.12, 0.14)	0.19 (0.17, 0.22)		0.66 (0.56, 0.78); p<0.001	34 (22, 44)
ICS use at screening (n=4,448)	0.14 (0.13, 0.16)	0.22 (0.19, 0.26)		0.65 (0.54, 0.80); p<0.001	35 (20, 46)
No ICS use at screening (n=1,766)	0.09 (0.07, 0.11)	0.14 (0.10, 0.19)		0.65 (0.45, 0.93); p=0.018	35 (7, 55)

Model-estimated annual rates (95% CI)

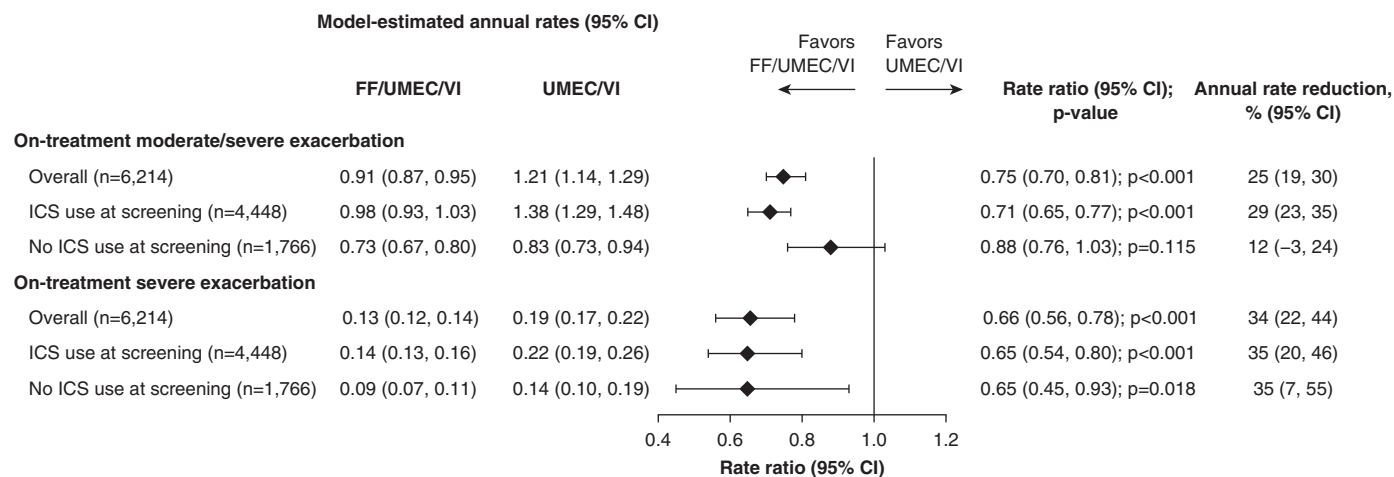Rate ratio (95% CI): 0.4 0.6 0.8 1.0 1.2

Figure 2. On-treatment moderate/severe and severe exacerbations overall and by inhaled corticosteroid (ICS) use at screening for fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) versus UMEC/VI (primary analysis). Throughout, *n* represents the number of patients on FF/UMEC/VI and UMEC/VI, excluding those with missing covariates (overall: FF/UMEC/VI, *n* = 6; FF/VI, *n* = 1; UMEC/VI, *n* = 1; ICS use at screening: FF/UMEC/VI, *n* = 4; FF/VI, *n* = 1; no ICS use at screening: FF/UMEC/VI, *n* = 2; UMEC/VI, *n* = 1). CI = confidence interval.
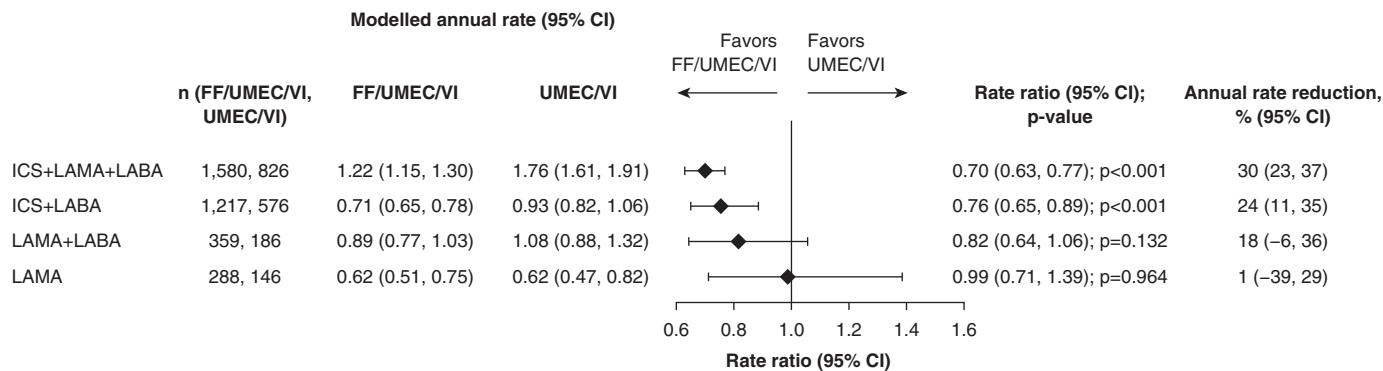
Modelled annual rate (95% CI)

