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Effect of Age on the Efficacy and Safety of Once-Daily Single-Inhaler Triple Therapy Fluticasone Furoate/Umeclidinium/Vilanterol in Patients With Chronic Obstructive Pulmonary Disease: A Post Hoc Analysis of the IMPACT Trial

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Abbreviations

AE, adverse event; AESI, adverse event of special interest; BMI, body mass index; CI, confidence interval; CFB, change from baseline; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FF, fluticasone furoate; ICS, inhaled corticosteroid; IMPACT, InforMing the Pathway of COPD Treatment; ITT, intent-to-treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SAE, serious adverse event; SD, standard deviation; SMQ, Standardized Medical Dictionary for Regulatory Activity Query; SGRQ, St George's Respiratory Questionnaire; SAE, serious adverse event; UMEC, umeclidinium;

VI, vilanterol.

Abstract

Background

In the IMPACT trial, single-inhaler triple therapy fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) reduced moderate/severe exacerbation rates versus FF/VI and UMEC/VI in patients with symptomatic chronic obstructive pulmonary disease (COPD) and a history of exacerbations, with a similar safety profile.

Research Question

Does age have an effect on trial outcomes?

Study Design and Methods

IMPACT was a Phase III, double-blind, 52-week trial. Patients ≥40 years of age with symptomatic COPD and ≥1 moderate/severe exacerbation in the prior year were randomized 2:2:1 to FF/UMEC/VI 100/62.5/25 mcg, FF/VI 100/25 mcg, or UMEC/VI 62.5/25 mcg. Endpoints assessed by age included annual rate of moderate/severe exacerbations, change from baseline (CFB) in trough forced expiratory volume in 1 second (FEV_1), proportion of St George's Respiratory Questionnaire (SGRQ) responders (≥4 units decrease from baseline in SGRQ total score) and safety.

Results

The intent-to-treat population comprised 10,355 patients; 4724 (46%), 4225 (41%), and 1406 (14%) were ≤64, 65–74, and ≥75 years of age, respectively. FF/UMEC/VI reduced on-treatment moderate/severe exacerbation rates versus FF/VI (% reduction [95% confidence interval (CI)], ≤64 years: 8% [-1, 16], p=0.070; 65–74 years: 22% [14, 29], p<0.001; ≥75 years 18% [3, 31], p=0.021) and versus UMEC/VI (≤64 years: 16% [7, 25], p=0.002; 65–74 years: 33% [25, 41], p<0.001; ≥75 years 24% [6, 38], p=0.012), with greatest rate reduction seen in the 65–74 and ≥75 years subgroups. Post hoc analyses of CFB in trough FEV_1, and proportion of SGRQ responders at Week 52 were significantly greater with FF/UMEC/VI than FF/VI or UMEC/VI in all subgroups. No new safety signals were identified.

Interpretation

FF/UMEC/VI reduced the rate of moderate/severe exacerbations and improved lung function and health status versus FF/VI and UMEC/VI irrespective of age for most endpoints, with a similar safety profile.

Clinical Trial Registration: GSK (CTT116855/NCT02164513).

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide, with prevalence increasing steadily with age.[1-3] Increasing age and the presence of comorbidities are some of the factors associated with greater COPD exacerbation frequency.[4] Furthermore, mortality rates after hospitalization from acute exacerbations of COPD rise with increasing age.[5]

It is important to consider the safety of medications across age groups, as different adverse event (AE) profiles may be observed between older and younger patients.[6,7] Older patients tend to have greater disease burden and frailty is a common characteristic which can negatively impact treatment and prognosis.[7-11] Increased comorbidities requiring multiple concomitant medications, and the inability to generate adequate inspiratory flow when administering inhaled COPD medication in older patients has led to concerns regarding the ability of this patient population to administer inhaled medications. [8,11-13] As such, the use of a single inhaler may benefit this patient population.[11]

The fixed-dose combination of long-acting muscarinic antagonist/long-acting β_2-agonist (LAMA/LABA) umeclidinium/vilanterol (UMEC/VI) has been evaluated in a set of post hoc analyses conducted by age in patients with symptomatic COPD.[12] Patients ≥65 and ≥75 years of age demonstrated consistently and significantly improved lung function versus placebo with no notable diminution of effect with advanced age, and a safety profile that was comparable across all age groups.[12] Additionally, a separate post hoc analysis in older (≥65 and ≥75 years) and younger (40–64 years) patients with COPD with inhalers containing only placebo demonstrated that the ease and correct use of the Ellipta dry powder inhaler (DPI) was similar across age subgroups.[14]

In the InforMing the Pathway of COPD Treatment (IMPACT) trial, once-daily single-inhaler triple therapy with fluticasone furoate/UMEC/VI (FF/UMEC/VI) via the Ellipta DPI reduced the annual rate of moderate/severe exacerbations and improved health-related quality of life and lung function compared with once-daily single-inhaler dual therapy with FF/VI or UMEC/VI in patients ≥40 years of age with symptomatic COPD and a history of exacerbations.[15] These pre-specified and post hoc

analyses of the IMPACT trial evaluated the efficacy and safety of FF/UMEC/VI versus FF/VI and UMEC/VI by age (≤64, 65–74, and ≥75 years).

