

Original Research

Higher COPD Assessment Test Score Associated With Greater Exacerbations Risk: A Post Hoc Analysis of the IMPACT Trial

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Abstract

Background: In the InforMing the Pathway of COPD Treatment (IMPACT) trial, single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) reduced moderate/severe exacerbation rates versus FF/VI and UMEC/VI in patients with chronic obstructive pulmonary disease (COPD). This post hoc analysis tested the relationship between baseline health status, risk of future exacerbations, and efficacy outcomes.

Methods: IMPACT was a Phase 3, double-blind, 52-week trial in patients with symptomatic COPD (COPD Assessment Test [CAT] score ≥ 10) and ≥ 1 moderate/severe exacerbation in the prior year randomized 2:2:1 to FF/UMEC/VI 100/62.5/25mcg, FF/VI 100/25mcg, or UMEC/VI 62.5/25mcg. Annual rate of on-treatment moderate/severe exacerbations, lung function, and safety were analyzed by continuous baseline CAT score.

Results: Moderate/severe exacerbation rates increased with increasing baseline CAT scores in FF/UMEC/VI and UMEC/VI arms. There was a very small increase in on-treatment pneumonia rates at higher baseline CAT scores across all treatment arms. FF/UMEC/VI reduced moderate/severe exacerbation rates versus UMEC/VI (i.e., the inhaled corticosteroid effect) consistently across the range of CAT scores. The reduction with FF/UMEC/VI versus FF/VI (i.e., the long-acting muscarinic antagonist effect) was greatest at lower CAT scores and appeared lesser at higher CAT scores. Improvements in lung function were observed with FF/UMEC/VI versus FF/VI and UMEC/VI, regardless of baseline CAT score.

Conclusion: The CAT score was predictive of exacerbation risk. Worse baseline health status was associated with higher moderate/severe exacerbation and pneumonia rates. Irrespective of baseline CAT score, FF/UMEC/VI improved lung function, and reduced the annual moderate/severe exacerbation rates versus dual therapy. Results indicate an overall favorable benefit-risk profile of triple versus dual therapy, irrespective of CAT score.

Clinical Trial Registration: GSK (CTT116855/NCT02164513).

Abbreviations: InforMing the Pathway of COPD Treatment, **IMPACT**; fluticasone furoate, **FF**; umeclidinium, **UMEC**; vilanterol, **VI**; chronic obstructive pulmonary disease, **COPD**; COPD Assessment Test, **CAT**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; St George's Respiratory Questionnaire, **SGRQ**; forced expiratory volume in 1 second, **FEV₁**; intent-to-treat, **ITT**; adverse events of special interest, **AESI**; standard deviation, **SD**; body mass index, **BMI**; inhaled corticosteroid, **ICS**; long-acting muscarinic antagonist, **LAMA**; fractional polynomial, **FP**; long-acting beta2-agonist, **LABA**; akaike information criterion, **AIC**

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease characterized by airflow limitation and persistent respiratory symptoms. It is a major cause of morbidity and mortality worldwide and as such is associated with substantial clinical and economic burden. To address these burdens, the 2021 Global initiative for chronic Obstructive Lung Disease (GOLD) strategy document recommends COPD management to include reducing symptoms, improving health status and exercise tolerance, and reducing the risk of exacerbations to ultimately prevent disease progression and reduce mortality.¹⁻³

The COPD Assessment Test (CAT) is a validated, disease-specific, patient-completed questionnaire that is simple and quick to perform.⁴ It comprises 8 items which assess: cough, phlegm, chest tightness, breathlessness when going uphill or upstairs, any activity limitation at home, confidence leaving home, sleep, and energy. Each item is scored 0–5 to provide an overall total score of 0–40. Higher CAT scores indicate increased disease burden and worse health status.⁴ The CAT score has also been incorporated into the GOLD strategy document to help guide initial pharmacological treatment of COPD.¹

A history of frequent exacerbations has been shown to be predictive of future exacerbations in patients with COPD.⁵⁻⁷ The CAT and other tools such as the St George's Respiratory Questionnaire (SGRQ) quantify the impact of COPD symptoms on the health status of patients. Elevated baseline CAT scores have been observed in patients with stable COPD with a history of frequent exacerbations,⁸ and the CAT and SGRQ have demonstrated their ability to predict future exacerbations.^{6,9,10} High baseline CAT scores have also been associated with shorter time-to-first exacerbation in patients with a history of exacerbations in the preceding year.¹¹ However, there is a paucity of data evaluating the relationship between CAT score and treatment on the risk of future exacerbations.

