Risk of Exacerbation and Pneumonia with Single Inhaler Triple Versus Dual Therapy in IMPACT

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Abstract

Rationale: In the Informing the Pathway of COPD Treatment (IMPACT) trial, single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) triple therapy reduced exacerbation risk versus FF/VI and UMEC/VI and mortality risk versus UMEC/VI. However, pneumonia incidence was higher in the inhaled corticosteroid (FF)containing arms raising questions about the relative benefit of exacerbation reduction compared with the increased risk of pneumonia.

Objectives: Determine benefit–risk of the three treatments by evaluating time-to-first and rates of composite exacerbation or pneumonia outcomes.

Methods: We evaluated time-to-first (pre-specified) and rates (post hoc) of investigator-reported pneumonia, serious pneumonia leading to hospitalization or death, and the composite endpoints of 1) moderate (required antibiotics/corticosteroids)/severe (hospitalized) exacerbation or pneumonia and 2) severe exacerbation or serious (hospitalized) pneumonia. Analyses were repeated for radiographically confirmed pneumonia (post hoc).

Results: Moderate/severe exacerbations occurred in 47%, 49%, and 50% of patients randomized to FF/UMEC/VI, FF/VI and UMEC/VI, and pneumonias in 8%, 7%, and 5%, respectively. FF/UMEC/VI reduced the risk of combined moderate/severe exacerbation or pneumonia (time-to-first) versus FF/VI (hazard ratio 0.87 [95%CI 0.82-0.92]) and UMEC/VI (0.87 [0.81-0.94]), as well as the risk of combined severe exacerbation or serious pneumonia versus UMEC/VI (0.83 [0.72-0.96]). FF/UMEC/VI reduced the rate of combined moderate/severe exacerbation or pneumonia (rate ratio 0.78 [0.72-0.84]) and combined severe exacerbation or serious pneumonia (rate ratio 0.76 [0.65-0.89]) versus UMEC/VI. Results were similar for radiographically confirmed pneumonia endpoints.

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Conclusions: Despite higher incidence of pneumonia in FF-containing arms, these composite exacerbation/pneumonia outcomes support a favorable benefit–risk profile of FF/UMEC/VI versus FF/VI and UMEC/VI in patients with symptomatic chronic obstructive pulmonary disease and a history of exacerbations.

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Chronic obstructive pulmonary disease (COPD) is a known risk factor for community-acquired pneumonia (1) and factors further enhancing pneumonia risk in this population include older age, prior exacerbation or pneumonia, low body mass index (BMI), and severe airflow limitation (2,3). Though inhaled corticosteroids (ICS) reduce the risk of exacerbations of COPD, they also increase the risk of pneumonia whether pneumonia is recorded as an investigator-reported adverse event (AE) or based on the presence of chest x-ray confirmed infiltrates (4,5). The signs and symptoms of exacerbations and pneumonia overlap and the treatments for the two are similar. However, observational studies suggest that the presence of infiltrates on chest x-ray increases the risk of intensive care unit admission, the need for mechanical ventilation, length of stay, and mortality in patients hospitalized for exacerbations (6,7).

The current Global Initiative for Obstructive Lung Disease (GOLD) strategy document recommends triple therapy with an ICS, long-acting β_2-agonist (LABA), and long-acting muscarinic antagonist (LAMA) for COPD patients who remain symptomatic or continue to suffer exacerbations despite maintenance treatment with either an ICS/LABA or LABA/LAMA combination (8). The Informing the Pathway of COPD Treatment (IMPACT) trial demonstrated a reduction in the risk of moderate or severe exacerbation with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) as compared with dual therapy with either FF/VI or UMEC/VI, as well as a lower risk of death compared with UMEC/VI (9-11). IMPACT enrolled patients with documented airflow limitation (forced expiratory volume (FEV_1)/forced vital capacity (FVC) <0.70), a significant burden of chronic symptoms as defined by a COPD Assessment Test score of 10 or higher, and a history of exacerbations. The study was designed prior to the modification to the GOLD strategy that eliminated consideration of lung function for

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

risk assessment and thus the exacerbation requirement varied based on FEV_1. Patients with FEV_1 <50% predicted were required to have 1 or more moderate or severe exacerbations in the year prior to screening; those with FEV_1 between 50% and <80% predicted were required to have 2 or more moderate or 1 or more severe exacerbations. Compatible with prior reports, the incidence of investigator-reported pneumonia was higher in patients assigned to ICS-containing arms (8% for FF/UMEC/VI, 7% for FF/VI and 5% for UMEC/VI) (9). We aimed to determine the overall benefit of exacerbation reduction compared with the risk of pneumonia for triple therapy with FF/UMEC/VI compared with each dual therapy by examining the combined outcome of exacerbation and pneumonia. We also examined whether the benefit–risk was altered based on whether pneumonia was confirmed radiographically and based on the severity of those events.

Methods

The IMPACT trial (GSK study CTT116855; NCT02164513) was a Phase III, randomized, double-blind, parallel-group, multicenter study evaluating the effects of once-daily single-inhaler triple therapy, containing FF/UMEC/VI 100/62.5/25 µg, or once-daily dual therapy (FF/VI 100/25 µg or UMEC/VI 62.5/25 µg), on the rate of moderate/severe exacerbations over 52 weeks in symptomatic patients with COPD and ≥1 moderate/severe exacerbation in the previous year (9). Patients were randomized in a 2:2:1 ratio to FF/UMEC/VI, FF/VI, or UMEC/VI, respectively.

Occurrence of exacerbations during the study was evaluated based on the worsening for ≥2 consecutive days of ≥2 major symptoms (dyspnea, sputum volume, or purulence), or any one

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

major symptom together with any one minor symptom (sore throat, colds [nasal discharge/congestion], fever, increased cough, or wheeze). Moderate exacerbations were defined as worsening of symptoms requiring treatment with antibiotics or oral/systemic corticosteroids. Severe exacerbations were defined as worsening of symptoms resulting in hospitalization or death.

Safety endpoints included the incidence of on-treatment AEs of special interest (AESI), defined as AEs that are pharmacologically related to ICS, LAMA, or LABA, allowing for a comprehensive review of safety data not limited to a specific Preferred Term as coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.0; International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland).

Pneumonia AESI included all investigator-reported pneumonia-related terms and is referred to as investigator-reported pneumonia throughout. Chest radiographs were required by protocol for any investigator-reported moderate/severe exacerbation or pneumonia and were independently reviewed to determine if infiltrates compatible with pneumonia were present. This subset of investigator-reported pneumonia is reported as radiographically-confirmed pneumonia throughout. Time to first (TTF) pneumonia and TTF serious pneumonia (resulting in hospitalization, prolonged hospitalization, or death) were analyzed using a Cox Proportional Hazards (PH) model with covariates of treatment group and geographical region. TTF pneumonia or moderate/severe exacerbation, and TTF serious pneumonia or severe exacerbation composite endpoints were analyzed using a Cox PH model with covariates of treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), smoking status (Screening), geographical region and post-bronchodilator percent predicted forced expiratory

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

volume in 1 second (FEV_1) (Screening). These pre-specified endpoints were repeated for radiographically confirmed pneumonia as post hoc analyses.

Kaplan–Meier curves for pneumonia and moderate/severe exacerbations were also produced and repeated for serious pneumonia and severe exacerbations. Post hoc analyses were also performed for rate of pneumonia, pneumonia or moderate/severe exacerbation, and serious pneumonia or severe exacerbation using a generalized linear model assuming a negative binomial distribution with covariates of treatment group and geographical region with the addition of sex, exacerbation history (≤1, ≥2 moderate/severe exacerbations), smoking status (Screening), and post-bronchodilator percent predicted FEV_1 (Screening) for the composite endpoints. If a patient experienced both a pneumonia and an exacerbation with overlapping duration then both events were reported with the exception of the composite endpoint, where these were counted as a single event. These analyses were repeated for radiographically confirmed pneumonia and by use of ICS within 3 days prior to and including the screening date (post hoc). Note that the rate of serious pneumonia or radiographically confirmed serious pneumonia were not performed due to insufficient number of events.