Materials and Methods

Study design

The IMPACT trial (GSK study CTT116855; NCT02164513) was a 52-week, randomized, double-blind, parallel-group, multicenter Phase III study comparing once-daily single-inhaler triple therapy with FF/UMEC/VI with once-daily dual therapy with FF/VI or UMEC/VI. The trial design has been previously described.[15,16] Patients were randomized (2:2:1) to FF/UMEC/VI 100/62.5/25 mcg, FF/VI 100/25 mcg, or UMEC/VI 62.5/25 mcg, all administered once daily via the Ellipta DPI.[15]

Study population

Inclusion/exclusion criteria have been described previously.[15,16] Briefly, eligible patients were ≥40 years of age with symptomatic COPD (COPD Assessment Test score ≥10), and either a forced expiratory volume in 1 second (FEV_1) <50% of predicted normal values and ≥1 moderate or severe exacerbation in the previous year, or FEV_1 50–<80% of predicted normal values and ≥2 moderate or ≥1 severe exacerbation in the previous year.[15] Patients were excluded if they had a current diagnosis of asthma or other known respiratory disease or had used required supplemental long-term oxygen therapy >3L/min at screening. The intent-to-treat (ITT) population comprised all randomized patients, excluding those who were randomized in error. Subgroups based on age (≤64, 65–74, and ≥75 years) were derived from the ITT population. The study was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki and received approval from local institutional review boards and independent ethics committees.

Endpoints

The study endpoints have been described previously.[15,16] These analyses evaluated the following efficacy outcomes by age group (≤64, 65–74, and ≥75 years): annual rate of on-treatment

moderate/severe exacerbations with FF/UMEC/VI versus FF/VI and UMEC/VI (pre-specified) and change from baseline (CFB) in trough FEV_1 and forced vital capacity (FVC) at Week 52, CFB in St George's Respiratory Questionnaire (SGRQ) total score at Week 52, and proportion of SGRQ responders (patients with ≥4 units decrease from baseline in SGRQ total score) at Week 52 (all post hoc). Moderate exacerbations were defined as those 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 incidence of on-treatment AEs, serious AEs (SAEs), and AEs of special interest (AESIs) derived from Standardized Medical Dictionary for Regulatory Activity Query (SMQ). AESIs are AEs which have specified areas of interest for FF, UMEC, or VI, or for patients with COPD and allow for a comprehensive review of safety data that is not limited to a specific Preferred Term.

Statistical analyses

The ITT population comprised of all subjects randomized, excluding those who were randomized in error (ie, screen failures who did not take randomized therapy). The annual rate of on-treatment moderate/severe exacerbations was analyzed using a generalized linear model assuming a negative binomial distribution. Change from baseline in trough FEV_1, FVC, and SGRQ total score were analyzed using a repeated measures model. SGRQ responder analysis was performed using a generalized linear mixed model with a logit link function. Covariates for each analysis are described in e-Appendix 1. SGRQ response was defined as a ≥4-unit decrease from baseline in SGRQ total score at Week 52. Rate of moderate/severe exacerbations by age was pre-specified. All other analyses by this subgroup were conducted post-hoc. Safety was summarized descriptively.

Results

Patients

Of the 10,355 patients randomized in the ITT population, 4724 (46%), 4225 (41%), and 1406 (14%), patients were ≤64, 65–74, and ≥75 years of age, respectively. Some differences in demographics and baseline characteristic were observed (Table 1, e-Table 1, and e-Table 2). A slightly higher proportion

of male patients, a lower proportion of current smokers, a decrease in post-bronchodilator FEV_1, a higher proportion of patients with ≥2 cardiovascular (CV) risk factors and with cardiac and vascular disorders at baseline were observed with increasing age. Baseline SGRQ total score was also slightly higher across treatment groups in the ≤64 age group. All other demographics and baseline characteristics were similar across treatment groups within each age subgroup.

Efficacy endpoints

Treatment with FF/UMEC/VI significantly reduced the annual rate of on-treatment moderate/severe exacerbations compared with FF/VI in the 65–74 and ≥75 years subgroups (rate reduction of 22% [95% confidence interval [CI]: 14, 29], p<0.001 and 18% [95% CI: 3, 31], p=0.021, respectively). There was a numerical reduction in exacerbation rate favoring FF/UMEC/VI over FF/VI in the ≤64 years subgroup, but this was not statistically significant (rate reduction of 8% [95% CI: -1, 16], p=0.070). FF/UMEC/VI significantly reduced the annual rate of on-treatment moderate/severe exacerbations compared with UMEC/VI in all age subgroups, with the greatest reductions observed in the older subgroups (65–74 years: 33% [95% CI: 25, 41], p<0.001; ≥75 years: 24% [95% CI: 6, 38], p=0.012) and the smallest reduction in the ≤64 years subgroup (16% [95% CI: 7, 25], p=0.002) (Figure 1).

