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Brief Report

Any Decrease in Lung Function is Associated With Worse Clinical Outcomes: Post Hoc Analysis of the IMPACT Interventional Trial

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Abbreviations:

CAT=COPD Assessment Test; **CI**=confidence interval; **COPD**=chronic obstructive pulmonary disease; **FEV$_1$**=forced expiratory volume in 1 second; **FF**=fluticasone furoate; **IMPACT**=InforMing the Pathway of COPD Treatment; **ITT**=intent-to-treat; **OR**=odds ratio; **PROs**=patient-reported outcomes; **RR**=rate ratio; **SGRQ**=St George's Respiratory Questionnaire; **SD**=standard deviation; **UMEC**=umeclidinium; **VI**=vilanterol

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Introduction

Clinical trials of pharmacological treatments in chronic obstructive pulmonary disease (COPD) often focus on improvements in forced expiratory volume in 1 second (FEV$_1$).[1] Preventing disease progression, including an FEV$_1$ decrease, is an established goal of clinical management.[2,3] Worsening lung function is associated with worse patient outcomes and increased risk of hospitalizations and mortality.[4-6] A threshold of ≥100mL has commonly been used to define a clinically significant FEV$_1$ decrease.[7,8] The relationship between different magnitudes of FEV$_1$ worsening (also previously termed deterioration[3]), including <100mL/year, and clinical outcomes is not well understood. This post hoc analysis of the InforMing the Pathway of COPD Treatment (IMPACT) trial (CTT116855; NCT02164513)[9] investigated the relationship between the magnitude of different FEV$_1$ decreases and clinical outcomes over 1 year, and the effect of fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) on FEV$_1$ and other clinical outcomes versus FF/VI or UMEC/VI.

Methods

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the relevant national, regional, or independent ethics committees or institutional review boards. Study details for IMPACT have been previously described.[9] IMPACT was a phase 3, double-blind, parallel-group, 52-week, multicenter study with participants randomized 2:2:1 to FF/UMEC/VI 100/62.5/25µg, FF/VI 100/25µg, or UMEC/VI 62.5/25µg once daily via a single inhaler (ELLIPTA, GSK).[9] Visits were conducted at screening (baseline), randomization (Day 1), and Weeks 4, 16, 28, 40, and 52. FEV_1 decrease at Week 52 was defined as any decrease from baseline in trough FEV_1 >0mL. On-treatment moderate/severe exacerbations, defined as those requiring antibiotics and/or oral/systemic corticosteroids (moderate), and events resulting in inpatient hospitalization or death (severe), were compared between participants with an FEV_1 increase/no change at 52 weeks versus a decrease at Week 52 using a generalized linear model assuming a negative binomial distribution. Covariates included deterioration, treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), geographical region, postbronchodilator percentage predicted FEV_1 (screening), and age. The St George's Respiratory Questionnaire (SGRQ) total score and the COPD Assessment Test (CAT) score at Week 52 were also compared between participants with an FEV_1 increase/no change versus any decrease at Week 52 using a mixed measures model, with covariates of deterioration, treatment group, smoking status (screening), geographical region, baseline SGRQ total score (SGRQ total score analysis only), baseline CAT score (CAT score analysis only), sex, and age. Treatment comparisons for participants with and without an FEV_1 decrease in the intent-to-treat (ITT) population were performed using logistic regression with covariates of treatment group, smoking status (screening), geographical region, and baseline trough FEV_1. Participants were allocated into quartile subgroups based on their FEV_1 decrease (>0mL and <60mL, ≥60mL and <110mL, ≥110mL and <210mL, and ≥210mL). Differences between FEV_1-decrease subgroups were evaluated for change from baseline SGRQ total score and CAT score at Week 52, and moderate and/or severe exacerbation rates over 52 weeks. For participants with evaluable data at Week 52, defined as having both baseline and Week 52 trough FEV_1, the frequency of the FEV_1 decrease at prior visits was evaluated. Evaluable data at Week 52 was selected for evaluation to enable worsening to be analyzed throughout the study duration.