Results

The overall intent-to-treat (ITT) population comprised 10,355 patients (FF/UMEC/VI, n=4151; FF/VI, n=4134; UMEC/VI, n=2070). Table 1 displays the demographic and clinical characteristics by randomized treatment of the ITT population as well as the characteristics of the patients who had an investigator-reported pneumonia and radiographically confirmed by chest x-ray.

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

Compared with the overall ITT population, patients with an investigator-reported pneumonia were more likely to be older than 65 years of age, male, have BMI ≤21 kg/m^2, have a history of prior pneumonia, have had severe exacerbation in the year prior to enrollment, have GOLD III/IV airflow limitation, and be enrolled in Asia. There was no clear association of investigator-reported pneumonia with baseline blood eosinophils as has been reported (12). Radiographic confirmation of investigator-reported pneumonia was more common in the ICS-containing arms (FF/UMEC/VI 154/317 [49%], FF/VI 147/292 [50%], UMEC/VI 40/97 [41%]) but the pattern of risk factors was similar to those for investigator-reported pneumonia.

Risk of Exacerbation or Pneumonia

In the FF/UMEC/VI, FF/VI, and UMEC/VI groups, the number of patients who experienced a moderate/severe exacerbation up to Week 52 was 1959 (47%), 2039 (49%) and 1036 (50%), respectively (Figure 1a) and severe exacerbations was 447 (11%), 461 (11%), and 272 (13%), respectively (Figure 2). The incidence of investigator-reported pneumonia up to Week 52 was higher in ICS- versus non-ICS-containing treatment arms (FF/UMEC/VI, N=317 [8%]; FF/VI, N=292 [7%]; UMEC/VI, N=97 [5%]) (Table 1; Figure 1a) as was the incidence of investigator-reported serious pneumonia (FF/UMEC/VI, N=199 [5%]; FF/VI, N=170 [4%]; UMEC/VI, N=57 [3%]) (Figure 2a). The cumulative plot of moderate/severe exacerbations and investigator-reported pneumonia events, and of severe exacerbations and investigator-reported serious pneumonia events are presented in Figures 1b and 2b, respectively.

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

FF/UMEC/VI versus FF/VI

There was no difference in TTF pneumonia or TTF serious pneumonia between FF/UMEC/VI and FF/VI regardless of whether the pneumonia was investigator-reported or radiographically confirmed (Figure 3a). Similarly, there was no difference in the rate ratios for investigator-reported pneumonia and radiographically confirmed pneumonia between FF/UMEC/VI and FF/VI (Figure 3b). By TTF analysis, FF/UMEC/VI reduced the risk of combined investigator-reported pneumonia or moderate/severe COPD exacerbation (hazard ratio [HR] 0.87; 95% confidence interval [CI] 0.82–0.92) and radiographically confirmed pneumonia or moderate/severe exacerbation (HR 0.85; 95% CI 0.80–0.91) compared with FF/VI (Figure 3a). Similar differences were observed for the rates of combined investigator-reported and radiographically confirmed pneumonia or moderate/severe exacerbations (rate ratio 0.86; 95% CI 0.81–0.91 and 0.85; 95% CI 0.80–0.91, respectively) (Figure 3b). No differences in the rates of combined serious pneumonia or severe exacerbation were observed.

FF/UMEC/VI versus UMEC/VI

By TTF analysis, FF/UMEC/VI increased the risk of investigator-reported pneumonia (HR 1.53; 95% CI 1.22–1.92) and investigator-reported serious pneumonia (HR 1.62; 95% CI 1.21–2.17) compared with UMEC/VI. An increase in the risk of radiographically confirmed pneumonia was also observed with FF/UMEC/VI (Figure 4a). The rates of pneumonia and radiographically confirmed pneumonia were also higher with FF/UMEC/VI than with UMEC/VI (rate ratio 1.53; 95% CI 1.21–1.94 and rate ratio 1.90; 95% CI 1.33–2.72, respectively) (Figure 4b). By both TTF and rates, FF/UMEC/VI reduced the risk of combined pneumonia or exacerbation,

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

radiographically confirmed pneumonia or exacerbation, serious pneumonia or severe exacerbation, and serious radiographically confirmed pneumonia or severe exacerbation compared with UMEC/VI (Figure 4a and 4b).

FF/VI versus UMEC/VI

The occurrence of investigator-reported pneumonia (TTF and rate), radiographically confirmed pneumonia (TTF and rate), serious pneumonia (TTF), and radiographically confirmed serious pneumonia (TTF) was lower with UMEC/VI than with FF/VI (Figure 5a and 5b). There was no difference between FF/VI and UMEC/VI in the TTF combined pneumonia or exacerbation endpoints, with the exception of the serious pneumonia and severe exacerbation composite endpoint and the corresponding radiographically confirmed endpoint where a numerical decrease in risk with FF/VI was observed (Figure 5a), but the rate of combined investigator-reported or radiographically confirmed pneumonia with moderate/severe exacerbation was lower with FF/VI (rate ratio 0.91; 95% CI 0.84–0.98 and 0.90; 95% CI 0.83–0.97, respectively) as were the rates of combined investigator-reported or radiographically confirmed serious pneumonia with severe exacerbation (rate ratio 0.82; 95% CI 0.70–0.96 and 0.81; 95% CI 0.68–0.95) (Figure 5b).

Analyses by Baseline ICS Use

Approximately 77% (N=7960/10,355) of patients enrolled in IMPACT were taking ICS within 3 days prior to screening and the overall rates of moderate/severe exacerbations or investigator-reported pneumonia after randomization were higher in ICS users compared with non-users

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

across study arms (Table E1 in the Online Supplement). The same was seen for rates of severe exacerbations and serious investigator-reported pneumonia (Table E1 in the Online Supplement). Among ICS users, FF/UMEC/VI reduced the rate of moderate/severe exacerbations or pneumonia compared with FF/VI (rate ratio 0.85; 95% CI 0.80–0.91) and UMEC/VI (rate ratio 0.74; 95% CI 0.68–0.80) (Table E1 and Figure E1a in the Online Supplement). Among non-ICS users, FF/UMEC/VI reduced the rate of moderate/severe exacerbations or pneumonia compared with FF/VI (rate ratio 0.87; 95% CI 0.76–1.00) but there was no difference in the rate of moderate/severe exacerbation or pneumonia in the FF/UMEC/VI and UMEC/VI arms (rate ratio 0.94; 95% CI 0.80–1.12) (Table E1 and Figure E1b in the Online Supplement). FF/UMEC/VI reduced the risk of the combined endpoint of severe exacerbation or serious investigator-reported pneumonia compared with UMEC/VI in ICS users (rate ratio 0.73; 95% CI 0.61–0.87) but not in non-ICS users (rate ratio 0.87; 95% CI 0.60–1.24), and there was no significant difference between FF/UMEC/VI and FF/VI for this endpoint in either ICS use subgroup (Table E1 and Figure E2a and E2b in the Online Supplement).

Discussion

This analysis of the results of the IMPACT study confirms multiple prior studies showing that although ICS reduce the risk of acute exacerbations they also increase the risk of pneumonia whether captured as an investigator-reported adverse event or confirmed with chest radiographs (4,5,13). However, as we now demonstrate, the risk of the combined pneumonia or exacerbation endpoint was lower with FF/UMEC/VI compared with both FF/VI and UMEC/VI.