In this post hoc analysis of the large-scale

InforMing the PATHway of COPD Treatment (IMPACT) trial,¹² we examined the relationship between baseline CAT score as a continuous variable and the efficacy and safety of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI and UMEC/VI.

Methods

Study Design

The IMPACT study (GSK study CTT116855; NCT02164513) was a 52-week, randomized, double-blind, parallel-group, multicenter Phase 3 study comparing single-inhaler triple therapy with FF/UMEC/VI with FF/VI or UMEC/VI dual therapy. Patients were randomized (2:2:1) to receive FF/UMEC/VI 100/62.5/25mcg, FF/VI 100/25mcg or UMEC/VI 62.5/25mcg, all administered once daily via the ELLIPTA dry-powder inhaler. The study design and primary results have been previously published.^{12,13}

Study Population

Inclusion and exclusion criteria have been described previously.^{12,13} Briefly, eligible patients were ≥ 40 years of age with symptomatic COPD (CAT score ≥ 10 at screening), and either a forced expiratory volume in 1 second (FEV₁) $< 50\%$ of predicted normal values and ≥ 1 moderate or severe exacerbation in the previous year, or FEV₁ 50% to $< 80\%$ of predicted normal values and ≥ 2 moderate or ≥ 1 severe exacerbation in the previous year.¹³ The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and received approval from local institutional review boards or independent ethics committees. All patients provided written informed consent.

Endpoints

This post hoc analysis evaluated endpoints by baseline CAT score from the IMPACT intent-to-treat (ITT) population.¹² Baseline CAT scores were assessed on the randomization visit (Day 1) of the study, approximately 2 weeks following the screening visit.¹³ CAT scores of 10–20 indicate medium impact of COPD on health status, scores of 20–30 and > 30 indicate high and very high impact, respectively.^{14,15}

Baseline characteristics were described by baseline

CAT score subgroup (< 20 and ≥ 20). Analysis of the efficacy of FF/UMEC/VI versus FF/VI and UMEC/VI using continuous CAT score at baseline was carried out for the following outcomes: annual rate of on-treatment moderate/severe exacerbations, change from baseline in trough FEV₁ and percentage FEV₁ responders (patient achieving a ≥ 100 mL increase from baseline in trough FEV₁) at Week 52. Moderate exacerbations were defined as requiring treatment with antibiotics and/or oral/systemic corticosteroids, and severe exacerbations were defined as events resulting in hospitalization or death.

Safety endpoints included the post hoc assessment of annual rate of on-treatment pneumonias by continuous CAT score at baseline. Adverse events of special interest (AESI) by baseline CAT score subgroup (< 20 and ≥ 20) were also evaluated. AESIs were defined using Standardized Medical Dictionary for Regulatory Activities Queries and allowed for a comprehensive review of safety data that is not limited to a specific preferred term.

Statistical Analyses

Fractional polynomials were used to model the relationship between CAT score as a continuous variable and the treatment outcomes. The selected best fitting model was plotted as CAT score versus moderate/severe exacerbation rate, trough FEV₁, probability of FEV₁ response, and annual rate of pneumonias in each treatment group. The non-fractional polynomial covariates included in each of the models mirror those covariates that were included in the analysis of those endpoints in the primary study and were defined a priori (please see figure footnotes for covariate details). Pointwise confidence bands for fractional polynomials are included to provide an indication of whether the difference in the estimates occurred by chance, they are not formal statistical tests with p values. Safety data were also summarized descriptively.

Results

Patients

Of the 10,355 patients randomized in the ITT population, 10,157 had baseline CAT score data available and were included within this analysis. Of these, 5952 (59%) had a baseline CAT score < 20 and 4205 (41%) had a

score ≥ 20 . Demographics and baseline characteristics are shown in Table 1 and were generally similar across treatments within each CAT score subgroup, with some notable differences. Patients with a baseline score ≥ 20 were slightly younger and had lower post-bronchodilator FEV₁ % predicted than patients in the <20 subgroup; a greater proportion of patients with a score ≥ 20 were current smokers.

Efficacy Endpoints

Annual Rate of On-treatment Exacerbations:

The annual rate of on-treatment moderate/severe exacerbations was higher in patients with higher baseline CAT scores (Figure 1).

