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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Running Head: Lung Function Decrease and COPD Outcomes

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triple therapy; exacerbations; health status; minimally important clinical difference

**Abbreviations:** CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FF, fluticasone furoate; ITT, intent-to-treat; OR, odds ratio; PROs, patient-reported outcomes; QoL, quality of life; RR, rate ratio; SGRQ, St George’s Respiratory Questionnaire; 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 (FEV₁) [1]. Preventing disease progression, including FEV₁ 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 FEV₁ decrease [7,8]. The relationship between different magnitudes of FEV₁ worsening (also previously termed deterioration [3]), including <100mL/year, and clinical outcomes is not well understood. This post hoc analysis of the IMPACT trial (CTT116855; NCT02164513) [9] investigated the relationship between the magnitude of different FEV₁ decrease and clinical outcomes over 1 year, and the effect of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) on FEV₁ and other clinical outcomes versus FF/VI or UMEC/VI.

Methods

Study details for IMPACT have been previously described [9]. IMPACT was a Phase III, 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. FEV₁ decrease at Week 52 was defined as any decrease from baseline in trough FEV₁ >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 FEV₁ increase/no change at 52 weeks versus 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, post-bronchodilator % predicted FEV₁ (Screening), and age. St George’s Respiratory Questionnaire (SGRQ) total score and COPD Assessment Test (CAT) score at Week 52 were also compared between participants with FEV₁ 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 FEV₁ 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 FEV₁. Participants were allocated into quartile subgroups based on their FEV₁ decrease (>0mL and <60mL, ≥60mL and <110mL, ≥110mL and <210mL, and ≥210mL). Differences between FEV₁-decrease subgroups were evaluated for: change from baseline St George’s Respiratory Questionnaire (SGRQ) total score and COPD Assessment Test (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 FEV₁, frequency of FEV₁ 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 FEV₁ 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 FEV₁ decrease (Table 1). Of the participants with FEV₁ decrease at Week 52,
2873 (88%) also had FEV₁ decrease at previous visits, including 1190 (37%) who experienced 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 decrease at Week 52 only, Week 52 and one prior visit, Week 52 and two prior visits, and Week 52 and three prior visits, respectively. Percentages were calculated using the number of participants at Week 52 with an FEV₁ decrease (n=3274) with no missing prior visit data.

Overall, participants with an increase/no change in FEV₁ at Week 52 had a mean (standard deviation [SD]) change from baseline in trough FEV₁ of 207mL (212.2) (FF/UMEC/VI: 218mL [212.5], FF/VI: 190mL [216.9], UMEC/VI: 210mL [200.4]). Participants with FEV₁ decrease at Week 52 had an overall mean (SD) change from baseline in trough FEV₁ –158mL (159.6) (FF/UMEC/VI: –148mL [186.1], FF/VI: –169mL [145.6], UMEC/VI: –149mL [142.5]). Participants with the greatest FEV₁ mL decrease at Week 52 (decrease ≥210mL) showed negligible improvement in SGRQ and CAT (Figure 1). A significant reduction in the odds of having any FEV₁ 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 FEV₁ increase/no change at Week 52, compared with those with decrease (rate ratio [RR] 0.74; 95% CI 0.70, 0.79; p<0.001) (Figure 2). Participants with FEV₁ 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 decrease. In all Week 52 FEV₁-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 FEV1-decrease ≥210mL subgroup compared with the increase/no change subgroup (moderate/severe, 1.098 vs 0.753 per patient-year [950 events among 864 participants vs 3502 events among 4642 participants]) (Table 2). Overall exacerbation rates in all decrease subgroups were similar.

SGRQ total score was significantly better among participants with FEV1 increase/no change at Week 52 compared with those with FEV1 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 FEV1 decrease at Week 52, 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 FEV1 increase/no change at Week 52 (Figure 1, Table 1).

CAT score was significantly better among participants with FEV1 increase/no change at Week 52 compared with those with FEV1 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 FEV1 decrease at Week 52, mean change from baseline in CAT score at Week 52 ranged from −0.1 to −1.3, versus −2.6 in participants with FEV1 increase/no change at Week 52 (Figure 1, Table 1).