	n (FF/UMEC/VI, UMEC/VI)	FF/UMEC/VI	UMEC/VI		Rate ratio (95% CI); p-value	Annual rate reduction, % (95% CI)
ICS+LAMA+LABA	1,580, 826	1.22 (1.15, 1.30)	1.76 (1.61, 1.91)		0.70 (0.63, 0.77); p<0.001	30 (23, 37)
ICS+LABA	1,217, 576	0.71 (0.65, 0.78)	0.93 (0.82, 1.06)		0.76 (0.65, 0.89); p<0.001	24 (11, 35)
LAMA+LABA	359, 186	0.89 (0.77, 1.03)	1.08 (0.88, 1.32)		0.82 (0.64, 1.06); p=0.132	18 (−6, 36)
LAMA	288, 146	0.62 (0.51, 0.75)	0.62 (0.47, 0.82)		0.99 (0.71, 1.39); p=0.964	1 (−39, 29)

Figure 3. Forest plot of on-treatment moderate/severe chronic obstructive pulmonary disease (COPD) exacerbation rates by prior COPD medication class: fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) versus UMEC/VI. Throughout, *n* represents the number of patients on FF/UMEC/VI and UMEC/VI, excluding those with missing covariates (inhaled corticosteroid [ICS] + long-acting muscarinic antagonist [LAMA] + long-acting β_2-agonist [LABA]: FF/UMEC/VI, *n* = 1; ICS + LABA: FF/UMEC/VI, *n* = 3; FF/VI, *n* = 1; LAMA + LABA: FF/UMEC/VI, *n* = 2; UMEC/VI, *n* = 1). CI = confidence interval.

for all treatment arms were most pronounced among patients not previously on ICS treatment. In Figure E4, a similar analysis was conducted for the change from baseline in the SGRQ total score by ICS use at screening with data available at 4, 28, and 52 weeks (Week 52 data in Table E2). Among both prior ICS users and nonusers, the FF/UMEC/VI treatment arm experienced the greatest SGRQ-score reduction at all time points. Among both prior ICS users and nonusers, the FF/VI and UMEC/VI treatment arms experienced similar SGRQ-score reductions relative to each other but experienced lesser reductions than those in the FF/UMEC/VI arm. On the basis of the time points available for analysis, maximal SGRQ-score reduction for all treatment arms appeared to occur by Week 28. Hence, for both FEV_1 and SGRQ-score improvements, FF/UMEC/VI resulted in the greatest clinical improvements as compared with other treatment arms, which was demonstrated at all measured time points, regardless of prior ICS use.

AESI Incidence by Prior ICS Use and Study Treatment
The incidence of AESI was similar in patients on ICS-containing therapy at screening and in those who were not (Table E3). Results were also consistent between these ICS user subgroups when split by treatment (Table E3).