FF/UMEC/VI significantly increased trough FEV_1 from baseline at Week 52 compared with either FF/VI or UMEC/VI therapy across all age subgroups, with no differences seen between age subgroups for FF/UMEC/VI versus FF/VI (≤64 years: 90 mL; 65-74 years: 112 mL and ≥75 years: 78 mL) and UMEC/VI (≤64 years: 62 mL; 65–74 years: 49 mL and ≥75 years: 41 mL) (Figure 2A).

FF/UMEC/VI significantly improved trough FVC from baseline compared with FF/VI across all age subgroups (≤64 years: 160 mL; 65–74 years: 184 mL; ≥75 years: 119 mL; p<0.001 for all comparisons) and compared with UMEC/VI in the ≤64 years subgroup (47 mL improvement; p<0.015). Point estimates favored FF/UMEC/VI over UMEC/VI in the 65–74 (24 mL improvement) and ≥75 years (12 mL improvement) subgroups but were not statistically significant (Figure 2B).

The proportion of SGRQ responders at Week 52 was higher across all age subgroups with FF/UMEC/VI versus FF/VI (≤64 years: 43% vs 36%; 65–74 years: 42% vs 32%; ≥75 years: 38% vs 31%)

and UMEC/VI (≤64 years: 43% vs 37%; 65–74 years: 42% vs 32%; ≥75 years: 38% vs 30%). The odds of being a responder according to SGRQ total score was significantly higher for FF/UMEC/VI compared to both FF/VI and UMEC/VI (p≤0.032) across all age subgroups (Figure 3A). The odds ratio for FF/UMEC/VI versus UMEC/VI was numerically higher in patient subgroups ≥65 years compared with the odds ratio in the ≤64 patient subgroup. The odds ratio for FF/UMEC/VI versus FF/VI was numerically highest in the patient subgroup 65–74 years compared with the other two subgroups, which had similar odds ratios (Figure 3A). FF/UMEC/VI significantly improved (decreased) baseline SGRQ scores compared with FF/VI in all age subgroups, and with UMEC/VI in the ≤64 and 65–74 years subgroups. In the ≥75 years subgroup, the point estimate favored FF/UMEC/VI over UMEC/VI but was not significant (Figure 3B).

Safety

Across all age subgroups, the safety profile of FF/UMEC/VI was similar to FF/VI and UMEC/VI and no new safety signals were identified (Table 2). The incidence of on-treatment AEs and SAEs increased with age but was similar across all three treatment groups.

Rates of pneumonia and CV AESIs increased in the older age groups (65–74 and ≥75 years) across all treatment arms. Pneumonia AESIs were more common in the inhaled corticosteroid (ICS)-containing treatment arms (FF/UMEC/VI and FF/VI) than with UMEC/VI in all age categories; however, the difference in pneumonia AESI incidence between ICS-containing arms and UMEC/VI remained consistent with advancing age (Table 2).

Discussion

In this analysis of the IMPACT trial, overall efficacy and safety outcomes by age subgroup (≤64, 65–74, ≥75 years) were generally consistent with those reported in the overall ITT population. Across all age subgroups, single-inhaler triple therapy with FF/UMEC/VI reduced the rate of moderate/severe exacerbations, and improved lung function and health status versus dual therapy with FF/VI or UMEC/VI regardless of age for most endpoints. The greatest reduction in annual rate of

moderate/severe exacerbations and greatest improvement in SGRQ response with FF/UMEC/VI versus FF/VI and UMEC/VI was seen in the 65–74 and ≥75 years age subgroups. Studies have shown that increasing age is associated with greater COPD exacerbation frequency and higher mortality rates after hospitalization for acute exacerbations.[4,5] The observation that, in these analyses of IMPACT, the greatest reductions in moderate/severe exacerbation rates were achieved with FF/UMEC/VI within the older age subgroups is therefore of clinical relevance as it is important to decrease exacerbations in this patient population.