Results

Of the ITT population, 7916 participants had evaluable data at Week 52; 3274 (41%) had an FEV_1 decrease at Week 52 (FF/UMEC/VI: 1065 [32%], FF/VI: 1555 [51%], UMEC/VI: 654 [44%]). Baseline characteristics were similar across treatment groups for both patients with and without an FEV_1 decrease (Table 1). Of the participants with an FEV_1 decrease at Week 52, 2873 (88%) also had an FEV_1 decrease at previous visits, including 1190 (37%) who experienced a decrease at all previous visits (FF/UMEC/VI: 283 [8%], FF/VI: 709 [23%], UMEC/VI: 198 [13%]), and a total of 325 (10%), 444 (14%), 546 (17%), and 693 (21%) participants experienced a decrease at Week 52 only, Week 52 and one prior visit, Week 52 and 2 prior visits, and Week 52 and 3 prior visits, respectively. Percentages were calculated using the number of participants at Week 52 with an FEV_1 decrease (n=3274) with no missing prior visit data.

Overall, participants with an increase/no change in FEV_1 at Week 52 had a mean (standard deviation [SD]) change from baseline in trough FEV_1 of 207mL (212.2) (FF/UMEC/VI: 218mL [212.5], FF/VI: 190mL [216.9], UMEC/VI: 210mL [200.4]). Participants with an FEV_1 decrease at Week 52 had an overall mean (SD) change from baseline in trough FEV_1 −158mL (159.6) (FF/UMEC/VI: −148mL [186.1], FF/VI: −169mL [145.6], UMEC/VI: −149mL [142.5]). Participants with the greatest FEV_1 mL decrease at Week 52 (decrease ≥210mL) showed negligible improvement in SGRQ and CAT (Figure 1) scores. A significant reduction in the odds of having any FEV_1 decrease when treated with FF/UMEC/VI was observed at Week 52 versus FF/VI (odds ratio [OR], 0.45; 95% confidence interval [CI] 0.40–0.50; $p<0.001$) and UMEC/VI (OR, 0.59; 95% CI, 0.52–0.67; $p<0.001$).

On-treatment moderate/severe exacerbation rates were significantly lower among participants with an FEV_1 increase/no change at Week 52, compared with those with a decrease (rate ratio [RR] 0.74; 95% CI 0.70, 0.79; $p<0.001$) (Figure 2). Participants with an FEV_1 increase/no change had an annual exacerbation rate of 0.72 (95% CI 0.69, 0.75), compared with 0.97 (95% CI 0.93, 1.02) for participants with a decrease. In all Week 52 FEV_1-decrease subgroups (where a decrease in lung function ranged from >0mL to ≥210 mL), a higher percentage of participants experienced moderate (49%), severe (11%), and moderate/severe (54%) exacerbations versus those with no lung function decrease (39%, 7%, and 43%, respectively) (Table 2). Annual exacerbation rates were highest in the FEV_1-decrease ≥210mL subgroup compared with the increase/no change subgroup (moderate/severe, 1.098 versus 0.753 per patient-year [950 events among 864 participants versus 3502 events among 4642 participants]) (Table 2). Overall exacerbation rates in all decrease subgroups were similar.