A consistent reduction in the annual rate of on-treatment moderate/severe exacerbations of similar magnitude was observed with FF/UMEC/VI compared with UMEC/VI (i.e., the effect of the inhaled corticosteroid [ICS] component), regardless of baseline CAT score. FF/UMEC/VI reduced on-treatment moderate/severe exacerbation rates versus FF/VI (i.e., the effect of the long-acting muscarinic antagonist [LAMA] component) at lower CAT scores, but at higher CAT scores (approximately above 25) the 95% confidence interval crossed 1 (Figure 2).

Lung Function:

Trough FEV₁ at Week 52 remained consistent across all treatment groups, regardless of CAT score at baseline. Irrespective of baseline CAT score, improvements in trough FEV₁ Week 52 were observed with FF/UMEC/VI compared with either FF/VI or UMEC/VI therapy (Figure 3).¹⁶

Safety

The annual rate of on-treatment pneumonias was marginally higher in patients with higher CAT scores across all treatment groups (Figure 4). The AESI profile of FF/UMEC/VI was similar to FF/VI and UMEC/VI in both CAT subgroups and no new safety signals were identified (Table S1 in the online supplement). These results are consistent with the overall ITT population.¹²

Discussion

In this post hoc analysis of patients with COPD and a prior history of exacerbations enrolled in the IMPACT trial, patients with greater CAT scores (worse health status) at baseline experienced a higher rate of moderate/severe exacerbations during the 1-year treatment period. The benefit of the ICS component (i.e., FF/UMEC/VI versus UMEC/VI) was the same across the whole range of baseline CAT scores, but the benefit of the LAMA component (i.e., FF/UMEC/VI versus FF/VI) was less apparent at higher baseline CAT scores (above ~ 25), as shown in Figure 2. The risk of pneumonia appeared to be slightly higher at very high CAT scores in the ICS-containing treatment groups; however, the sparseness of the data, resulting in wider confidence intervals in this region, limit interpretation (Figure 4). Overall, the benefit-risk profile of FF/UMEC/VI versus UMEC/VI appears to be very similar in patients with low and high CAT scores.

The benefit of the LAMA component on reducing exacerbation rates diminished at CAT scores >20 , but it is noteworthy that the benefit of the LAMA on trough FEV₁ was also slightly lower with CAT scores in this range. This suggests that the lung function benefit and the exacerbation benefit are linked, as has been shown before.¹⁷ These observations are consistent with a similar analysis using baseline CAT to examine the benefit of UMEC/VI versus UMEC in which the symptomatic benefit of adding the long-acting beta2-agonist (LABA) was a little lower at higher CAT scores.¹⁸ A small study has also shown that higher baseline CAT score was a predictor of short-term ineffectiveness (defined as COPD exacerbations, need for additional treatment, and no improvement in functional parameters) for the LAMA tiotropium.¹⁹ Regardless of mechanisms, the clinical importance of these findings is that, in terms of exacerbation reduction, the benefit of triple therapy over ICS/LABA or LAMA/LABA is at least as great in patients with better preserved health status as in those in whom the disease impact is severe. Furthermore, in terms of the ICS component, this benefit in the less symptomatic patients does not come at a greater risk of pneumonia. Patients with worse health status (CAT score ≥ 20) at baseline experienced a higher rate of moderate/severe exacerbations, corroborating findings from other studies that have identified an association between higher CAT score and a greater exacerbation

Table 1. Baseline Demographics and Disease Characteristics by COPD Assessment Test Score Subgroup^a