There were notable differences in clinical characteristics at baseline between the age subgroups. Patients ≤64 years of age were more likely to be female, current smokers, and have worse baseline SGRQ total score or higher body mass index. These differences in clinical characteristics could account for the fact that the greatest improvements in annual rate of moderate/severe exacerbations and SGRQ response with FF/UMEC/VI were seen in the older age subgroups (65–74 and ≥75 years) compared with the ≤64 years subgroup. Indeed, other studies have consistently observed worse health status (as measured by SGRQ) in younger patients,[17] and have shown current smoking status and obesity to be negatively associated with treatment response in patients with COPD.[18-20] Lung function declines with age.[21,22] Indeed, within the IMPACT study population lower baseline post-bronchodilator FEV_1 values were observed with increasing age. In this study, FF/UMEC/VI significantly improved lung function, as measured by CFB in FEV_1, compared with FF/VI or UMEC/VI regardless of age. Treatment with FF/UMEC/VI also significantly improved lung function compared with FF/VI, as measured by CFB in FVC, with greater between-treatment differences seen than those for trough FEV_1; however, these improvements were not as pronounced compared with UMEC/VI. FVC has been suggested to be associated with survival and decreased FVC may indicate increased air trapping within the lung, which can lead to increased morbidity and mortality.[23,24] FVC may also be effective in stratifying the risk of mortality by coronary heart disease risk over 10 years in individuals not previously diagnosed with heart disease.[25,26] FVC may therefore be more reflective of CV status than FEV_1 and is an important consideration in older patients with a greater number of

risk factors. Indeed, within this analysis, a higher percentage of the older patient subgroups had two or more CV risk factors at baseline compared with the <65 years subgroup.

The safety of any treatments prescribed in older patients are important considerations as these patients experience more comorbidities and are often more susceptible to AEs.[27] The safety profile of FF/UMEC/VI compared with FF/VI or UMEC/VI was similar across all age subgroups in these analyses. The older patient subgroups had a slightly higher incidence of pneumonia compared with the <65 years subgroup. The older patient subgroups also benefited the most from single-inhaler triple therapy across most study endpoints. As this patient population experiences increased frequency of COPD exacerbations and associated mortality compared with younger patients, these results indicate a positive benefit-risk profile for single-inhaler triple therapy in older patients.[28,29]

The ability of older patients to generate adequate inspiratory flow with DPIs has been questioned.[11,12] Studies have also reported that comorbidities in older patients make the use of inhalers more difficult than for younger patients.[11,13,30,31] Although measurements of inspiratory flow were not performed on patients enrolled into the IMPACT study, the Ellipta DPI has previously demonstrated consistency in the delivered dose and fine particle mass fraction at flows of 30–90 L/min.[32] Furthermore, peak inspiratory flows of at least 41.6–52 L/min have been demonstrated by patients with COPD and a FEV_1 <30% predicted.[33,34] The results from this post hoc analysis suggest that there is a sustained benefit on lung function, exacerbation reduction, and health status outcomes in older patients (≥65 years) using the Ellipta DPI and this does not alter with increasing age. This is consistent with previously reported results in which no diminution of effect of UMEC/VI on lung function was observed in older patients with COPD (≥65 or ≥75 years) when delivered via the Ellipta DPI.[12] Although inhaler use was not assessed in the analyses presented here it is an important factor to consider due to the number of patients that do not use their inhaler correctly; a systematic review showed that, depending on the inhaler, between 4% and 94% of patients use their inhaler incorrectly.[35] With the ELLIPTA inhaler, critical error rates have been shown to be between 5% and 14%.[36] Incorrect inhaler usage can lead to reduced disease control and an increase in health care

resource consumption and cost.[37,38] Inhaler misuse may also be a greater problem in the older population with a review by Barbara et al.[39] that indicated a negative correlation between increasing age and correct inhaler usage for metered dose inhalers and DPI inhalers with some studies finding a statistically significant difference between older adulthood and inaccurate technique. However, other analyses have demonstrated that correct use of the Ellipta DPI does not differ between older and younger patients (≥65 and ≥75 years vs 40–64 years).[14]

The inclusion of data examining frailty, concomitant medications, and increased susceptibility to side effects in older patients may be useful in future studies to provide further context in determining the benefits of triple therapy in older patient populations.

Some limitations of these analyses should be considered. The IMPACT trial was extensive with a large sample size, allowing for more accurate interpretation of the relevance of differences in findings between treatment groups. However, IMPACT was not powered to detect a difference in subgroups and these analyses were conducted post hoc, with the exception of rate of moderate/severe exacerbations. The ability of older patients to use inhalers were not investigated in these analyses.

Conclusions

In these analyses of the IMPACT trial, FF/UMEC/VI had a favorable benefit-risk profile versus FF/VI and UMEC/VI in patients with symptomatic COPD and a history of exacerbations, irrespective of age. In the older age groups (65–74 and >75 years), FF/UMEC/VI significantly reduced the rate of moderate/severe exacerbations versus FF/VI and UMEC/VI and improved lung function and health status. The safety profile of FF/UMEC/VI was as expected for patients with COPD and increasing age, and consistent with the extensive safety database of the component treatments.

Guarantor statement

DA Lipson takes responsibility for the integrity of the work as a whole.

Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. All authors had full access to the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All authors contributed to data analysis and interpretation. GJ Criner, MT Dransfield, DMG Halpin, and NA Hanania contributed to the acquisition of data and data analysis and interpretation. DA Lipson 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.