Discussion

In this series of analyses, we attempted to understand the effect of prior therapy and, in particular, ICS withdrawal on treatment outcomes during the IMPACT trial. We used a combination of analysis methods, including examining cumulative exacerbation event curves, examining patients by prior medication class, and removing the first 30 days of data to probe for how ICS withdrawal may have influenced the results. The entirety of these data suggests that the improvements in exacerbations, lung function, and quality of life in the IMPACT trial are not being driven by sudden ICS withdrawal.

The IMPACT trial enrolled patients with symptomatic COPD who were at risk of exacerbations on COPD maintenance therapy for at least 3 months before the study (1). Patients were allowed to remain on this therapy during the run-in period. At randomization, patients were immediately switched from their current treatment to FF/UMEC/VI, FF/VI, or UMEC/VI. This trial design is more reflective of medication changes occurring in clinical practice. It should also be noted IMPACT was not designed as an ICS withdrawal study, with only 14% of the
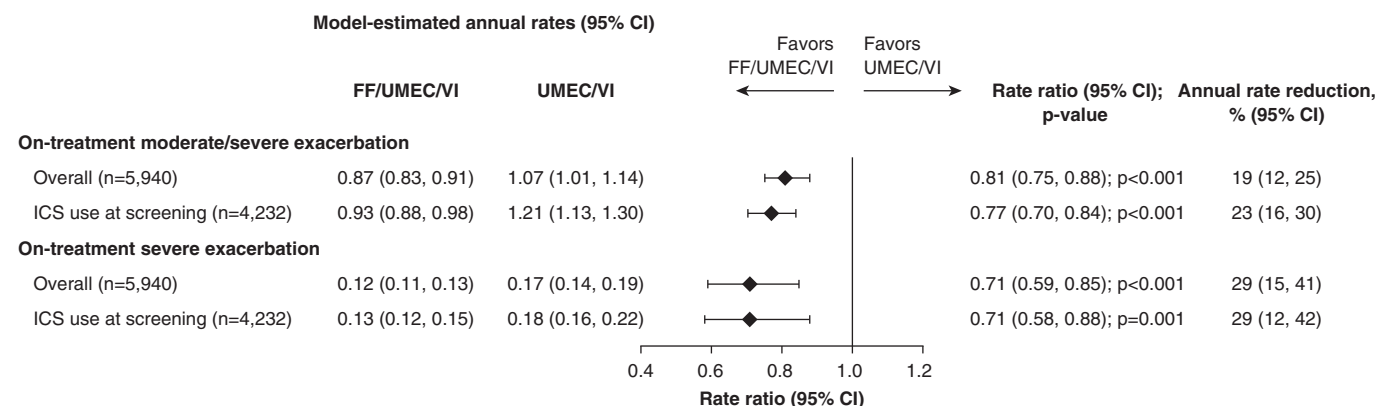
Model-estimated annual rates (95% CI)

	FF/UMEC/VI	UMEC/VI		Rate ratio (95% CI); p-value	Annual rate reduction, % (95% CI)
On-treatment moderate/severe exacerbation					
Overall (n=5,940)	0.87 (0.83, 0.91)	1.07 (1.01, 1.14)		0.81 (0.75, 0.88); p<0.001	19 (12, 25)
ICS use at screening (n=4,232)	0.93 (0.88, 0.98)	1.21 (1.13, 1.30)		0.77 (0.70, 0.84); p<0.001	23 (16, 30)
On-treatment severe exacerbation					
Overall (n=5,940)	0.12 (0.11, 0.13)	0.17 (0.14, 0.19)		0.71 (0.59, 0.85); p<0.001	29 (15, 41)
ICS use at screening (n=4,232)	0.13 (0.12, 0.15)	0.18 (0.16, 0.22)		0.71 (0.58, 0.88); p=0.001	29 (12, 42)

Figure 4. On-treatment moderate/severe and severe exacerbations overall and in patients on ICS treatment at screening for fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) versus UMEC/VI, examining only after Day 30 data. Throughout, *n* represents the number of patients on FF/UMEC/VI and UMEC/VI, excluding those with missing covariates and patients who are no longer at risk of an exacerbation after the first 30 days. CI = confidence interval; ICS = inhaled corticosteroid.

population experiencing ICS withdrawal through randomization.