	CAT Score <20 ^b			CAT Score ≥20 ^b		
	FF/UMEC/VI (N=2429)	FF/VI (N=2327)	UMEC/VI (N=1196)	FF/UMEC/VI (N=1647)	FF/VI (N=1720)	UMEC/VI (N=838)
Age , mean (SD) years	66.2 (8.1)	66.0 (8.1)	66.1 (8.2)	64.0 (8.3)	64.4 (8.5)	64.1 (8.2)
Male , n (%)	1666 (69)	1619 (70)	812 (68)	1050 (64)	1075 (63)	518 (62)
BMI (kg/m ²), mean (SD)	26.3 (5.6)	26.4 (5.7)	26.2 (5.5)	27.1 (6.9)	27.0 (6.5)	27.1 (6.3)
Smoking Status , n (%)						
Current	733 (30)	698 (30)	364 (30)	683 (41)	688 (40)	353 (42)
Former	1696 (70)	1629 (70)	832 (70)	964 (59)	1032 (60)	485 (58)
COPD Exacerbation History , n (%)						
Moderate						
0	434 (18)	417 (18)	197 (16)	314 (19)	356 (21)	172 (21)
1	810 (33)	792 (34)	399 (33)	579 (35)	603 (35)	290 (35)
≥2	1185 (49)	1118 (48)	600 (50)	754 (46)	761 (44)	376 (45)
Severe						
0	1815 (75)	1768 (76)	913 (76)	1203 (73)	1234 (72)	619 (74)
1	549 (23)	485 (21)	250 (21)	369 (22)	416 (24)	179 (21)
≥2	65 (3)	74 (3)	33 (3)	75 (5)	70 (4)	40 (5)
Moderate/Severe						
0	0 (0)	5 (<1)	1 (<1)	2 (<1)	0 (0)	1 (<1)
1	1070 (44)	1045 (45)	523 (44)	749 (45)	823 (48)	389 (46)
≥2	1359 (56)	1277 (55)	672 (56)	896 (54)	897 (52)	448 (53)
Post-bronchodilator FEV₁ % Predicted , mean (SD)	47.2 (14.9)	47.3 (14.7)	47.0 (14.6)	43.5 (14.9)	42.9 (14.5)	43.3 (14.6)
COPD Medication at Screening , ^c n (%)						
ICS+LAMA+LABA	776 (32)	798 (34)	411 (34)	593 (36)	597 (35)	305 (36)
ICS+LABA	654 (27)	612 (26)	319 (27)	431 (26)	440 (26)	197 (24)
LAMA+LABA	221 (9)	193 (8)	100 (8)	104 (6)	109 (6)	60 (7)
LAMA	176 (7)	211 (9)	91 (8)	92 (6)	116 (7)	48 (6)

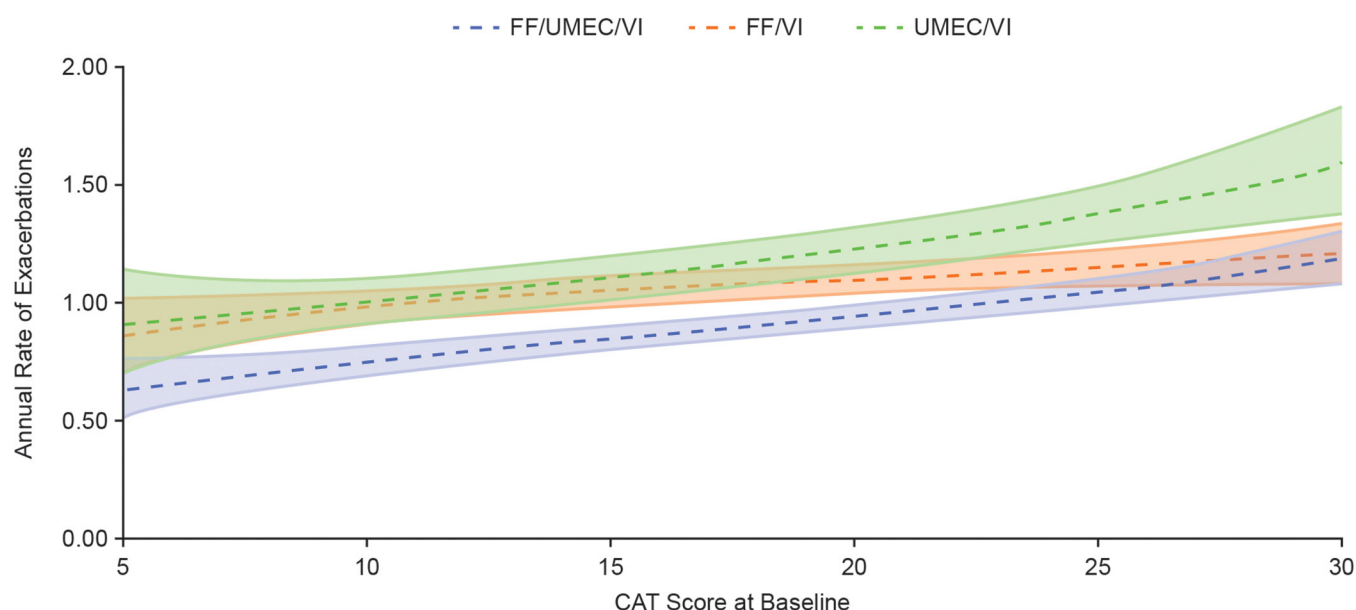
^aIntent-to-treat population^bBaseline CAT scores were assessed on the randomization study visit (Day 1), approximately 2 weeks following the screening visit.^cIncludes all COPD medications taken on the day of the screening visit, excluding medications that stopped on the day of the screening visit.COPD=chronic obstructive pulmonary disease; CAT=COPD Assessment Test; FF=fluticasone furoate; UMEC=umeclidinium; VI=vilanterol; SD=standard deviation; BMI= body mass index; FEV₁=forced expiratory volume in 1 second; ICS=inhaled corticosteroid; LAMA=long-acting muscarinic receptor antagonist; LABA=long-acting beta2-agonist