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

The benefits of triple therapy compared with UMEC/VI were most pronounced in those who were taking ICS at baseline, reflecting their higher baseline risk of exacerbations and reinforcing the GOLD recommendations supporting ICS use in those with frequent events. These findings, along with the lower risk of death in those randomized to triple therapy (9), support a favorable benefit–risk profile of once-daily FF/UMEC/VI compared with FF/VI and UMEC/VI in symptomatic patients with COPD who are at risk for exacerbation.

The incidence of pneumonia in patients randomized to FF-containing treatments was between 1.5- and 2-fold the incidence in patients randomized to UMEC/VI, regardless of pneumonia severity or whether the pneumonia was radiographically confirmed. This is comparable to the increased risk reported in some (4), but not all (14), prior studies of FF/VI versus VI, as well as with fluticasone propionate compared with salmeterol (2) and indacaterol/glycopyrronium (13). There has been debate about whether this is a FF or fluticasone propionate specific risk, but differences in study populations, event definitions, and reporting requirements confound comparisons with other molecules, and a Cochrane Review and an Assessment Report issued by the European Medicines Agency have concluded that pneumonia is likely an ICS-related class effect (5,15).

As has been the case in other studies (4), between 40% and 50% of investigator-reported pneumonias were confirmed on chest radiographs submitted as part of the protocol. This rate was somewhat higher in patients randomized to FF-containing treatments perhaps suggesting differences in the clinical presentation of respiratory events in those receiving ICS. Though the overall results were not impacted by the definition of pneumonia that was used, investigator-reported pneumonia was viewed as the most conservative endpoint as individual investigators

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

may have had access to clinical or radiographic data, including follow-up chest x-rays or computerized tomography scans, not available for independent review.

We did not identify new risk factors for pneumonia but confirmed many that have been previously reported including older age, male gender, prior pneumonia, low BMI, and more severe airflow limitation (2,4,16). These risks were similar whether pneumonia was recorded as investigator-reported or x-ray confirmed. We did not identify current smoking as a clear risk factor though this has been reported in prior studies in the general population (1) as well as in some COPD trials (4). It is possible that the effect of smoking was confounded by the fact that patients with more severe airflow limitation and at higher risk for pneumonia were more likely to be former smokers.

There was also no relationship between blood eosinophils and the risk of pneumonia, as has been reported (12). This contrasts with data from the Copenhagen General Population Study that demonstrated an adjusted risk for pneumonia of 2.17 in individuals with COPD, FEV_1 <50%, and blood eosinophils greater than 340 cells/µL compared with those with counts less than that threshold (17). The adjusted risk was even higher (4.52) in those with elevated blood eosinophils, COPD, FEV_1 <70% predicted and recent exacerbation. It also contrasts with a pooled analysis of trials that found a higher risk of pneumonia in patients with COPD and blood eosinophils <2% (18). It is difficult to reconcile these disparate results, but the current data suggest that blood eosinophils do not affect the risk of pneumonia in patients meeting inclusion criteria for IMPACT, regardless of treatment assignment.

Though the use of triple therapy was associated with a reduced risk of combined pneumonia and exacerbation events, it could be argued that the overall benefit–risk is not

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

favorable because pneumonic exacerbations are associated with worse outcomes than non-pneumonic events. Indeed, data from the European COPD audit found that the presence of infiltrates on admission for COPD exacerbation, which occurred in 19% of more than 14,000 cases reviewed, was associated with longer length of stay, more severe acidosis, and higher adjusted mortality than exacerbations without infiltrates (odds ratio for death 1.36; 95% CI 1.20–1.55) (6).

Although adjusted for in the analysis, the presence of infiltrates was also associated with other factors that might influence outcomes including older age, overall and cardiovascular comorbidity, and frequent admission in the year prior, and thus residual confounding related to these or other characteristics could affect the estimates of risk. It is important to note that the presence of infiltrates does not definitively indicate a pneumonia as they may be caused by other processes including pulmonary edema, atelectasis, lung cancer, or bleeding that have no association with inhaled steroids but may relate to prognosis. In the European COPD audit, it is notable that the presence of infiltrates was not associated with prior use of inhaled steroids. A similar 2014 UK COPD Audit found the same 19% rate of consolidation at the time of admission for exacerbation and again the risk of mortality in that group was higher than in those without infiltrates (6.7% vs 3.6%) (19,20). The presence of consolidation is also included in the Dyspnea, Eosinopenia, Consolidation, Acidemia, and atrial Fibrillation (DECAF) prognostic scoring system for in-hospital mortality during exacerbations that has been prospectively validated (21,22).

Prior observational studies have also shown that hospitalized pneumonic exacerbations are associated with a stronger inflammatory response than non-pneumonic events (23) as well as a greater need for intensive care unit admission and mechanical ventilation (7,23), but at

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

least one report suggests that the short- and long-term consequences of each are generally similar though with a higher risk of 30-day readmission in those without infiltrates on chest radiograph (23).

Less is known about differences in pathobiology and outcomes for exacerbations with and without infiltrates treated in the outpatient setting though data from Williams et al suggests a comparable rate of detected infiltrates of 20% and again a greater inflammatory response in those cases (24). That study also demonstrated no major differences in bacterial detection or lung microbiota between these groups suggesting exacerbations and pneumonia occur along a continuum rather than as distinct entities. Despite convincing data that ICS increase the risk of pneumonia, and that exacerbations associated with infiltrates appear associated with worse outcomes, we observed lower overall mortality in patients randomized to FF/UMEC/VI than to UMEC/VI, supporting an overall benefit to treatment despite an increased pneumonia risk (9). This is compatible with the results of the majority of observational and randomized trials showing either no difference or reduced mortality in patients with COPD taking ICS who develop pneumonia (25).

There are several limitations to our analysis. Despite the availability of clinical summaries for all pneumonias and exacerbations requiring hospitalization, it was not possible to directly compare the manifestations, severity, or outcomes of these events. As such, it is not possible to draw conclusions about the relative prognostic implications of these episodes and in these analyses the benefits of exacerbation reduction are given equal weight to the risk of pneumonia. The results of these analyses do not inform the relative exacerbation benefit and

ANNALSATS Articles in Press. Published October 27, 2020 as 10.1513/AnnalsATS.202002-096OC

pneumonia risk of ICS-containing treatments in COPD patients not meeting the IMPACT eligibility criteria.

Conclusions

In summary, there was an increased risk of pneumonia in the FF-containing arms in patients at risk for exacerbations enrolled in IMPACT. However, FF/UMEC/VI reduced the overall risk and rate of combined exacerbation and pneumonia events as well as overall mortality compared with UMEC/VI.

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Table 1. Baseline demographics and clinical characteristics of ITT population and patients with investigator-reported and radiographically confirmed pneumonia.