Table 1. Baseline Characteristics

Characteristics	FEV_1 Increase/No Change at Week 52 (N=4642)			Decrease at Week 52 (N=3274)		
	FF/UMEC/VI (N=2301)	FF/VI (N=1505)	UMEC/VI (N=836)	FF/UMEC/VI (N=1065)	FF/VI (N=1555)	UMEC/VI (N=654)
Age, years, mean (SD)	65.2 (8.2)	64.7 (8.4)	64.9 (8.3)	65.2 (8.1)	65.2 (8.1)	64.7 (8.2)
Female, n (%)	780 (34)	500 (33)	283 (34)	324 (30)	474 (30)	211 (32)
Smoking Status						
Number of Pack Years, mean (SD)	45.3 (26.1)	46.0 (26.5)	45.6 (26.7)	48.3 (27.7)	45.8 (24.9)	46.3 (26.8)
Moderate COPD Exacerbations, n (%)[a]						
0	391 (17)	237 (16)	143 (17)	210 (20)	308 (20)	118 (18)
1	768 (33)	468 (31)	284 (34)	354 (33)	557 (36)	215 (33)
2	945 (41)	676 (45)	338 (40)	422 (40)	557 (36)	266 (41)
≥3	197 (9)	124 (8)	71 (8)	79 (7)	133 (9)	55 (8)
Severe COPD Exacerbations, n (%)[a]						
0	1755 (76)	1171 (78)	661 (79)	763 (72)	1132 (73)	483 (74)
1	484 (21)	300 (20)	150 (18)	266 (25)	367 (24)	149 (23)
2	52 (2)	31 (2)	20 (2)	25 (2)	42 (3)	19 (3)
≥3	10 (<1)	3 (<1)	5 (<1)	11 (1)	14 (<1)	3 (<1)
Moderate/Severe COPD Exacerbations, n (%)[a]						
0	2 (<1)	2 (<1)	1 (<1)	0	1 (<1)	1 (<1)
1	1005 (44)	614 (41)	377 (45)	477 (45)	743 (48)	1508 (46)
2	1048 (46)	729 (48)	375 (45)	471 (44)	631 (41)	1390 (42)
≥3	246 (11)	160 (11)	83 (10)	117 (11)	180 (12)	375 (11)
Prebronchodilator FEV_1 at Baseline mL						
n	2299	1505	836	1065	1554	654
Mean (SD)	1187 (461.1)	1231 (483.8)	1190 (461.8)	1198 (474.0)	1185 (457.0)	1206 (468.3)
CAT Score at Baseline						
n	2260	1479	828	1046	1516	639
Mean (SD)	18.1 (6.9)	18.6 (6.9)	18.0 (6.8)	17.6 (6.9)	17.6 (6.8)	17.7 (6.9)
SGRQ Total Score at Baseline						
n	2280	1496	833	1054	1533	645
Mean (SD)	50.0 (16.8)	50.6 (17.1)	49.1 (16.7)	49.8 (16.6)	49.0 (17.2)	48.9 (17.0)

[a]In the 12 months prior.
On-treatment moderate exacerbations were defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics. On-treatment severe exacerbations were defined as exacerbations that required hospitalization or resulted in death.

FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; UMEC=umeclidinium; VI=vilanterol; SD=standard deviation; COPD=chronic obstructive pulmonary disease; CAT=COPD Assessment Test; SGRQ=St George's Respiratory Questionnaire