risk.^{8,11} Furthermore, higher CAT scores in the period after an exacerbation have also been shown to predict risk of recurrence, hospitalization, and death.^{10,20,21} In a study that followed 45 patients admitted to the hospital for an exacerbation of COPD, those who re-exacerbated within 3 months had higher CAT scores during their first admission compared with patients who did not.²² Our results greatly strengthen the evidence for a relationship between CAT score and rate of COPD exacerbations, since the previously noted studies, each of which recruited less

than 600 patients, whereas this analysis of the IMPACT trial included 10,157 of the 10,355 patients in the ITT population.

Patients with a baseline CAT score ≥20 were slightly younger, had worse lung function, and were more likely to be current smokers than those with a baseline score <20. This association between current smoking status and higher CAT and SGRQ scores in patients with COPD is consistent with previous reports.²³ There was only a

Figure 1. Annual Rate of On-Treatment Moderate/Severe Exacerbations by Baseline COPD Assessment Test Score^a



^aBaseline CAT scores were assessed on the randomization study visit (Day 1), approximately 2 weeks following the screening visit. Best fitting fractional polynomial model from FP(2) class presented. The fitted negative binomial models contained covariates of treatment group, sex, exacerbation history (≤ 1 , ≥ 2 moderate/severe), smoking status (screening), geographical region, post-bronchodilator percent predicted FEV₁ (screening), FP1, FP2, FP1 by treatment interaction, and FP2 by treatment interaction. FP1 and FP2 represent continuous transformations of baseline CAT.

FF=fluticasone furoate; UMEC=umeclidinium; VI=vilanterol; CAT=COPD Assessment Test; COPD=chronic obstructive pulmonary disease; FP=fractional polynomial; FEV₁=forced expiratory volume in 1 second

weak correlation between CAT score and lung function,²⁴ indeed in this analysis there was a slight trend for better on-treatment FEV₁ in patients with worse baseline CAT score (Figure 3A). The benefit of FF/UMEC/VI over the other 2 therapies, however, was generally consistent over the range of baseline CAT scores (Figure 3B).

Some limitations of this investigation should be considered. For instance, these analyses were conducted post hoc. The study also enrolled patients with a prior history of exacerbations (and, therefore, were at risk of further exacerbations), which limits the generalizability of the findings to patients of this type. Nevertheless, the IMPACT study was a large, prospective COPD clinical trial in which patients were well characterized at baseline, providing an extensive and robust dataset for these analyses.