		Patients with investigator-reported pneumonia				Patients with radiographically confirmed pneumonia			
	ITT (N=10,355)	All treatments (N=706)	FF/UMEC/VI (N=317)	FF/VI (N=292)	UMEC/VI (N=97)	All treatments (N=341)	FF/UMEC/VI (N=154)	FF/VI (N=147)	UMEC/VI (N=40)
Age, n (%)	n=10,355	n=706	n=317	n=292	n=97	n=341	n=154	n=147	n=40
<65	4742 (46)	225 (32)	102 (32)	87 (30)	36 (37)	103 (30)	44 (29)	45 (31)	14 (35)
≥65	5631 (54)	481 (68)	215 (68)	205 (70)	61 (63)	238 (70)	110 (71)	102 (69)	26 (65)
Female, n (%)	n=10,355	n=706	n=317	n=292	n=97	n=341	n=154	n=147	n=40
	3485 (34)	183 (26)	83 (26)	75 (26)	25 (26)	72 (21)	37 (24)	29 (20)	6 (15)
BMI, n (%)	n=10,352	n=706	n=317	n=292	n=97	n=341	n=154	n=147	n=40
≤21 kg/m^2	1776 (17)	179 (25)	73 (23)	83 (28)	23 (24)	98 (29)	36 (23)	51 (35)	11 (28)
>21 kg/m^2	8576 (83)	527 (75)	244 (77)	209 (72)	74 (76)	243 (71)	118 (77)	96 (65)	29 (73)
Current smoker, n (%)	n=10,355	n=706	n=317	n=292	n=97	n=341	n=154	n=147	n=40
	3587 (35)	206 (29)	90 (28)	82 (28)	34 (35)	92 (27)	38 (25)	38 (26)	16 (40)
History of pneumonia, n (%)	n=10,342	n=706	n=317	n=292	n=97	n=341	n=154	n=147	n=40
	2343 (23)	265 (38)	110 (35)	118 (40)	37 (38)	127 (37)	57 (37)	54 (37)	16 (40)
GOLD stage predicted, n (%)	n=10,347	n=705	n=316	n=292	n=97	n=341	n=154	n=147	n=40
I	22 (<1)	3 (<1)	3 (<1)	0 (0)	0 (0)	3 (<1)	3 (2)	0 (0)	0 (0)
II	3719 (36)	205 (29)	96 (30)	90 (31)	19 (20)	97 (28)	46 (30)	46 (31)	5 (13)
III	4982 (48)	359 (51)	157 (50)	147 (50)	55 (57)	168 (49)	77 (50)	67 (46)	24 (60)
IV	1624 (16)	138 (20)	60 (19)	55 (19)	23 (24)	73 (21)	28 (18)	34 (23)	11 (28)
Number of moderate exacerbations in year prior, n (%)	n=10,355	n=706	n=317	n=292	n=97	n=341	n=154	n=147	n=40
	3542 (34)	244 (35)	107 (34)	104 (36)	33 (34)	107 (31)	52 (34)	44 (30)	11 (28)
1	4877 (47)	269 (38)	125 (39)	107 (37)	37 (38)	123 (36)	56 (36)	48 (33)	19 (48)
≥2									

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Number of severe exacerbations in year prior, n (%)	n=10,355	n=706	n=317	n=292	n=97	n=341	n=154	n=147	n=40
1	2300 (22)	220 (31)	96 (30)	93 (32)	31 (32)	125 (37)	53 (34)	60 (41)	12 (30)
≥2	371 (4)	51 (7)	28 (9)	18 (6)	5 (5)	22 (6)	13 (8)	8 (5)	1 (3)
Baseline blood eosinophils, n (%)	n=10,333	n=705	n=317	n=292	n=96	n=341	n=154	n=147	n=40
<150 cells/µL	4482 (43)	316 (45)	143 (45)	133 (46)	40 (42)	151 (44)	66 (43)	67 (46)	18 (45)
≥150 cells/µL	5851 (57)	389 (55)	174 (55)	159 (54)	56 (58)	190 (56)	88 (57)	80 (54)	22 (55)
Geographic region, n (%)	n=10,355	n=706	n=317	n=292	n=97	n=341	n=154	n=147	n=40
Western Europe	3164 (31)	154 (22)	70 (22)			70 (21)	30 (19)	29 (20)	11 (28)
Eastern Europe	685 (7)	40 (6)	18 (6)	54 (18)	30 (31)	28 (8)	13 (8)	11 (7)	4 (10)
Asia	1644 (16)	210 (30)	91 (29)			117 (34)	47 (31)	59 (40)	11 (28)
North America	2639 (25)	205 (29)	99 (31)	15 (5)	7 (7)	80 (23)	45 (29)	29 (20)	6 (15)
South America	1708 (16)	73 (10)	29 (9)			29 (9)	12 (8)	12 (8)	5 (13)
Other	515 (5)	24 (3)	10 (3)	98 (34)	21 (22)	17 (5)	7 (5)	7 (5)	3 (8)
				86 (29)	20 (21)				
				30 (10)	14 (14)				
				9 (3)	5 (5)				

Number of patients in the ITT population: FF/UMEC/VI N=4151, FF/VI N=4134, UMEC/VI N=2070.
BMI, body mass index; FF, fluticasone furoate; ITT, intent-to-treat; n, number of patients with available data; UMEC, umeclidinium; VI, vilanterol.

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Figure Legends

Figure 1. Moderate/severe exacerbation and investigator-reported pneumonia: (A) Kaplan–Meier plot of time-to-first event and (B) cumulative plot. Panel A: Patients experiencing a moderate/severe exacerbation up to Week 52: FF/UMEC/VI, n=1959 (47%); FF/VI, n=2039 (49%); UMEC/VI, n=1036 (50%). Patients with investigator-reported pneumonia up to Week 52: FF/UMEC/VI, n=317 (8%); FF/VI: n=292 (7%); UMEC/VI, n=97 (5%). FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

Figure 2. Severe exacerbation and investigator-reported pneumonia resulting in hospitalization/prolonged hospitalization or death: (A) Kaplan–Meier plot of time-to-first event and (B) cumulative plot. Panel A: Patients experiencing a severe exacerbation up to Week 52: FF/UMEC/VI, n=447 (11%); FF/VI, n=461 (11%); UMEC/VI, n=272 (13%). Patients with investigator-reported pneumonia resulting in hospitalization/prolonged hospitalization or death up to Week 52: FF/UMEC/VI, n=199 (5%); FF/VI: n=170 (4%); UMEC/VI, n=57 (3%).
COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

Figure 3. Forest plot of (A) hazard ratios for time-to-first and (B) rate ratios for pneumonia alone or combined with exacerbation: FF/UMEC/VI versus FF/VI. CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

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Figure 4. Forest plot of (A) hazard ratios for time-to-first and (B) rate ratios for pneumonia alone or combined with exacerbation: FF/UMEC/VI versus UMEC/VI. CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

Figure 5. Forest plot of (A) hazard ratios for time-to-first and (B) rate ratios for pneumonia alone or combined with exacerbation: FF/VI versus UMEC/VI. CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