Discussion
This analysis of the IMPACT study demonstrated that 41% of participants experienced FEV1 worsening (FEV1 decrease >0mL) at Week 52, with most (88%) experiencing FEV1 worsening at an earlier visit, and 37% experiencing FEV1 worsening at all prior study visits.
The clinical relevance of FEV\textsubscript{1} worsening was highlighted by the significantly higher rate of exacerbations and significantly worse patient-reported outcome scores (SGRQ and CAT) for participants that experienced any FEV\textsubscript{1} decrease compared with FEV\textsubscript{1} increase/no change. The IMPACT population included patients who were ≥40 years of age with symptomatic COPD and with either an FEV\textsubscript{1} <50% of predicted normal values and ≥1 moderate or severe exacerbation in the previous year, or FEV\textsubscript{1} 50–80% of predicted normal values and ≥2 moderate or ≥1 severe exacerbations 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 100 mL to 140 mL as clinically important, a change between 5% and 10% from baseline [10], or a decrease ≥100mL as the definition for FEV\textsubscript{1} decrease [7,8]. While a trend towards greatest clinical worsening in the ≥210mL FEV\textsubscript{1}-decrease subgroup was seen, there was little distinguishing the other FEV\textsubscript{1}-decrease subgroups, which all displayed similarly worse clinical outcomes. These results suggest all levels of FEV\textsubscript{1} decrease are associated with worse clinical outcomes in terms of exacerbations and quality of life (QoL), 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 decreased FEV\textsubscript{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 which 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 FEV\textsubscript{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 FEV₁ are associated with high medical costs and healthcare resource utilization [11-15]. However, almost a third of patients who received FF/UMEC/VI still experienced a decrease in FEV₁ 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 FEV₁ decrease may have dropped out of the study, potentially leading to underestimation of participants with FEV₁ worsening, a sensitivity analysis showed that imputing missing data for the odds of having >0mL FEV₁ 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 FEV₁ decrease and changes in symptoms or exacerbations cannot be performed. Further, the relationships between FEV₁ 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 FEV₁ and then experienced an exacerbation, or vice versa. However, as patients with an FEV₁ decrease had worse outcomes on the CAT and SGRQ, this indicates that exacerbation was not the sole outcome affected by FEV₁ decrease. This post hoc analysis used absolute changes in FEV₁ 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], 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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Declaration of Interest

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**Ethics approval and informed consent**

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.

**Data sharing statement**

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


doi: https://doi.org/10.2147/copd.s234942


## Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; increase/no change at Week 52 (N=4642)</th>
<th>Decrease at Week 52 (N=3274)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FF/UMEC/VI (N=2301)</td>
<td>FF/VI (N=1505)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>65.2 (8.2)</td>
<td>64.7 (8.4)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>780 (34)</td>
<td>500 (33)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of pack years, mean (SD)</td>
<td>45.3 (26.1)</td>
<td>46.0 (26.5)</td>
</tr>
<tr>
<td>Moderate COPD exacerbations, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>391 (17)</td>
<td>237 (16)</td>
</tr>
<tr>
<td>1</td>
<td>768 (33)</td>
<td>468 (31)</td>
</tr>
<tr>
<td>2</td>
<td>945 (41)</td>
<td>676 (45)</td>
</tr>
<tr>
<td>≥3</td>
<td>197 (9)</td>
<td>124 (8)</td>
</tr>
<tr>
<td>Severe COPD exacerbations, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1755 (76)</td>
<td>1171 (78)</td>
</tr>
<tr>
<td>1</td>
<td>484 (21)</td>
<td>300 (20)</td>
</tr>
<tr>
<td>2</td>
<td>52 (2)</td>
<td>31 (2)</td>
</tr>
<tr>
<td>≥3</td>
<td>10 (&lt;1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Moderate/Severe COPD exacerbations, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>1</td>
<td>1005 (44)</td>
<td>614 (41)</td>
</tr>
<tr>
<td>2</td>
<td>1048 (46)</td>
<td>729 (48)</td>
</tr>
<tr>
<td>≥3</td>
<td>246 (11)</td>
<td>160 (11)</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV&lt;sub&gt;1&lt;/sub&gt; at baseline mL</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2299</td>
<td>1505</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1187 (461.1)</td>
<td>1231 (483.8)</td>
</tr>
<tr>
<td>CAT score at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>2260</td>
</tr>
<tr>
<td>----------------</td>
<td>----</td>
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</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
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<td>18.1</td>
</tr>
<tr>
<td><strong>SGRQ total score at baseline</strong></td>
<td>n</td>
<td>2280</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td>50.0</td>
</tr>
</tbody>
</table>

*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.