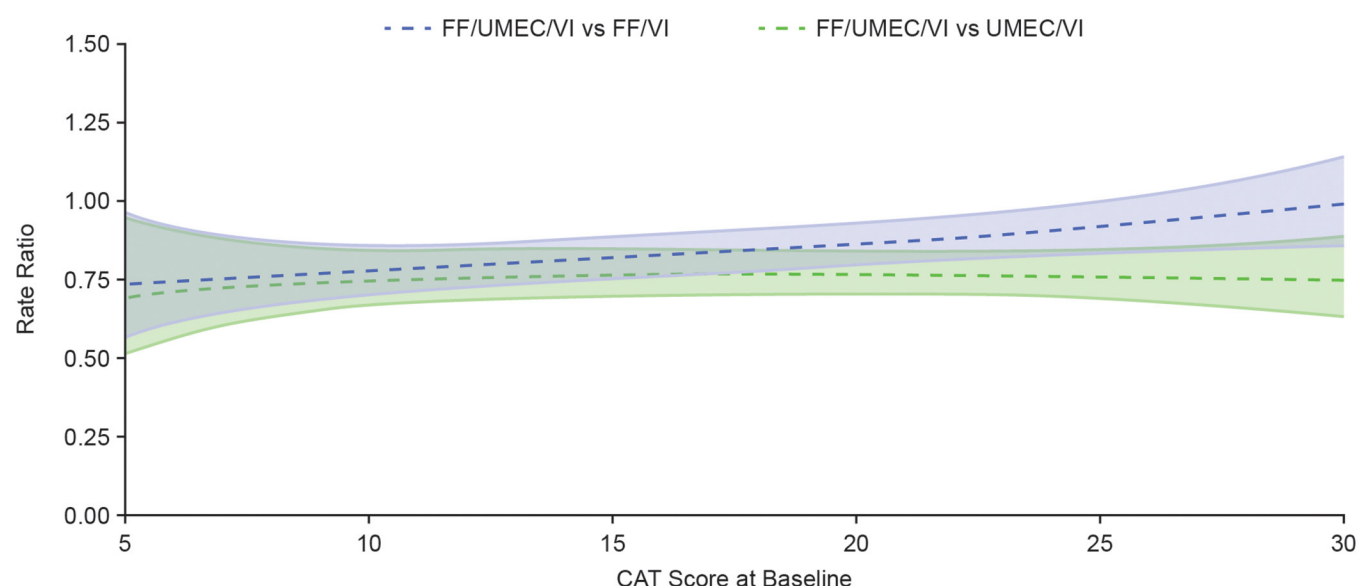
In conclusion, in this population of patients at risk of COPD exacerbations, patients with worse health status at baseline experienced a higher rate of exacerbations,

confirming that CAT is predictive of exacerbation risk. Regardless of CAT score, treatment with FF/UMEC/VI reduced exacerbation rates versus FF/VI and UMEC/VI. While pneumonia rates increased slightly at the highest CAT scores in patients receiving ICS-containing therapy, the overall safety profile was similar across the range of CAT scores studied in this analysis. Overall, these results indicate that single-inhaler triple therapy provides treatment benefit over dual therapy in patients with COPD and at risk of exacerbations regardless of symptom burden severity.

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Figure 2. Treatment Comparison in Annual Rate of Moderate/Severe Exacerbations by Continuous Baseline COPD Assessment Test Score^a



^aBaseline CAT scores were assessed on the randomization study visit (Day 1), approximately 2 weeks following the screening visit. Best fitting fractional polynomial model from FP(2) class presented. The fitted negative binomial models contained covariates of treatment group, sex, exacerbation history (≤ 1 , ≥ 2 moderate/severe), smoking status (screening), geographical region, post-bronchodilator percent predicted FEV₁ (screening), FP1, FP2, FP1 by treatment interaction, and FP2 by treatment interaction. FP1 and FP2 represent continuous transformations of baseline CAT.

FF=fluticasone furoate; UMEC=umeclidinium; VI=vilanterol; CAT=COPD Assessment Test; COPD=chronic obstructive pulmonary disease; FP=fractional polynomial; FEV₁=forced expiratory volume in 1 second

the data and accuracy of the data analysis. All authors contributed to data analysis and interpretation. GJ Criner, MT Dransfield, and DMG Halpin also contributed to the acquisition of data and data analysis and interpretation. DA Lipson and M Tabberer also contributed to study conception and design, and data analysis and interpretation. All authors contributed to the writing and reviewing of the manuscript and have given final approval for the version to be published.