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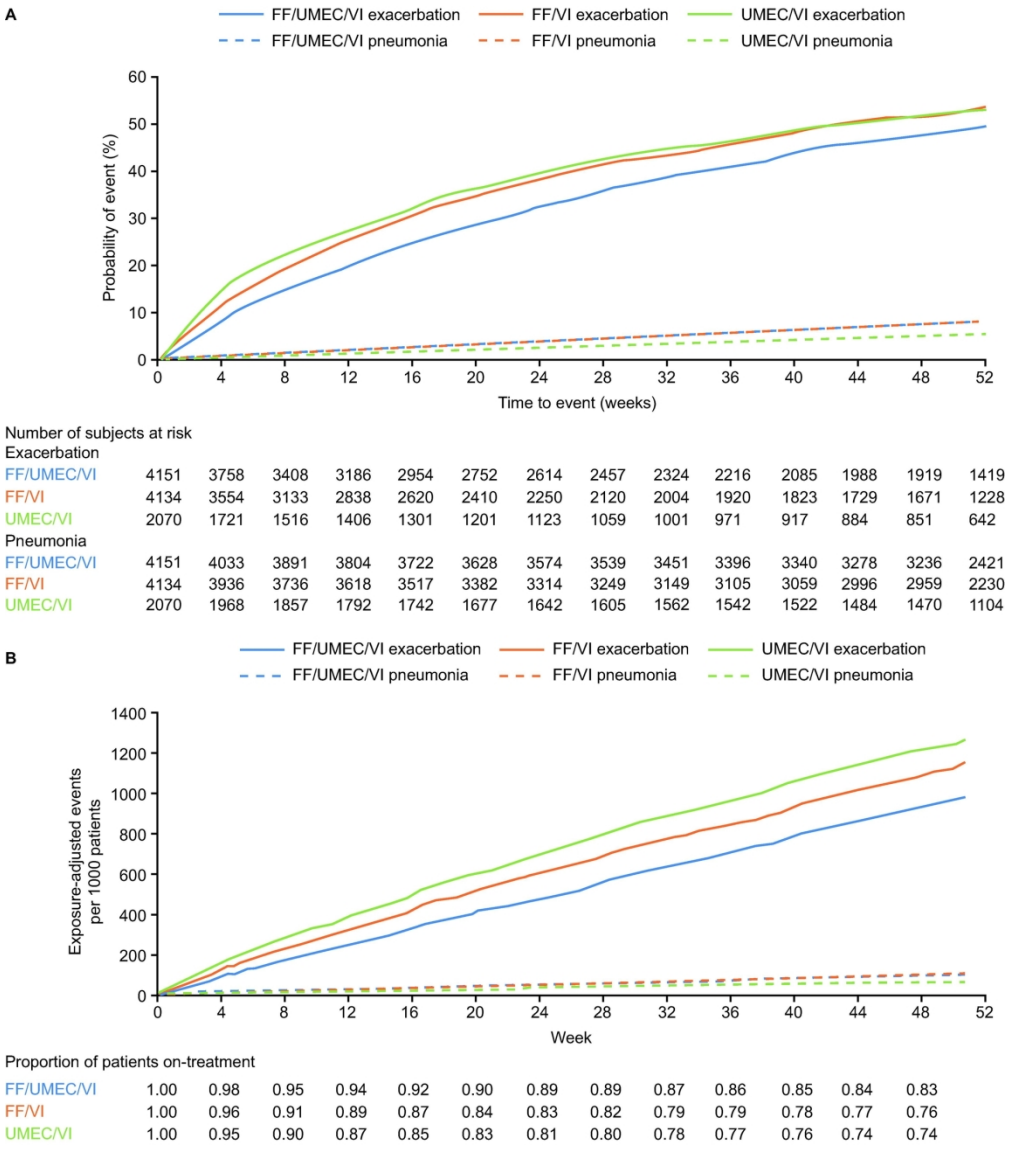

Figure 1. Moderate/severe exacerbation and investigator-reported pneumonia: (A) Kaplan–Meier plot of time-to-first event and (B) cumulative plot.

Panel A: Patients experiencing a moderate/severe exacerbation up to Week 52: FF/UMEC/VI, n=1959 (47%); FF/VI, n=2039 (49%); UMEC/VI, n=1036 (50%). Patients with investigator-reported pneumonia up to Week 52: FF/UMEC/VI, n=317 (8%); FF/VI: n=292 (7%); UMEC/VI, n=97 (5%).
FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

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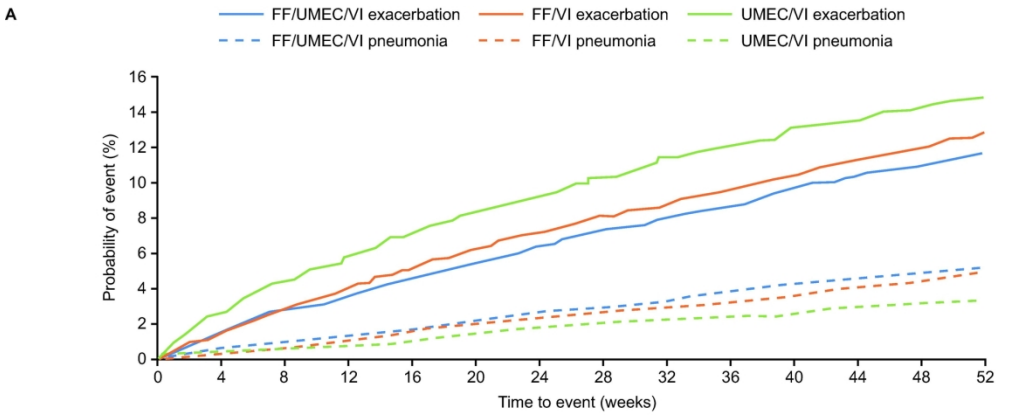
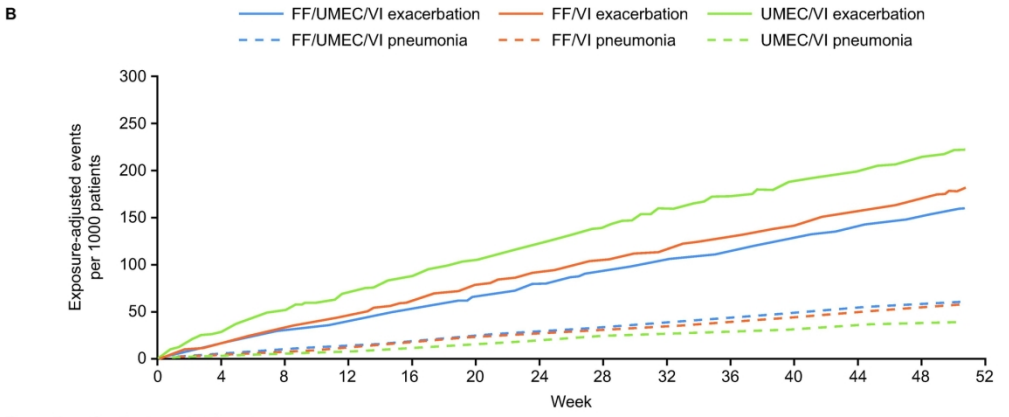


Number of subjects at risk

Exacerbation														
FF/UMEC/VI	4151	4023	3866	3780	3692	3587	3529	3469	3386	3336	3270	3209	3167	2367
FF/VI	4134	3910	3702	3570	3467	3335	3260	3185	3083	3032	2982	2923	2880	2162
UMEC/VI	2070	1937	1813	1744	1689	1626	1586	1549	1495	1473	1444	1412	1393	1046
Pneumonia														
FF/UMEC/VI	4151	4050	3921	3845	3772	3681	3631	3598	3517	3470	3418	3360	3326	2500
FF/VI	4134	3948	3758	3649	3557	3431	3374	3314	3218	3180	3140	3083	3049	2303
UMEC/VI	2070	1971	1865	1804	1758	1695	1661	1628	1586	1568	1548	1512	1499	1125



Proportion of patients on-treatment

FF/UMEC/VI	1.00	0.98	0.95	0.94	0.92	0.90	0.89	0.89	0.87	0.86	0.85	0.84	0.83
FF/VI	1.00	0.96	0.91	0.89	0.87	0.84	0.83	0.82	0.79	0.79	0.78	0.77	0.76
UMEC/VI	1.00	0.95	0.90	0.87	0.85	0.83	0.81	0.80	0.78	0.77	0.76	0.74	0.74

Figure 2. Severe exacerbation and investigator-reported pneumonia resulting in hospitalization/prolonged hospitalization or death: (A) Kaplan–Meier plot of time-to-first event and (B) cumulative plot.