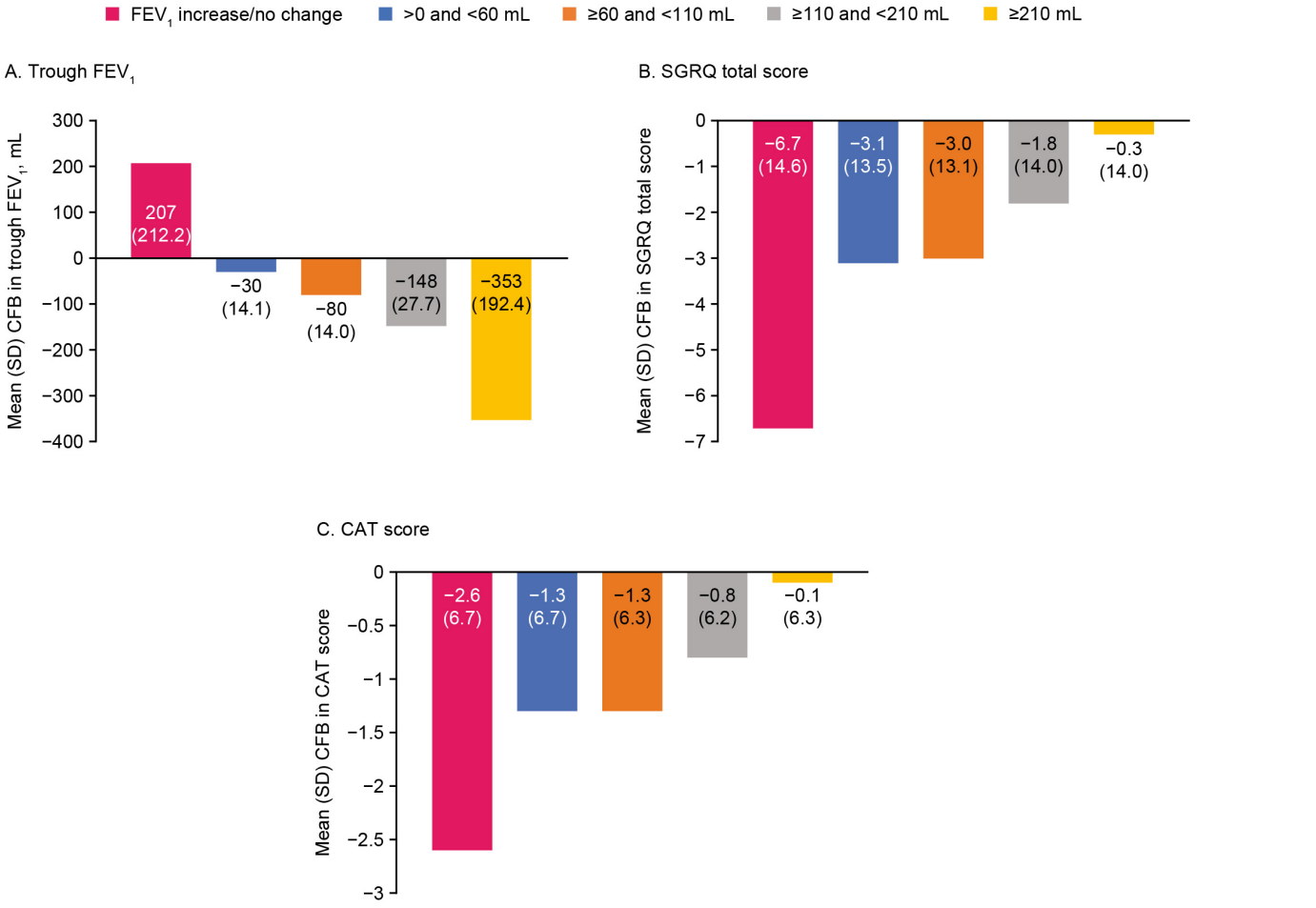
SGRQ total score was significantly better among participants with an FEV_1 increase/no change at Week 52 compared with those with an FEV_1 decrease, with a mean change (95% CI) from baseline –6.5 (–6.9, –6.1) and –2.3 (–2.8, –1.8), respectively; difference: –4.2 (–4.9, –3.6; $p<0.001$) (Figure 2). In participants with any FEV_1 decrease at Week 52, the mean change from baseline in SGRQ total score at Week 52 ranged from −0.3 to −3.1, versus −6.7 in the subgroup of participants with an FEV_1 increase/no change at Week 52 (Figure 1, Table 1).

CAT scores were significantly better among participants with an FEV_1 increase/no change at Week 52 compared with those with an FEV_1 decrease, with a mean change (95% CI) from baseline –2.5 (–2.7, –2.3) and –1.0 (–1.2, –0.8), respectively; difference: –1.5 (–1.8, –1.3; $p<0.001$) (Figure 2). In participants with any FEV_1 decrease at Week 52, the mean change from baseline in CAT score at Week 52 ranged from −0.1 to −1.3, versus −2.6 in participants with an FEV_1 increase/no change at Week 52 (Figure 1, Table 1).