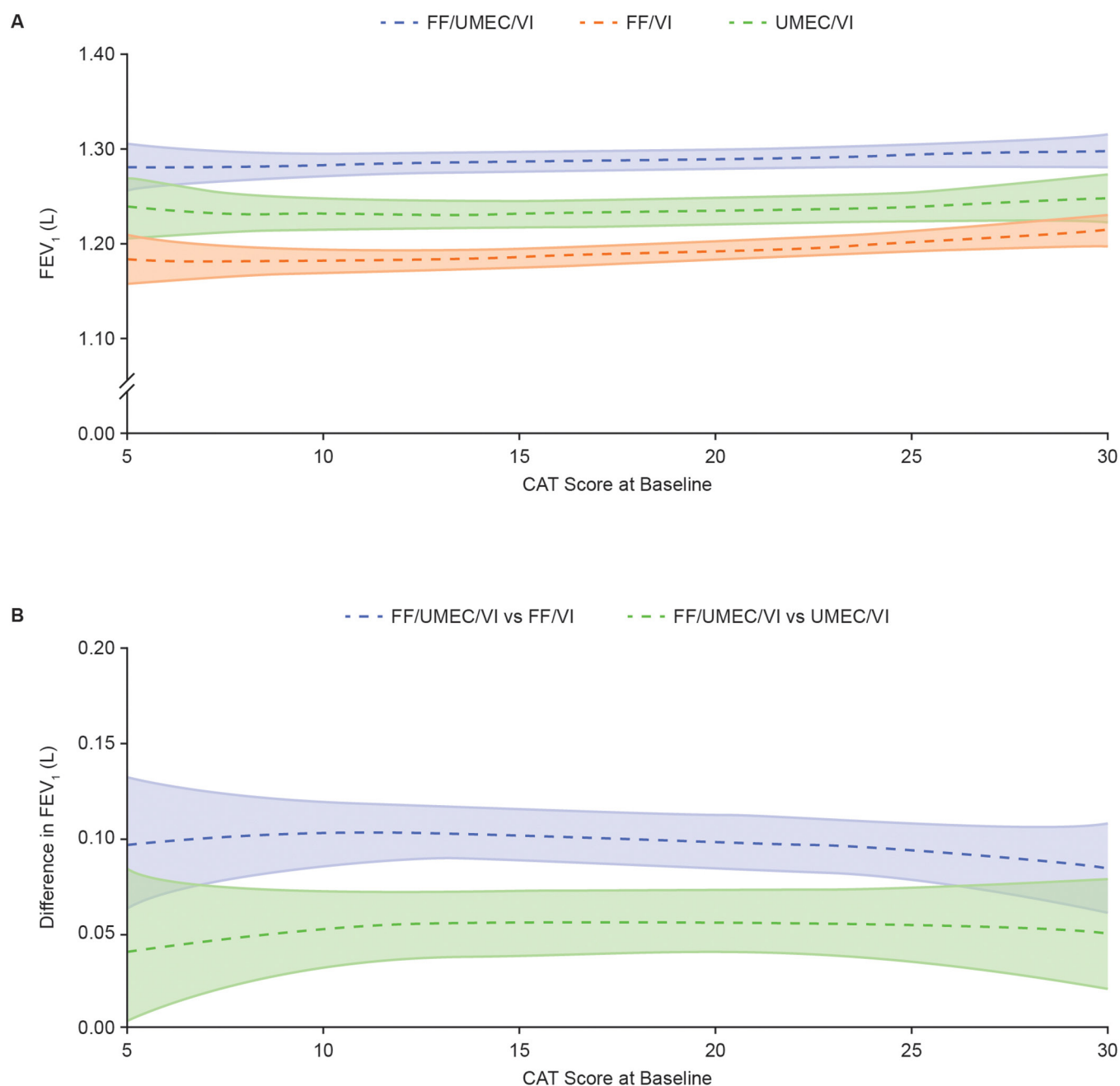
Data availability: Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Declaration of Interest