Panel A: Patients experiencing a severe exacerbation up to Week 52: FF/UMEC/VI, n=447 (11%); FF/VI, n=461 (11%); UMEC/VI, n=272 (13%). Patients with investigator-reported pneumonia resulting in hospitalization/prolonged hospitalization or death up to Week 52: FF/UMEC/VI, n=199 (5%); FF/VI: n=170 (4%); UMEC/VI, n=57 (3%).
COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

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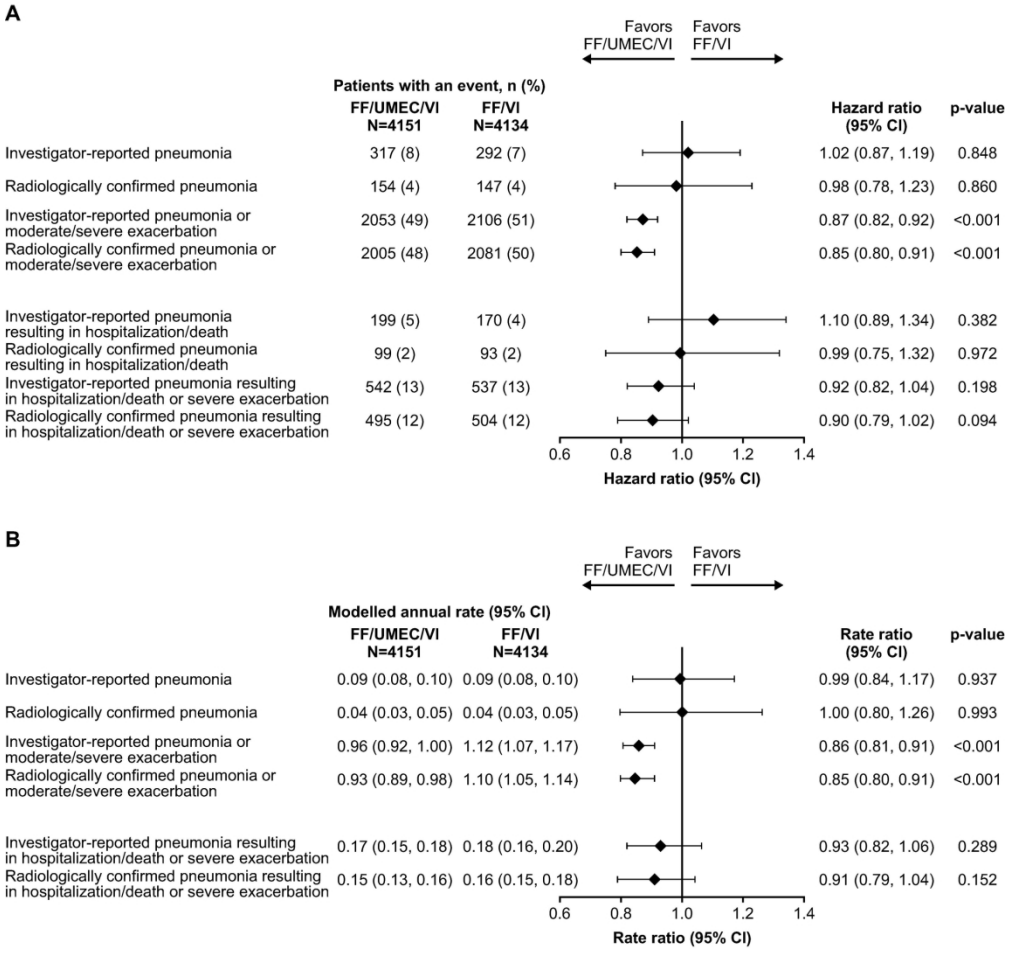

Figure 3. Forest plot of (A) hazard ratios for time-to-first and (B) rate ratios for pneumonia alone or combined with exacerbation: FF/UMEC/VI versus FF/VI.

CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol

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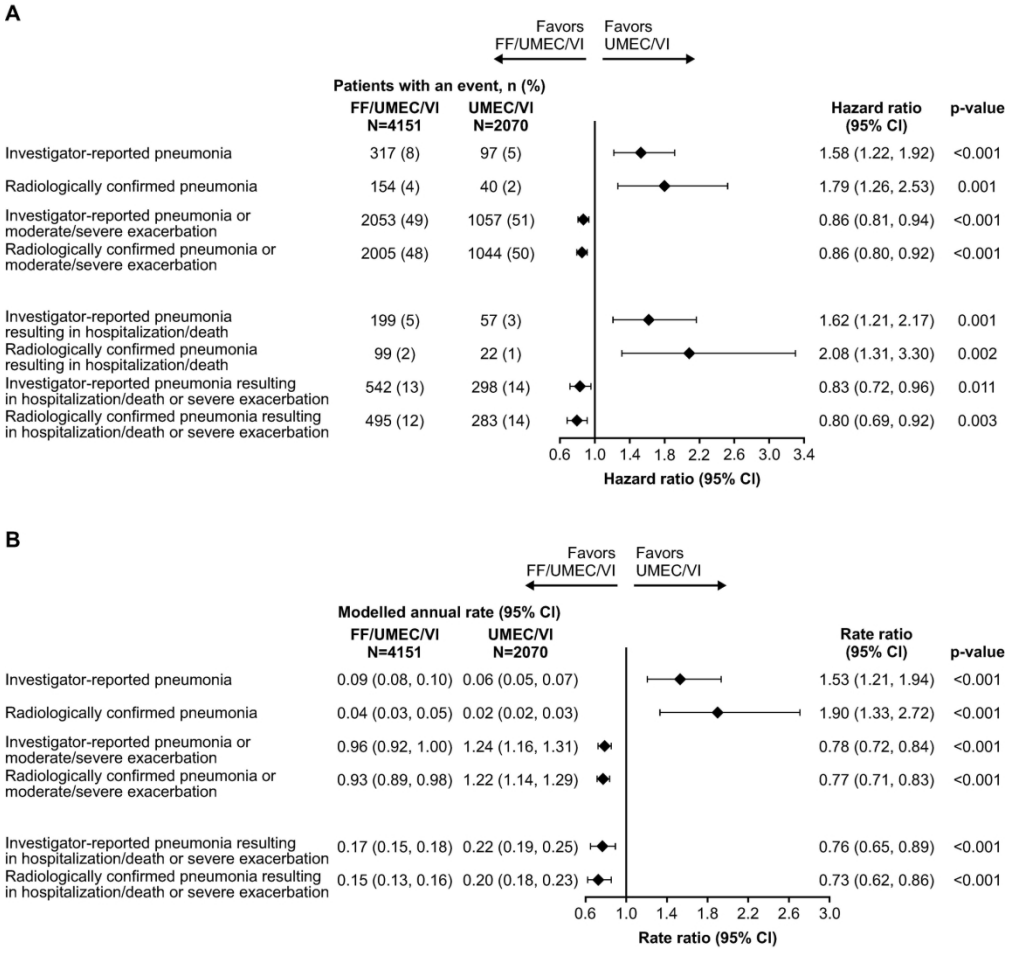

Figure 4. Forest plot of (A) hazard ratios for time-to-first and (B) rate ratios for pneumonia alone or combined with exacerbation: FF/UMEC/VI versus UMEC/VI.