It has previously been asserted the abrupt withdrawal of ICS is the driving factor behind the exacerbation reduction with triple therapy compared with the dual-bronchodilator therapy in IMPACT (5). These prior conclusions, however, were based on evaluation of time-to-first-exacerbation curves, which ignore all further exacerbations (5). Here, we present cumulative-event curves that demonstrate the complete data over the treatment period. No early "surge" in event rates was seen in the UMEC/VI treatment arm of the study, and the benefit of FF/UMEC/VI compared with UMEC/VI was not restricted to the first 30 days.

We also examined the associations between prior therapy and subsequent relative treatment effects. FF/UMEC/VI reduced severe exacerbation rates in comparison with UMEC/VI in both prior ICS users and nonusers, again suggesting that the benefit of FF/UMEC/VI was not due to an ICS withdrawal effect. We did see a dampening of the reduction in moderate and severe events with FF/UMEC/VI as compared with UMEC/VI for non-ICS versus ICS users at screening. To investigate this further, we subdivided patients by prior medication-class use. A clear benefit was noted among patients on prior ICS + LABA + LAMA and ICS + LABA therapies for FF/UMEC/VI over UMEC/VI. However, the number of non-ICS users for this comparison was quite small: 545 patients on LAMA + LABA and 434 patients on LAMA. These data still suggest a signal favoring FF/UMEC/VI among LAMA + LABA users but suggest no clear benefit of FF/UMEC/VI over UMEC/VI among LAMA users. Although ICS withdrawal is one interpretation for driving the signal of benefit for FF/UMEC/VI over UMEC/VI among ICS users, the data

suggest that prior LAMA users are likely a significantly different patient population that is less prone to exacerbations overall. For prior LAMA users, the mean exacerbation rate during the trial was 0.62 events/yr for patients in both the FF/UMEC/VI and UMEC/VI arms as compared with, for example, individuals entering the study on ICS/LABA/LAMA who experienced 1.22 and 1.76 moderate/severe events/yr in the FF/UMEC/VI and UMEC/VI arms, respectively. Hence, prior treatment with LAMA alone may suggest that a patient has greater "clinical stability" than those who were believed to need triple therapy, therefore suggesting that such patients represent a population that would not clearly benefit from escalation to triple therapy.

We next undertook an analysis of the rate of moderate/severe and severe exacerbations excluding the data from the first 30 days, during which the effect of ICS withdrawal was hypothesized to be greatest. The treatment effects of FF/UMEC/VI compared with UMEC/VI were maintained (29% for severe events; 19% for moderate/severe events). Although the magnitude of benefit was slightly reduced, as compared with the original analysis in which reductions in severe and moderate/severe exacerbation events were 34% and 25%, respectively, it should be noted that these analyses are also no longer randomized comparisons and represent a healthier survivor population.

Finally, we also demonstrated that FF/UMEC/VI significantly improved FEV_1 and SGRQ compared with both FF/VI and UMEC/VI throughout the study period. These results are maintained regardless of prior treatment with ICS.

Limitations of this analysis are that the trial was not powered for analysis of endpoints by prior ICS use or excluding

the first 30 days of treatment and that these analyses were *post hoc*, secondary analyses; therefore, all data should be considered within these contexts. However, even though the analyses excluding the first 30 days do not preserve randomization, and their impact on the interpretation of results should be seen as descriptive and exploratory for this purpose, we believe they help in understanding the effect of abrupt ICS withdrawal on patients enrolled in the IMPACT trial.

The results here show that patients with COPD who were using ICS before the study experienced more exacerbations during the study, and this is the population in which the benefits of FF/UMEC/VI were most clearly seen for moderate/severe exacerbations. However, the benefit for FF/UMEC/VI over UMEC/VI for severe exacerbations was seen irrespectively of whether patients were using ICS or not before the study. Taken together, these data demonstrate the beneficial treatment effect of FF/UMEC/VI from the combination of three effective molecules delivered once daily in a single inhaler. These data suggest that the benefit of FF/UMEC/VI is unlikely to simply reflect the abrupt withdrawal of previous ICS-containing treatment. These additional analyses from the IMPACT trial support the role of ICS treatment as part of triple therapy in reducing exacerbations and improving lung function and quality of life. ∎

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