Other contributions

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Data availability

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

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Tables

Table 1: Baseline characteristics (≤64, 65–74, and ≥75 years age groups of ITT population)

	≤64 years	65–74 years	≥75 years
	n=4724	n=4225	n=1406
Age, mean (SD), years	58.0 (4.8)	69.1 (2.8)	78.3 (3.1)
	n=4724	n=4225	n=1406
Male, n (%)	2853 (60)	2949 (70)	1068 (76)
	n=4723	n=4223	n=1406
BMI‡, mean (SD), kg/m^2	27.0 (6.6)	26.5 (5.8)	25.7 (5.1)
	n=4724	n=4225	n=1406
Current smoker, n (%)	2254 (48)	1143 (27)	190 (14)
	n=4720	n=4222	n=1405
Post-bronchodilator FEV_1, L, mean (SD)	1.348 (0.533)	1.224 (0.444)	1.162 (0.392)
	n=4720	n=4222	n=1405
Post-bronchodilator FVC, L, mean (SD)	2.830 (0.851)	2.684 (0.790)	2.503 (0.735)
	n=4720	n=4222	n=1405
Post-bronchodilator FEV_1 %	44.7 (15.4)	45.5 (14.4)	48.4 (13.9)

predicted, mean (SD)			
	n=4720	n=4221	n=1404
Reversible to salbutamol, n (%)*	1018 (22)	711 (17)	181 (13)
	n=4673	n=4186	n=1391
Baseline SGRQ total score, mean (SD)	52.1 (17.0)	49.6 (16.6)	48.9 (16.9)
	n=4724	n=4225	n=1406
Exacerbation history in prior 12 months, n (%)			
<2 moderate and 0 severe	1409 (30)	1275 (30)	372 (26)
≥2 moderate or ≥1 severe	3315 (70)	2950 (70)	1034 (74)
	n=4724	n=4225	n=1406
No. of CV risk factors, n (%)			
0	1954 (41)	1105 (26)	284 (20)
1	1316 (28)	1203 (28)	366 (26)
≥2	1454 (31)	1917 (45)	756 (54)
	n=4724	n=4225	n=1406
Current medical conditions, n (%)	2741 (58)	3144 (74)	1127 (80)

Cardiac disorder	568 (12)	725 (17)	327 (23)
Vascular disorder	2040 (43)	2417 (57)	886 (63)
	n=4724	n=4225	n=1406
COPD medication at screening†, n (%)			
LAMA	353 (7)	355 (8)	123 (9)
LAMA + LABA	401 (8)	405 (10)	128 (9)
ICS + LABA	1613 (34)	1290 (31)	438 (31)
ICS + LAMA + LABA	1856 (39)	1741 (41)	586 (42)

*Reversible is an increase in FEV_1 of ≥12% and ≥200 mL following administration of salbutamol; †In the 3 days prior to and including the screening date. BMI = body mass index; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; ITT = intent-to-treat; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist SD = standard deviation; SGRQ = St George's Respiratory Questionnaire.

Table 2: Incidence of on-treatment AEs

AE incidence, n (%)	≤64 years			65–74 years			≥75 years		
	FF/UMEC/VI n=1886	FF/VI n=1876	UMEC/VI n=962	FF/UMEC/VI n=1700	FF/VI n=1693	UMEC/VI n=832	FF/UMEC/VI n=565	FF/VI n=565	UMEC/VI n=276
Any on-treatment AE	1276 (68)	1231 (66)	660 (69)	1211 (71)	1181 (70)	566 (68)	410 (73)	388 (69)	203 (74)
On-treatment AESI*									
Anticholinergic syndrome (SMQ)	68 (4)	64 (3)	30 (3)	83 (5)	56 (3)	32 (4)	33 (6)	20 (4)	8 (3)
Asthma/bronchospasm (SMQ)	16 (<1)	19 (1)	7 (<1)	9 (<1)	11 (<1)	5 (<1)	2 (<1)	4 (<1)	4 (2)
Cardiovascular effects	171 (9)	176 (9)	99 (10)	186 (11)	176 (10)	91 (11)	93 (16)	78 (14)	34 (12)
Decreased BMD and associated fractures	49 (3)	29 (2)	18 (2)	35 (2)	33 (2)	14 (2)	14 (3)	23 (6)	5 (2)
Effects on potassium	17(<1)	7(<1)	4 (<1)	14 (<1)	14 (<1)	4 (<1)	3 (<1)	4 (<1)	0
Gastrointestinal obstruction (SMQ)	1 (<1)	6 (<1)	0	6 (<1)	3 (<1)	2 (<1)	2 (<1)	1 (<1)	0
Hyperglycemia/new onset DM (SMQ)	68 (4)	54 (3)	33 (3)	61 (4)	50 (3)	34 (4)	23 (4)	13 (2)	6 (2)
Hypersensitivity	92 (5)	89 (5)	43 (4)	77 (5)	79 (5)	38 (5)	27 (5)	27 (5)	14 (5)
LRTI excluding pneumonia	92 (5)	77 (4)	48 (5)	79 (5)	89 (5)	42 (5)	29 (5)	33 (6)	18 (7)
Local steroid effects	183 (10)	154 (8)	59 (6)	118 (7)	119 (7)	40 (5)	36 (6)	28 (5)	9 (3)
Ocular effects	19 (1)	18 (<1)	4 (<1)	29 (2)	21 (1)	16 (2)	7 (1)	6 (1)	6 (2)