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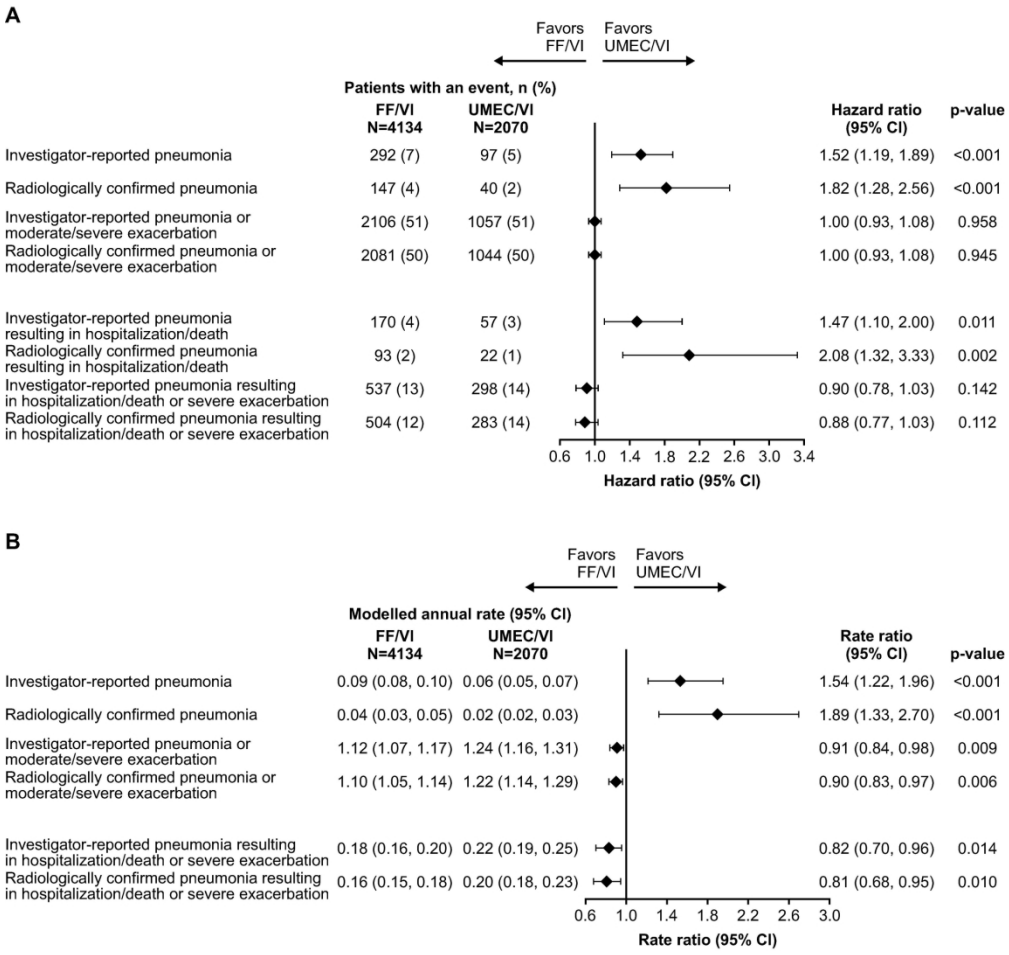

Figure 5. Forest plot of (A) hazard ratios for time-to-first and (B) rate ratios for pneumonia alone or combined with exacerbation: FF/VI versus UMEC/VI.

CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

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Online Supplement

Risk of Exacerbation and Pneumonia with Single Inhaler Triple Versus Dual Therapy in IMPACT

Mark T. Dransfield MD, Courtney Crim MD, Gerard J. Criner MD, Nicola C. Day PhD, David M.G. Halpin MD, MeiLan K. Han MD MS, C. Elaine Jones PhD, Sally Kilbride MSc, David LaFon MD, David A. Lipson MD, David A. Lomas MD PhD, Neil Martin MD, Fernando J. Martinez MD, Dave Singh MD, Robert A. Wise MD, and Peter Lange MD

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Table E1. Rates and rate ratios for the composite endpoints of exacerbation and pneumonia by ICS use at screening*.

	Model estimated annual rates (95% CI)			Rate ratio (95% CI)	
	FF/UMEC/VI	**FF/VI**	**UMEC/VI**	**FF/UMEC/VI vs FF/VI**	**FF/UMEC/VI vs UMEC/VI**
On-treatment moderate/severe exacerbations and investigator-reported pneumonia					
ICS use: Yes	1.01 (0.96, 1.06)	1.18 (1.13, 1.24)	1.36 (1.28, 1.46)	0.85 (0.80, 0.91)	0.74 (0.68, 0.80)
ICS use: No	0.80 (0.73, 0.89)	0.92 (0.84, 1.01)	0.85 (0.74, 0.98)	0.87 (0.76, 1.00)	0.94 (0.80, 1.12)
On-treatment severe exacerbations and investigator-reported pneumonia resulting in hospitalization/prolonged hospitalization or death					
ICS use: Yes	0.17 (0.15, 0.19)	0.19 (0.17, 0.21)	0.24 (0.20, 0.27)	0.90 (0.78, 1.04)	0.73 (0.61, 0.87)
ICS use: No	0.14 (0.11, 0.17)	0.13 (0.10, 0.16)	0.16 (0.12, 0.21)	1.05 (0.78, 1.42)	0.87 (0.60, 1.24)

Post hoc analyses. Number of patients in the analyses: ICS use: Yes: FF/UMEC/VI n=3198, FF/VI n=3157, UMEC/VI n=1600; ICS use: No: FF/UMEC/VI n=947, FF/VI n=976, UMEC/VI n=469. *In the 3 days prior to and including the screening date. CI, confidence interval; FF, fluticasone furoate; ICS, inhaled corticosteroid; UMEC, umeclidinium; VI, vilanterol.

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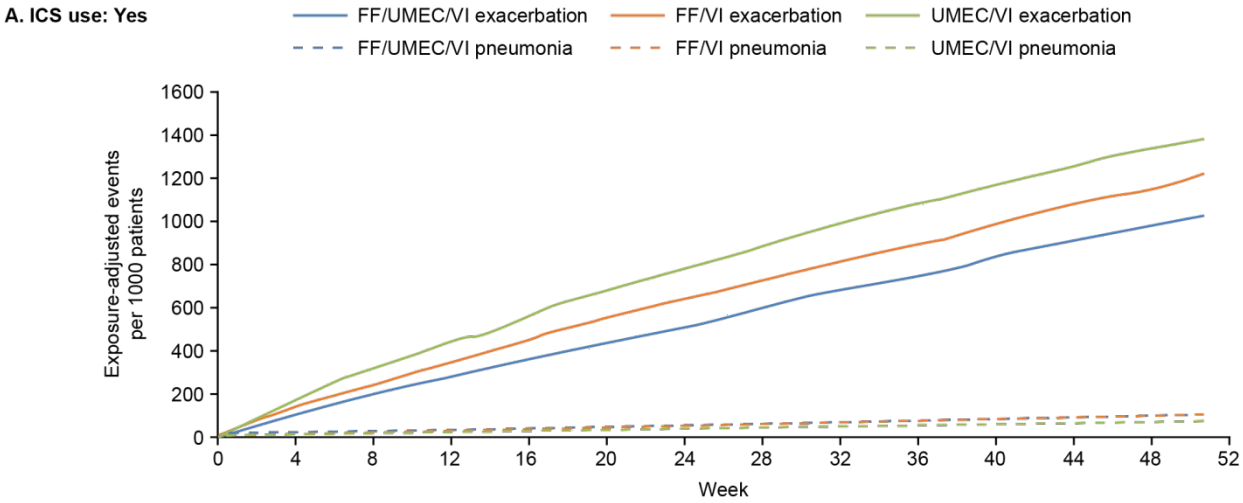
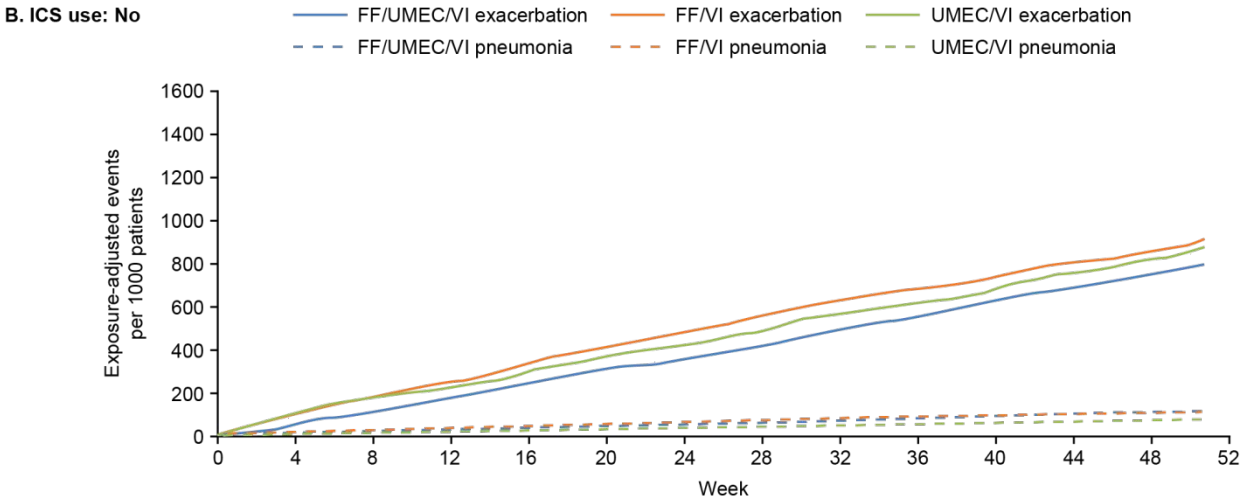
Figure E1. Cumulative plots of moderate/severe exacerbation and investigator-reported pneumonia by ICS use at screening*.



