The effect of ICS withdrawal and baseline inhaled treatment on exacerbations in the IMPACT study

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At a Glance Commentary

In the IMPACT 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 chronic obstructive pulmonary disease 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. Here we demonstrate that FF/UMEC/VI resulted in a 35% reduction in severe exacerbation rates as compared with UMEC/VI for both non-prior 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 non-users. In further analyses removing the first 30 days of data during where 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 manifest throughout the study for both trough forced expiratory volume in 1 second 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 do not appear to be related to abrupt ICS withdrawal.

ABSTRACT

Rationale: In the IMPACT trial fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/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: 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 forced expiratory volume in 1 second (FEV_1) and St George's Respiratory Questionnaire (SGRQ) were analyzed by prior ICS use. Exacerbations were also analyzed excluding data from the first 30 days.

Measurements and Main Results: FF/UMEC/VI significantly reduced annual moderate/severe exacerbation rate versus UMEC/VI in prior ICS users (29% reduction; $p<0.001$), but only a numerical reduction was seen among prior ICS non-users (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 annual on-treatment moderate/severe exacerbation rate (19%; $p<0.001$) versus UMEC/VI. Benefit of FF/UMEC/VI versus 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 versus UMEC/VI were also maintained throughout the study for both trough FEV_1 and SGRQ regardless of prior ICS use.

Conclusions: These data support important treatment effects from 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.

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INTRODUCTION

InforMing the PAthway of COPD Treatment (IMPACT) was a 52-week, randomized, double-blind, multicenter trial that showed a greater effect of once-daily single triple therapy with the inhaled corticosteroid (ICS) fluticasone furoate (FF) plus the long-acting muscarinic antagonist (LAMA) umeclidinium (UMEC) plus the long-acting β_2-agonist (LABA) vilanterol (VI) 100/62.5/25 mcg compared with treatment with the dual combinations FF/VI 100/25 mcg and UMEC/VI 62.5/25 mcg on the annual rate of moderate/severe exacerbations, lung function and quality of life in patients with symptomatic chronic obstructive pulmonary disease (COPD) and a history of exacerbations (1). FF/UMEC/VI also reduced severe exacerbations and risk of all-cause mortality versus 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 where the treatment is artificially changed (1). The nature of the IMPACT run-in period means that patients were allowed to take 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 arise mainly due to abrupt ICS withdrawal among patients taking a prior ICS-containing maintenance treatment who were then randomized to UMEC/VI (5). Suissa and Drazen suggested that a “rapid surge in exacerbations” occurred in IMPACT 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 group in months 2–12 (5). In these post-hoc

analyses of IMPACT, we address whether the efficacy of FF/UMEC/VI versus UMEC/VI is related to ICS withdrawal.

METHODS

The IMPACT trial was a randomized, double-blinded, parallel-group 52-week study comparing the efficacy and safety of the fixed-dose triple combination 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 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 a signed informed consent.

Patients were required to be ≥40 years of age, symptomatic (defined as COPD Assessment Test [CAT] score ≥10) and with either (1) a forced expiratory volume in 1 second (FEV_1) <50% of predicted normal values and a history of at least one moderate or severe (hospitalized) exacerbation or (2) FEV_1 of 50% to <80% of predicted 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 prior to being randomized (2:2:1) to one of the following double-blind treatment groups; FF/UMEC/VI (100/62.5/25 mcg), FF/VI (100/25 mcg) or UMEC/VI (62.5/25 mcg). 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 versus UMEC/VI excluding data prior to day 30 (i.e., within the first 4 weeks of the study) and only including time post day 30 as being at risk (post day 30 analysis); (4) on-treatment moderate/severe exacerbations with FF/UMEC/VI versus UMEC/VI excluding data prior to 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 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, ≥2 moderate/severe), smoking status (at screening), geographical region and post-bronchodilator percent predicted FEV_1 (at screening). Analyses of time-to-first moderate/severe exacerbation were performed using a Cox proportional hazards model with the same covariates as for 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, baseline by visit and treatment group by visit interactions.