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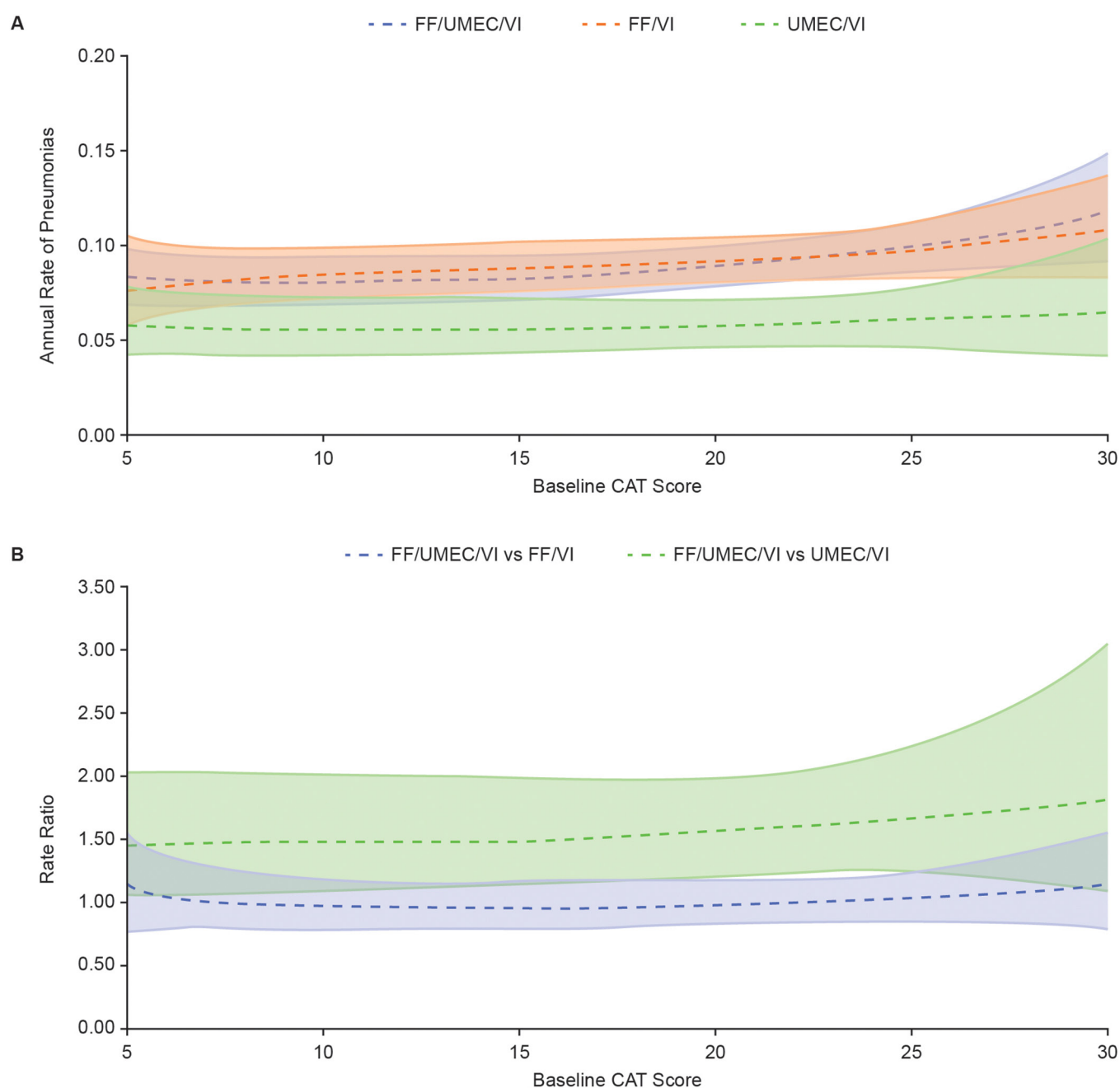
Figure 3. (A) Trough Forced Expiratory Volume in 1 Second at Week 52 and (B) Treatment Comparison in Change from Baseline in Trough Forced Expiratory Volume in 1 Second—by Continuous Baseline COPD Assessment Test Score^a



^aBaseline CAT scores were assessed on the randomization study visit (Day 1), approximately 2 weeks following the screening visit. Point estimates and 95% confidence intervals are from a repeated measures regression model of trough FEV₁ with covariates of treatment, visit, a treatment by visit interaction, baseline value, a baseline value by visit interaction, geographical region, smoking status (screening), selected transformation(s) of CAT, and interaction(s) of treatment with selected transformation(s) of CAT. CAT values are pre-transformed using the transformation suggested by Royston and Sauerbrei (2007).¹⁶ The best fitting (lowest AIC) fractional polynomial (FP2) model is then selected and presented. FEV₁ responders were defined as patients achieving a trough FEV₁ ≥ 100 mL increase from baseline.

FF=fluticasone furoate; UMEC=umeclidinium; VI=vilanterol; FEV₁=forced expiratory volume in 1 second; CAT=COPD Assessment Test; COPD=chronic obstructive pulmonary disease; AIC=akaike information criterion; FP=fractional polynomial

Figure 4. (A) Annual Rate of On-treatment Pneumonias and (B) Treatment Comparison of On-Treatment Pneumonias—by Continuous Baseline COPD Assessment Test Score^a



^aBaseline CAT scores were assessed on the randomization study visit (Day 1), approximately 2 weeks following the screening visit. Best fitting fractional polynomial model from FP(2) class presented. The fitted negative binomial models contained covariates of treatment group, geographical region, FP1, FP2, FP1 by treatment interaction, and FP2 by treatment interaction. FP1 and FP2 represent continuous transformations of baseline CAT.

FF=fluticasone furoate; UMEC=umeclidinium; VI=vilanterol; CAT=COPD Assessment Test; COPD=chronic obstructive pulmonary disease; FP=fractional polynomial

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