Pneumonia	102 (5)	87 (5)	36 (4)	146 (9)	146 (9)	42 (5)	69 (12)	59 (10)	19 (7)
Tremor	5 (<1)	0	4 (<1)	1 (<1)	2 (<1)	1 (<1)	2 (<1)	2 (<1)	1 (<1)
Urinary retention	1 (<1)	3 (<1)	3 (<1)	5 (<1)	4 (<1)	4 (<1)	2 (<1)	5 (2)	2 (<1)
Any on-treatment SAE	343 (18)	339 (18)	197 (20)	391 (23)	358 (21)	217 (26)	161 (28)	153 (27)	56 (20)
Any on-treatment fatal SAE	20 (1)	24 (1)	15 (2)	29 (2)	34 (2)	28 (3)	19 (3)	18 (3)	6 (2)
Any on-treatment SAEs by CV risk factor at baseline									
0 risk factor	117 (14)	124 (16)	66 (17)	80 (18)	91 (21)	51 (24)	24 (22)	32 (27)	10 (18)
1 risk factor	100 (20)	93 (17)	54 (20)	103 (21)	66 (14)	58 (25)	35 (24)	38 (26)	14 (19)
≥2 risk factors	126 (22)	122 (21)	77 (25)	208 (27)	201 (26)	108 (28)	102 (33)	83 (28)	32 (22)
Any on-treatment SAEs by presence of DM at baseline									
DM	50 (21)	48 (20)	30 (23)	87 (28)	90 (30)	40 (28)	24 (24)	25 (25)	11 (27)
No DM	293 (18)	291 (18)	167 (20)	304 (22)	268 (19)	177 (26)	137 (29)	128 (28)	45 (19)

*AEs which have specified areas of interest for FF, UMEC, or VI, or for patients with COPD.

AE = adverse event; AESI = adverse event of special interest; BMD = bone mineral density; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; DM = diabetes mellitus; FF = fluticasone furoate; LRTI = lower respiratory tract infection; SAE = serious adverse event; SMQ = Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query; UMEC = umeclidinium; VI = vilanterol.

Figure Legends

Figure 1. Rate of on-treatment moderate/severe exacerbations by age group

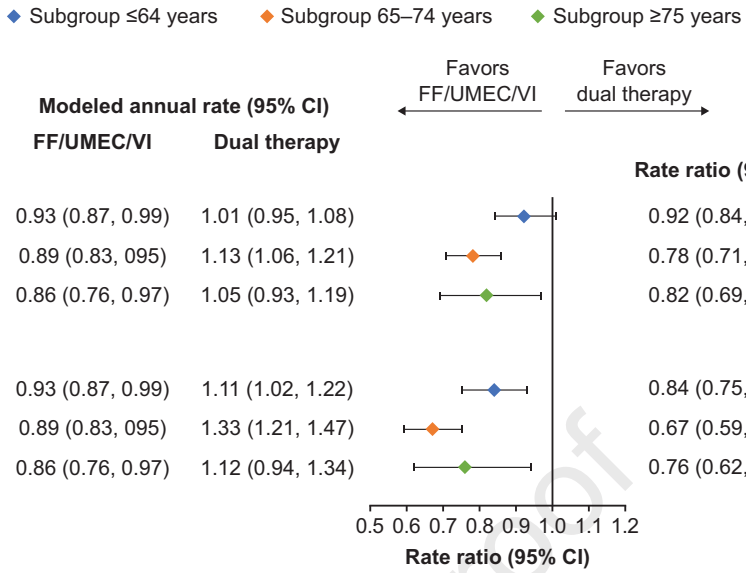
*N=4720 (FF/UMEC/VI, n=1882; FF/VI, n=1876; UMEC/VI, n=962); †N=4222 (FF/UMEC/VI, n=1699; FF/VI, n=1692; UMEC/VI, n=831); ‡N=1405 (FF/UMEC/VI, n=564; FF/VI, n=565; UMEC/VI, n=276). CI = confidence interval; FF = fluticasone furoate; UMEC = umeclidinium; VI = vilanterol.