Proportion of patients on-treatment

FF/UMEC/VI	1.00	0.98	0.95	0.93	0.91	0.90	0.89	0.88	0.86	0.85	0.84	0.83	0.83
FF/VI	1.00	0.95	0.91	0.88	0.86	0.84	0.82	0.81	0.79	0.78	0.77	0.76	0.75
UMEC/VI	1.00	0.95	0.89	0.86	0.84	0.81	0.79	0.77	0.75	0.74	0.74	0.72	0.72



Proportion of patients on-treatment

FF/UMEC/VI	1.00	0.98	0.96	0.95	0.94	0.93	0.92	0.91	0.90	0.89	0.88	0.86	0.85
FF/VI	1.00	0.97	0.93	0.91	0.89	0.86	0.85	0.84	0.82	0.81	0.81	0.80	0.79
UMEC/VI	1.00	0.97	0.93	0.92	0.91	0.89	0.88	0.87	0.86	0.86	0.84	0.82	0.82

*In the 3 days prior to and including the screening date. FF, fluticasone furoate; ICS, inhaled corticosteroid; UMEC, umeclidinium; VI, vilanterol.

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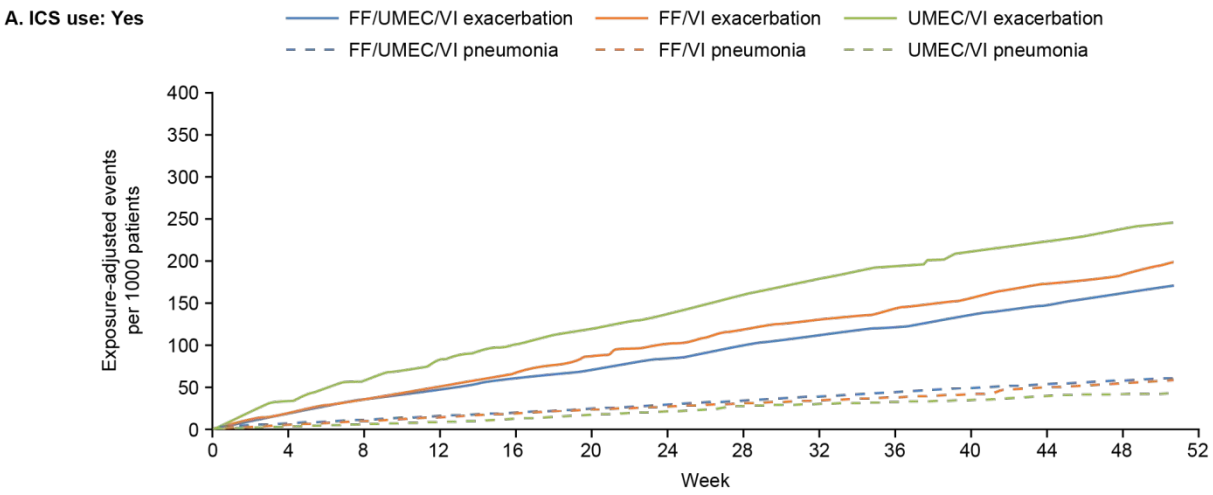
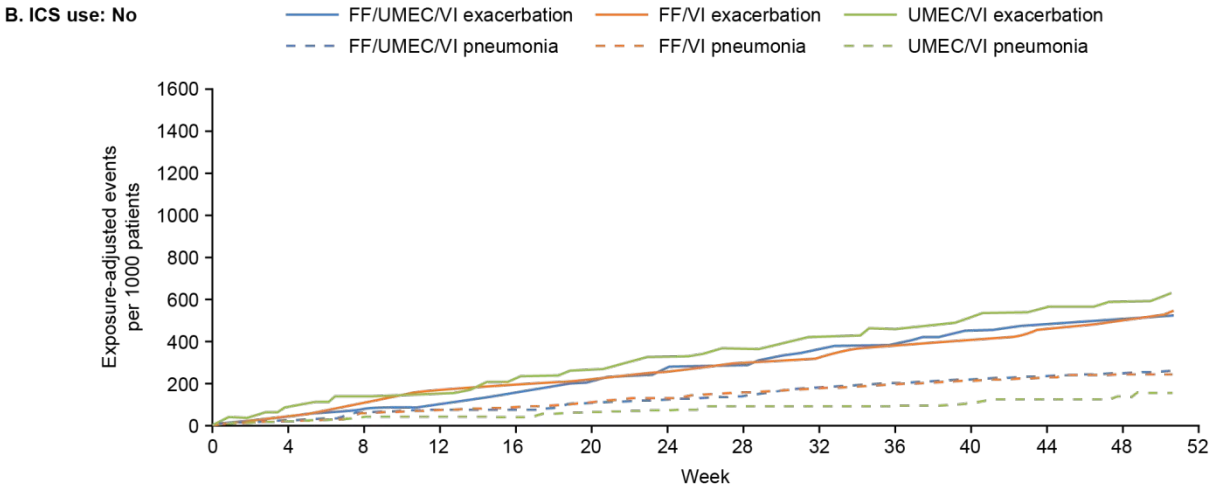
Figure E2. Cumulative plots of severe exacerbation and investigator-reported pneumonia resulting in hospitalization/prolonged hospitalization or death by ICS use at screening*.



Proportion of patients on-treatment

FF/UMEC/VI	1.00	0.98	0.95	0.93	0.91	0.90	0.89	0.88	0.86	0.85	0.84	0.83	0.83
FF/VI	1.00	0.95	0.91	0.88	0.86	0.84	0.82	0.81	0.79	0.78	0.77	0.76	0.75
UMEC/VI	1.00	0.95	0.89	0.86	0.84	0.81	0.79	0.77	0.75	0.74	0.74	0.72	0.72



Proportion of patients on-treatment

FF/UMEC/VI	1.00	0.98	0.96	0.95	0.94	0.93	0.92	0.91	0.90	0.89	0.88	0.86	0.85
FF/VI	1.00	0.97	0.93	0.91	0.89	0.86	0.85	0.84	0.82	0.81	0.81	0.80	0.79
UMEC/VI	1.00	0.97	0.93	0.92	0.91	0.89	0.88	0.87	0.86	0.86	0.84	0.82	0.82

*In the 3 days prior to and including the screening date. FF, fluticasone furoate; ICS, inhaled corticosteroid; UMEC, umeclidinium; VI, vilanterol.

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