Discussion

This analysis of the IMPACT study demonstrates that 41% of participants experienced FEV_1 worsening (FEV_1 decrease >0mL) at Week 52, with most (88%) experiencing FEV_1 worsening at an earlier visit, and 37% experiencing FEV_1 worsening at all prior study visits. The clinical relevance of FEV_1 worsening was highlighted by the significantly higher rate of exacerbations and significantly worse patient-reported outcome scores (SGRQ and CAT) for participants who experienced any FEV_1 decrease compared with an FEV_1 increase/no change. The IMPACT population included

Figure 1. Change from Baseline in Trough Forced Expiratory Volume in 1 Second, St George's Respiratory Questionnaire Total Score, and COPD Assessment Test Score at Week 52 Across Forced Expiratory Volume in 1 Second-Decrease Subgroups



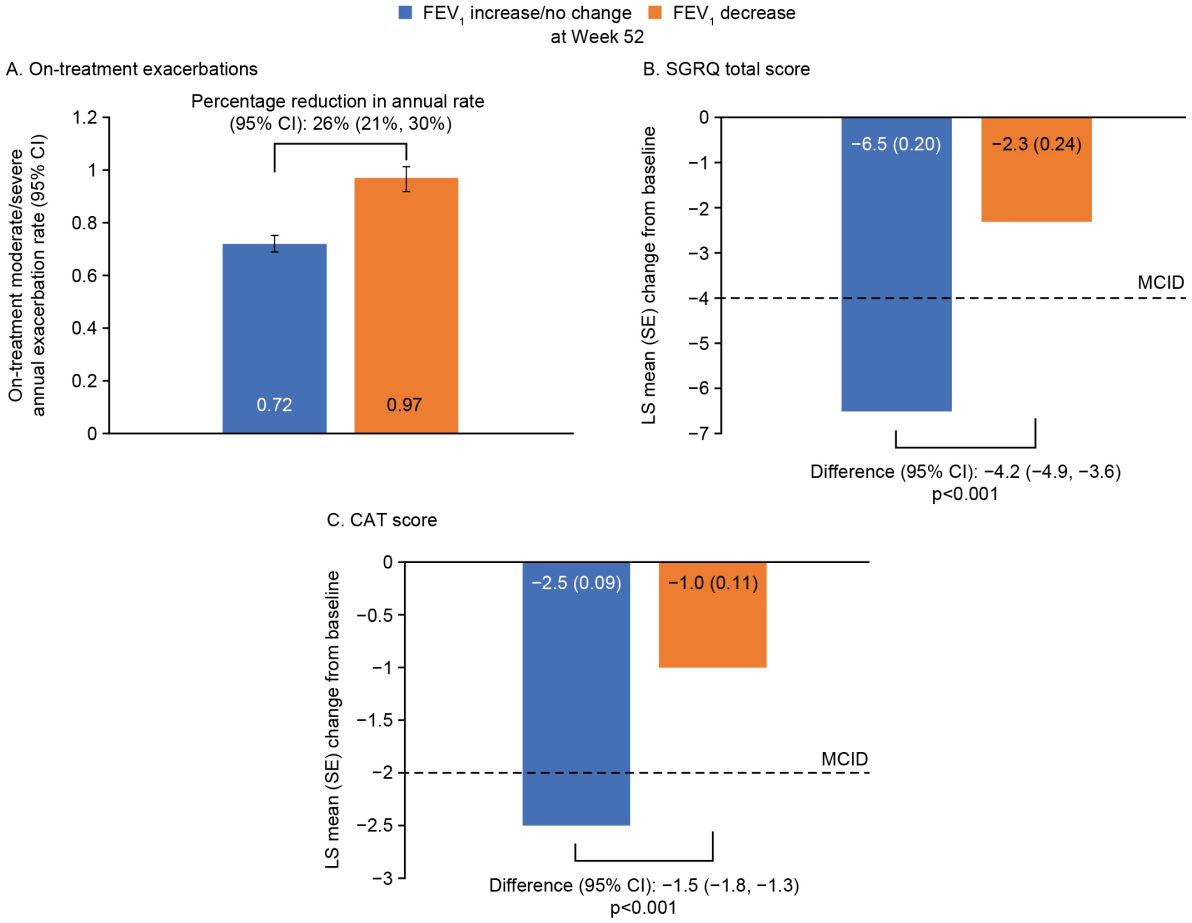
CFB trough FEV_1 at Week 52: >0mL and <60mL, n=795; ≥60mL and <110mL, n=727; ≥110mL and <210mL, n=888; ≥210mL, n=864. CFB SGRQ total score at Week 52: >0mL and <60mL, n=778; ≥60mL and <110mL, n=706; ≥110mL and <210mL, n=865; ≥210mL, n=837. CFB CAT score at Week 52: >0mL and <60mL, n=764; ≥60mL and <110mL, n=692; ≥110mL and <210mL, n=856; ≥210mL, n=826.