Figure 2. Change from baseline in measures of lung function: (A) Trough FEV_1 and (B) trough FVC at Week 52

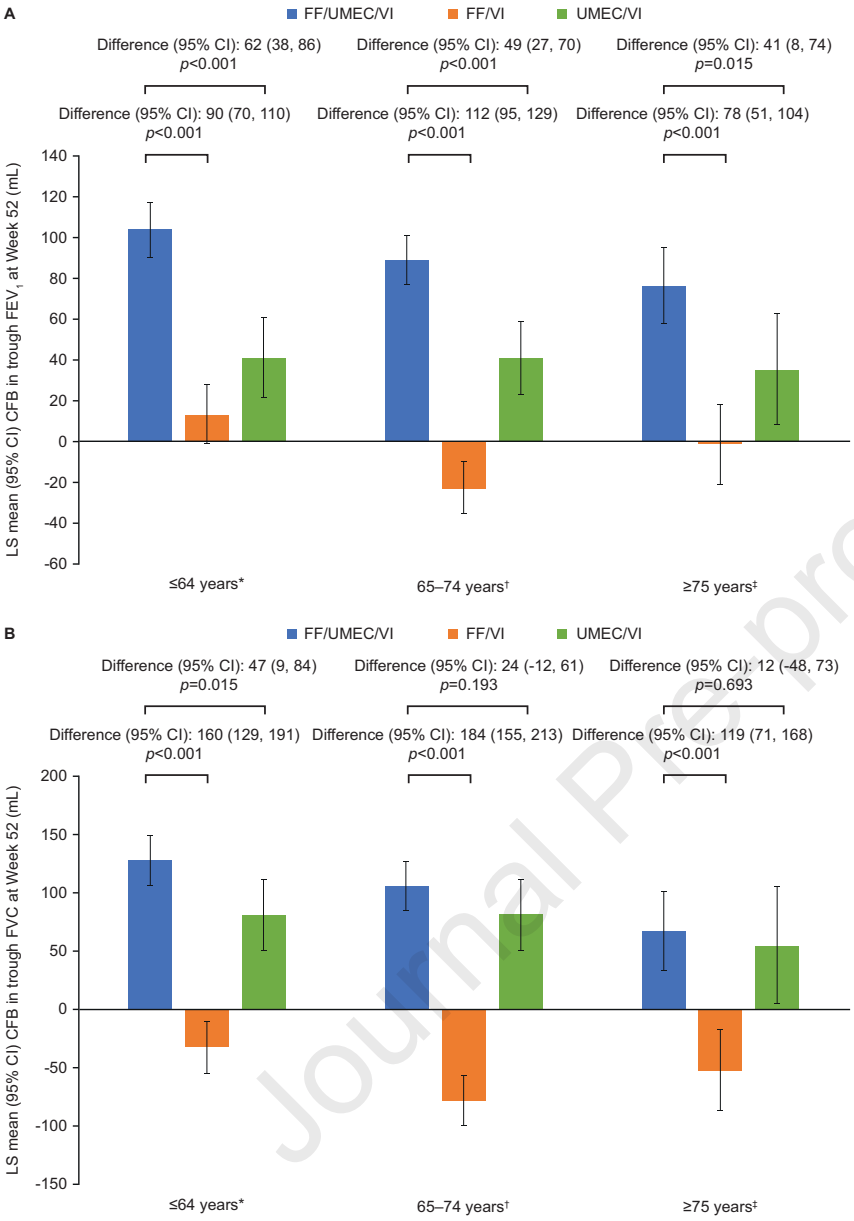
Post hoc analysis; *N=3716 (FF/UMEC/VI, n=1543; FF/VI, n=1440; UMEC/VI, n=733); †N=3191 (FF/UMEC/VI, n=1392; FF/VI, n=1230; UMEC/VI, n=569); ‡N=1009 (FF/UMEC/VI, n=431; FF/VI, n=390; UMEC/VI, n=188). CFB = change from baseline; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FVC = forced vital capacity; LS = least squares; UMEC = umeclidinium; VI, vilanterol