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FF, fluticasone furoate; SD, standard deviation; SGRQ, St George’s Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.
Table 2. Summary of on-treatment moderate/severe COPD exacerbations by Week 52 FEV₁-decrease subgroup

<table>
<thead>
<tr>
<th>FEV₁ increase/no change at Week 52 (N=4642)</th>
<th>Decrease at Week 52 (N=3274)</th>
<th>Decrease at Week 52 (N=3274), quartile subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&gt;0mL and &lt;60mL (N=795)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(N=795)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>796.0</td>
</tr>
</tbody>
</table>

On-treatment moderate/severe COPD exacerbations by decrease from baseline in FEV₁ at Week 52

Total duration at risk, participant-years

<table>
<thead>
<tr>
<th>n (%)</th>
<th>rate [#]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1833 (39)</td>
<td>0.659 [3062]</td>
</tr>
<tr>
<td>1589 (49)</td>
<td>0.898 [2945]</td>
</tr>
<tr>
<td>381 (48)</td>
<td>0.879 [700]</td>
</tr>
<tr>
<td>336 (46)</td>
<td>0.829 [603]</td>
</tr>
<tr>
<td>424 (48)</td>
<td>0.926 [823]</td>
</tr>
<tr>
<td>448 (52)</td>
<td>0.946 [819]</td>
</tr>
</tbody>
</table>

Participants with a moderate COPD exacerbation

<table>
<thead>
<tr>
<th>n (%)</th>
<th>rate [#]</th>
</tr>
</thead>
<tbody>
<tr>
<td>341 (7)</td>
<td>0.095 [440]</td>
</tr>
<tr>
<td>361 (11)</td>
<td>0.139 [454]</td>
</tr>
<tr>
<td>83 (10)</td>
<td>0.131 [104]</td>
</tr>
<tr>
<td>65 (9)</td>
<td>0.113 [82]</td>
</tr>
<tr>
<td>116 (13)</td>
<td>0.154 [137]</td>
</tr>
<tr>
<td>97 (11)</td>
<td>0.151 [131]</td>
</tr>
</tbody>
</table>

Participants with a severe COPD exacerbation

<table>
<thead>
<tr>
<th>n (%)</th>
<th>rate [#]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994 (43)</td>
<td>0.753 [3502]</td>
</tr>
<tr>
<td>1753 (54)</td>
<td>1.037 [3399]</td>
</tr>
<tr>
<td>423 (53)</td>
<td>1.010 [804]</td>
</tr>
<tr>
<td>367 (50)</td>
<td>0.941 [685]</td>
</tr>
<tr>
<td>474 (53)</td>
<td>1.080 [960]</td>
</tr>
<tr>
<td>489 (57)</td>
<td>1.098 [950]</td>
</tr>
</tbody>
</table>

Rate 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.

COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; SD, standard deviation.
Figures

Figure 1. Change from baseline in (A) trough FEV₁, (B) SGRQ total score and (B) CAT score, at Week 52 across FEV₁ decrease subgroups

Note: CFB trough FEV₁ 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.

CAT, COPD Assessment Test; CFB, change from baseline; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; MCID, minimal clinically important difference; SGRQ, St George’s Respiratory Questionnaire.
Figure 2. Comparison of (A) on-treatment moderate/severe COPD exacerbations, (B) SGRQ total score and (B) CAT score, at Week 52 between FEV₁ decrease and FEV₁ increase/no change

Note: Decreases in SGRQ total score and CAT score represent clinical improvement.
CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; LS, least squares; MCID, minimal clinically important difference; RR, rate ratio; SE, standard error; SGRQ, St George’s Respiratory Questionnaire.