RESULTS

Patient Disposition

At baseline, 71% (n=7360) of patients were on an ICS-containing treatment. Patients were required to be on maintenance therapy for at least 3 months prior to study entry and continue these medicines during the 2-week run-in period; 29% (n=2995) were not on an ICS-containing regimen at baseline (1), **Supplement Figure 1**. As expected, patients entering the trial with prior ICS use were slightly more severe according to their baseline characteristics compared with those without (**Table 1**). Despite treatment with ICS, this subgroup still had more severe airflow limitation as indicated by the proportion of patients with a percent predicted FEV_1 of <50% (66% vs 58%), 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. **Supplement Table 1** 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 (**Figure 1D, E and F**) 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 inflection in the curve is seen at any point that might indicate an ICS withdrawal effect. Further, exacerbation events

continue to occur throughout the treatment period. Findings were consistent when stratified by ICS use at screening for both the cumulative event curves (**Figure 1B** and **1C**), and time-to-first event curves (**Figure 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% CI: 23, 35; p<0.001) with FF/UMEC/VI versus 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, 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; 35% annual rate reduction (95% confidence interval [CI]: 20, 46; p<0.001) among prior ICS users and 35% (95% CI: 7, 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 FF/UMEC/VI significantly reduced annual moderate/severe exacerbation rates versus UMEC/VI by 30% (95% CI: 23, 37) among the 2406 patients who were on a multiple-inhaler ICS+LAMA+LABA triple therapy at screening. Similarly, FF/UMEC/VI significantly reduced moderate/severe exacerbation rates versus 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 randomized to FF/UMEC/VI or UMEC/VI, 545 were

taking LAMA+LABA at screening. Among these individuals, FF/UMEC/VI numerically reduced annual moderate/severe exacerbation rates versus UMEC/VI (18% rate reduction [95% CI: -6, 36]). However, there was no detectable difference in annual moderate/severe exacerbation rates with FF/UMEC/VI versus UMEC/VI in patients on LAMA (n=434 randomized to FF/UMEC/VI or UMEC/VI) at screening (1% rate reduction [95% CI: -39, 29]). Notably, exacerbation rates during the trial were highest for those entering on ICS/LABA/LAMA (1.22 and 1.76 events per year in the FF/UMEC/VI and UMEC/VI arms, respectively) and lowest for those entering the trial on LAMA alone (0.62 events per year for both FF/UMEC/VI and UMEC/VI treatment arms).

Next, we conducted an analysis of moderate/severe and severe exacerbations excluding the first 30 days of data when the effect of ICS withdrawal would be expected to be greatest (**Figure 4 and Supplement Figure 2**). 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) versus UMEC/VI as compared with the original analysis of 25% (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) versus UMEC/VI. Further, similar results were seen for severe exacerbations.

Impact of ICS Withdrawal on Lung Function and Quality of Life

We examined change from baseline in trough FEV_1 by ICS use at screening. Examining 4, 16, 28, 40, and 52-week time points (**Supplement Figure 3**; Week 52 data in **Supplement Table 2**), all three treatment arms demonstrated change from baseline in trough FEV_1 with FF/UMEC/VI that was similar across all time points in both prior ICS users

and non-users. The magnitude of change from baseline in trough FEV_1 was greatest with FF/UMEC/VI followed by UMEC/VI and FF/VI. Overall FEV_1 improvements for all treatment arms were most pronounced among patients not previously on ICS. In **Supplement Figure 4**, a similar analysis was conducted for change from baseline in SGRQ total score by ICS use at screening with data available at 4, 28, and 52 weeks (Week 52 data in **Supplement Table 2**). Among both prior ICS users and non-users, the FF/UMEC/VI treatment arm experienced the greatest SGRQ reduction at all time-points. Among both prior ICS users and non-users, the FF/VI and UMEC/VI treatment arms experienced similar SGRQ reductions relative to each other but lesser than FF/UMEC/VI. Based on time points available for analysis, maximal SGRQ reduction for all treatment arms appears to occur by week 28. Hence, for both FEV_1 and SGRQ 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 those who were not (**Supplement Table 3**). Results were also consistent between these ICS user subgroups when split by treatment (**Supplement Table 3**).

DISCUSSION

In this series of analyses, we attempt to understand the relationship between prior therapy and, in particular, ICS withdrawal on treatment outcomes during the IMPACT trial. We used a combination of analysis methods including examination of 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.