SD=standard deviation; CFB=change from baseline; FEV_1=forced expiratory volume in 1 second; SGRQ=St George's Respiratory Questionnaire; CAT=COPD Assessment Test

patients who were ≥40 years of age with symptomatic COPD and with either an FEV_1 <50% of predicted normal values and ≥1 moderate or severe exacerbation in the previous year, or an FEV_1 50%–80% of predicted normal values and ≥2 moderate or ≥1 severe exacerbation(s) in the previous year.[9] Subsequently, findings may differ in younger patients or those with milder disease. Studies in the general population have shown an association with more rapid lung function decrease over 3–4 years and increasing risk of COPD hospitalizations and mortality.[4,5] Guidance and previous studies have used either a range of 100mL to 140 mL as clinically important, a change between 5% and 10% from baseline,[10] or a decrease ≥100mL as the definition for an FEV_1 decrease.[7,8] While a trend towards greatest clinical worsening in the ≥210mL FEV_1-decrease subgroup was seen, there was little distinguishing the other FEV_1-decrease subgroups, with all displaying similarly worse clinical outcomes. These results suggest all levels of FEV_1 decrease are associated with worse clinical outcomes in terms of exacerbations and quality of life, with no clear "minimal clinically important difference" threshold. It is important to mention that while CAT and SGRQ scores were significantly worse for those with a decreased FEV_1, there was a trend towards improved patient-reported outcomes (PROs) for all patients. Notably, improvements in PROs over time are common in interventional studies, even those that are placebo-controlled, and the data presented here may be influenced by this. As such, this warrants further investigation in other datasets.

Participants were less likely to have an FEV_1 decrease at Week 52 and at earlier visits if they received FF/UMEC/VI rather than FF/VI or UMEC/VI, suggesting that triple therapy provides significantly greater preventive effects for exacerbations and lung function decrease compared with dual therapies. Such preventative effects conferred by FF/UMEC/VI may decrease the clinical and economic burden associated with COPD, as exacerbations and low FEV_1 are associated with high medical costs and health care resource utilization.[11-15] However,

Figure 2. Comparison of On-Treatment Moderate/Severe COPD Exacerbations, St George's Respiratory Questionnaire Total Score, and COPD Assessment Test Score, at Week 52 Between Forced Expiratory Volume in 1 Second Decrease and Increase/No Change



Decreases in SGRQ total score and CAT score represent clinical improvement.

COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; CI=confidence interval; SGRQ=St George's Respiratory Questionnaire; MCID=minimal clinically important difference; LS=least squares; SE=standard error; CAT=COPD Assessment Test

Table 2. Summary of On-Treatment Moderate/Severe COPD Exacerbations by Week 52 Forced Expiratory Volume in 1 Second-Decrease Subgroup

	FEV_1 Increase/ No Change at Week 52 (N=4642)	Decrease at Week 52 (N=3274)	Decrease at Week 52 (N=3274) Quartile Subgroups			
			>0mL and <60mL (N=795)	≥60mL and <110mL (N=727)	≥110mL and <210mL (N=888)	≥210mL (N=864)
On-Treatment Moderate/Severe COPD Exacerbations by Decrease from Baseline in FEV_1 at Week 52						
Total Duration at Risk, Participant Years	4648.9	3278.2	796.0	727.7	889.1	865.4
Participants With a Moderate COPD Exacerbation						
n (%)	1833 (39)	1589 (49)	381 (48)	336 (46)	424 (48)	448 (52)
rate [#]	**0.659** [3062]	**0.898** [2945]	**0.879** [700]	**0.829** [603]	**0.926** [823]	**0.946** [819]
Participants With a Severe COPD Exacerbation						
n (%)	341 (7)	361 (11)	83 (10)	65 (9)	116 (13)	97 (11)
rate [#]	**0.095** [440]	**0.139** [454]	**0.131** [104]	**0.113** [82]	**0.154** [137]	**0.151** [131]
Participants With a Moderate/Severe COPD Exacerbation						
n (%)	1994 (43)	1753 (54)	423 (53)	367 (50)	474 (53)	489 (57)
rate [#]	**0.753** [3502]	**1.037** [3399]	**1.010** [804]	**0.941** [685]	**1.080** [960]	**1.098** [950]

Rate (in bold) is the annual event rate per patient-year, calculated as the number of events, divided by the total duration at risk.
On-treatment moderate exacerbations were defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics. On-treatment severe exacerbations were defined as exacerbations that required hospitalization or resulted in death.

FEV_1=forced expiratory volume in 1 second; COPD=chronic obstructive pulmonary disease

almost a third of patients who received FF/UMEC/VI still experienced a decrease in FEV_1 at Week 52, suggesting that further investigation of this patient population is warranted to determine other potential factors (e.g., emphysema, secondary pulmonary hypertension, bronchiectasis), that may be contributing to this decrease.

The strength of this study is the large population size, and while participants with the worst FEV_1 decrease may have dropped out of the study, potentially leading to underestimation of participants with FEV_1 worsening, a sensitivity analysis showed that imputing missing data for the odds of having a >0mL FEV_1 decrease when treated with FF/UMEC/VI versus dual therapy provided similar results (data not shown). This was a post hoc analysis, therefore, inferences of causality between FEV_1 decrease and changes in symptoms or exacerbations cannot be performed. Further, the relationships between FEV_1 decrease and outcomes are associations and not predictions. Additionally, this analysis did not account for the temporality of exacerbations with respect to whether patients experienced a decrease in FEV_1 and then experienced an exacerbation, or vice versa. However, as patients with an FEV_1 decrease had worse outcomes on the CAT and SGRQ, this indicates that exacerbation was not the sole outcome affected by the FEV_1 decrease. This post hoc analysis used absolute changes in FEV_1 to assess the effect of lung function decline. While relative change has been suggested as a more meaningful measure in patients with more severe airflow limitation,[16] and as this analysis focuses on the clinical outcomes in subgroups based on lung function change, absolute and relative change offer comparable clinical relevance in this case. Finally, IMPACT was an interventional study, and further validation from real-world evidence is needed, particularly in younger populations and in those with milder disease.

This post hoc analysis of IMPACT demonstrated that any FEV_1 decrease is associated with worse clinical and patient-reported outcomes, however, no threshold for minimal clinically important differences for FEV_1 deterioration was apparent. Results also indicate that symptomatic patients with prior exacerbations treated with FF/UMEC/VI are less likely to experience FEV_1 worsening than patients treated with dual therapy.

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Data sharing statement: Anonymized individual participant data and study documents can be requested for further research from https://www.gsk-studyregister.com/en/

Declaration of Interest

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