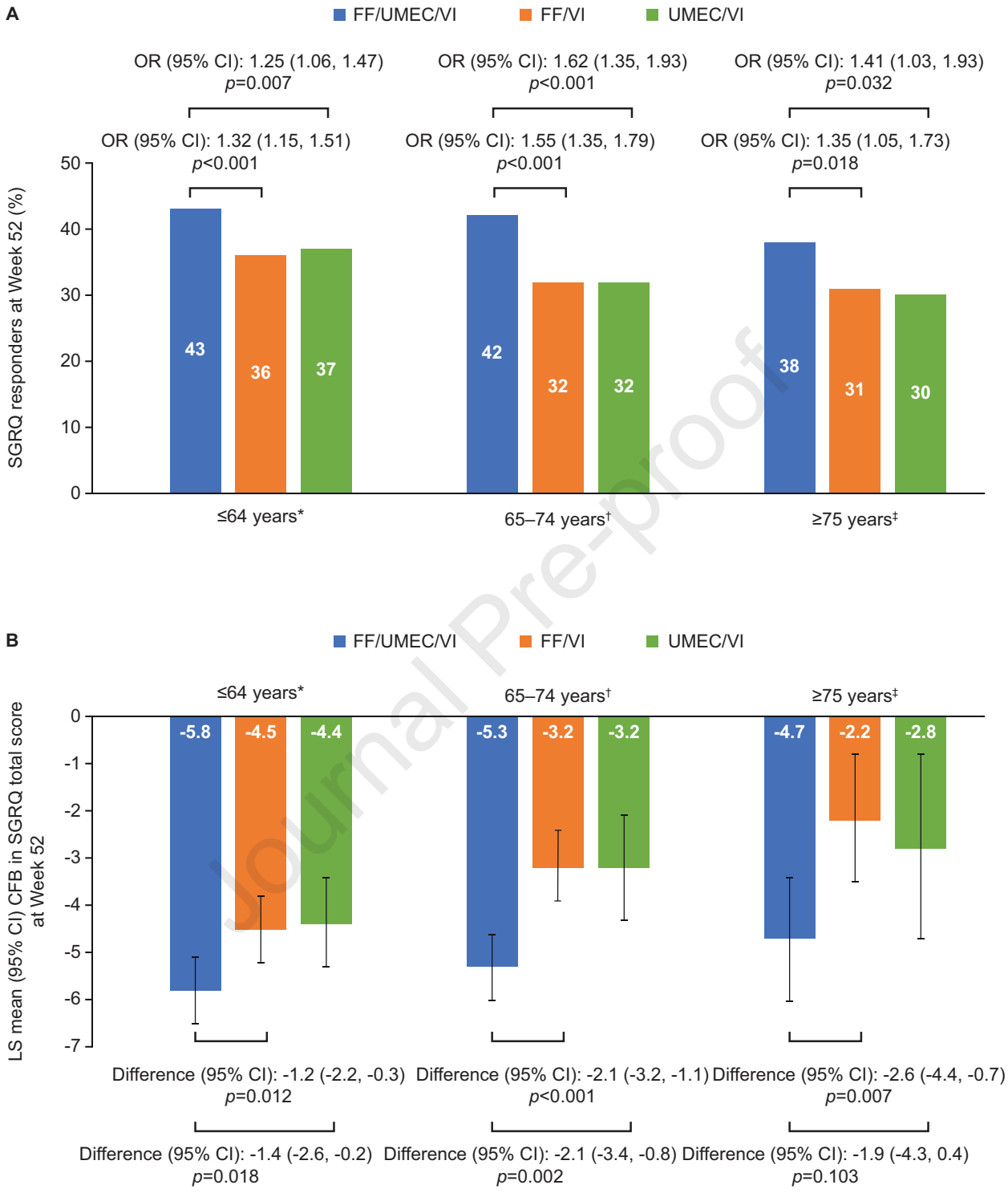
Figure 3. (A) Proportion of SGRQ responders at Week 52 and (B) Change from baseline in SGRQ total score

Post hoc analysis; *N=4673 (FF/UMEC/VI, n=1864; FF/VI, n=1857; UMEC/VI, n=952); †N=4186 (FF/UMEC/VI, n=1685; FF/VI, n=1676; UMEC/VI, n=825); ‡N=1391 (FF/UMEC/VI, n=559; FF/VI, n=559; UMEC/VI, n=273). CFB = change from baseline; CI = confidence interval; FF = fluticasone furoate; LS = least squares; SGRQ = St George's Respiratory Questionnaire; UMEC = umeclidinium; VI = vilanterol



	Modeled annual rate (95% CI)		
	FF/UMEC/VI	Dual therapy	Rate ratio (95% CI), p-value
FF/UMEC/VI vs FF/VI			
Subgroup ≤64 years*	0.93 (0.87, 0.99)	1.01 (0.95, 1.08)	0.92 (0.84, 1.01), *p*=0.070
Subgroup 65–74 years†	0.89 (0.83, 095)	1.13 (1.06, 1.21)	0.78 (0.71, 0.86), *p*<0.001
Subgroup ≥75 years‡	0.86 (0.76, 0.97)	1.05 (0.93, 1.19)	0.82 (0.69, 0.97), *p*=0.021
FF/UMEC/VI vs UMEC/VI			
Subgroup ≤64 years*	0.93 (0.87, 0.99)	1.11 (1.02, 1.22)	0.84 (0.75, 0.93), *p*<0.002
Subgroup 65–74 years†	0.89 (0.83, 095)	1.33 (1.21, 1.47)	0.67 (0.59, 0.75), *p*<0.001
Subgroup ≥75 years‡	0.86 (0.76, 0.97)	1.12 (0.94, 1.34)	0.76 (0.62, 0.94), *p*=0.012





Abbreviations

AE, adverse event; AESI, adverse event of special interest; BMI, body mass index; CI, confidence interval; CFB, change from baseline; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FF, fluticasone furoate; ICS, inhaled corticosteroid; IMPACT, InforMing the Pathway of COPD Treatment; ITT, intent-to-treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SAE, serious adverse event; SD, standard deviation; SMQ, Standardized Medical Dictionary for Regulatory Activity Query; SGRQ, St George's Respiratory Questionnaire; SAE, serious adverse event; UMEC, umeclidinium;

VI, vilanterol.