IMPACT enrolled patients with symptomatic COPD at risk of exacerbations on COPD maintenance therapy for at least 3 months prior to 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 either 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 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 arm in IMPACT (5). These prior conclusions, however, were based on evaluation of time-to-first exacerbation curves which ignores all further exacerbations (5). Here we present cumulative event curves that demonstrate the complete data over the treatment period. There was no early “surge” in event rates 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 versus UMEC/VI in both prior ICS users and non-users, again suggesting the benefit of FF/UMEC/VI was not due to an ICS withdrawal effect. We did see a dampening in the reduction in moderate and severe events combined with FF/UMEC/VI as compared with UMEC/VI for non-ICS users at screening as compared with ICS users. 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 is 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 no clear benefit of FF/UMEC/VI over UMEC/VI among LAMA users. While 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 the prior LAMA users are likely a significantly different patient population that is less prone to exacerbations overall. For prior LAMA users, their mean exacerbation rate during the trial was 0.62 events/year for 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 per year for the FF/UMEC/VI and UMEC/VI arms, respectively. Hence prior treatment with LAMA alone may suggest a patient with greater "clinical stability" than those who were felt to need a triple therapy, and therefore a patient population who would not clearly benefit from escalation to triple therapy.

We next undertook an analysis of the rate of moderate/severe and severe exacerbations in which the first 30 days of the data were excluded where 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). While the magnitude of benefit was slightly reduced, as compared with the original analysis where 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 demonstrate 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 and 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 analyses 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 COPD patients who were using ICS before the study experienced more exacerbations during the study, and this is the population where the benefits of FF/UMEC/VI were most clearly seen on moderate/severe exacerbations. However, the benefit for FF/UMEC/VI over UMEC/VI for severe exacerbations was seen irrespective 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 as part of triple therapy in reducing exacerbations and improving lung function and quality of life.

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Declaration of interests

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Data sharing statement

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

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Table 1. Baseline characteristics by ICS use at screening

	Prior ICS use N=7360	**No prior ICS use N=2995**
Age, mean (SD) years	65.3 (8.2)	65.2 (8.4)
Male, n (%)	4813 (65)	2057 (69)
BMI, mean (SD) kg/m^2	26.7 (6.1)	26.5 (6.1)
Current smoker, n (%)	2408 (33)	1179 (39)
Former smokers, n (%)	4952 (67)	1816 (61)
SGRQ total score, mean (SD)	51.5 (16.84)	48.6 (16.76)
Pre-bronchodilator FEV$_1$, mean (SD) L	1.14 (0.46)	1.24 (0.49)
Pre-bronchodilator 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 (%)	4861 (66)	1745 (58)
Percent 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	3360 (46)	1331 (44)
≥2	3995 (54)	1660 (55)
Severe exacerbations in the prior year, n (%)		
0	5343 (73)	2341 (78)
1	1725 (23)	575 (19)
≥2	292 (4)	79 (3)

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; SD, standard deviation.

FIGURE LEGENDS

Figure 1. Cumulative number of moderate/severe exacerbations. (A) overall; (B) ICS use at screening; (C) no ICS use at screening. Time to first moderate/severe exacerbations. (D) overall; (E) ICS use at screening; (F) no ICS use at screening.
FF, fluticasone furoate; ICS, inhaled corticosteroid; UMEC, umeclidinium; VI, vilanterol. Part A: 4151 subjects were randomized to FF/UMEC/VI, 4134 to FF/VI and 2070 to UMEC/VI. Part B: 2971 and 1180 were randomized to FF/UMEC/VI in the ICS use and no ICS groups, respectively, 2908 and 1226 to FF/VI and 1481 and 589 to UMEC/VI. In the cumulative plots (A, B and 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 events per 1000 patients on each arm and further adjusting to account for the proportion of patients left on-treatment. Part D from Lipson DA, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med 378(18): 1671–80

Figure 2. On-treatment moderate/severe and severe exacerbations overall and by ICS use at screening for FF/UMEC/VI versus UMEC/VI (primary analysis)
CI, confidence interval; FF, fluticasone furoate; ICS, inhaled corticosteroid; n, 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); UMEC, umeclidinium; VI, vilanterol.

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

Figure 4. On-treatment moderate/severe and severe exacerbations overall and in patients on ICS at screening for FF/UMEC/VI versus UMEC/VI examining only post day 30 data
CI, confidence interval; FF, fluticasone furoate; ICS, inhaled corticosteroid; n, 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; UMEC, umeclidinium; VI, vilanterol.