Reduction in All-Cause Mortality with Fluticasone Furoate/Umeclidinium/Vilanterol in COPD Patients

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Author's contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. 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. MT Dransfield, GJ Criner, DMG Halpin and P Manchester were involved

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Running title

Triple therapy: effect on mortality risk in COPD

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At a glance summary

Previous studies have suggested that inhaled corticosteroids convey a survival benefit in patients with chronic obstructive pulmonary disease (COPD). This study reports a

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statistically significant reduction in the risk of all-cause mortality comparing fluticasone furoate/umeclidinium/vilanterol (inhaled corticosteroid [ICS]/long-acting muscarinic antagonist [LAMA]/long-acting β_2-agonist [LABA]) with UMEC/VI (LAMA/LABA) in the IMPACT trial following additional collection and analysis of vital status data.

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ABSTRACT

Rationale: The IMPACT trial demonstrated a significant reduction in all-cause mortality (ACM) risk with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI or UMEC/VI in patients with COPD at risk of future exacerbations. 574 patients were censored from the original analysis due to incomplete vital status information.

Objective: Report ACM and impact of stepping down therapy, following collection of additional vital status data.

Methods: Patients were randomized 2:2:1 to FF/UMEC/VI 100/62.5/25μg, FF/VI 100/25μg or UMEC/VI 62.5/25μg following a run-in on their COPD therapies. Time to ACM was prespecified. Additional vital status data collection and subsequent analyses were performed *post hoc*.

Measurements and Main Results: We report vital status data for 99.6% of the intention-to-treat population (n=10,355), documenting 98(2.36%) deaths on FF/UMEC/VI, 109(2.64%) on FF/VI, and 66(3.19%) on UMEC/VI. For FF/UMEC/VI, the hazard ratio for death was 0.72 (95%CI: 0.53,0.99;P=0.042) versus UMEC/VI and 0.89 (95%CI: 0.67,1.16;P=0.387) versus FF/VI. Independent adjudication confirmed lower rates of cardiovascular and respiratory death, and death associated with the patient's COPD.

Conclusions: In this secondary analysis of an efficacy outcome from the IMPACT trial, once-daily single-inhaler FF/UMEC/VI triple therapy reduced the risk of ACM versus UMEC/VI in patients with symptomatic COPD and a history of exacerbations.

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INTRODUCTION

No pharmacologic therapy to date has prospectively demonstrated a reduction in all-cause mortality (ACM) in patients with chronic obstructive pulmonary disease (COPD). Only smoking cessation (1), oxygen therapy in severely hypoxemic patients (2,3), and lung volume reduction surgery in select individuals (4) have been shown to decrease mortality. Previous studies, such as TORCH (5), INSPIRE (6), UPLIFT (7) and SUMMIT (8) suggested a benefit for survival with pharmacologic therapy, but either did not achieve statistical significance or were limited by methodologic considerations.

The InforMing the PAthway of COPD Treatment (IMPACT) trial (NCT02164513, CTT116855) was a 52-week phase III, randomized, double-blind, parallel-group, multicenter trial that compared the efficacy, safety and tolerability of once-daily single-inhaler triple therapy containing an inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2-agonist (ICS/LAMA/LABA; fluticasone furoate/umeclidinium/vilanterol; FF/UMEC/VI) versus ICS/LABA (FF/VI) or LABA/LAMA (UMEC/VI) dual therapy (9). The primary efficacy and safety results have been previously reported (10). The trial demonstrated significant beneficial outcomes for FF/UMEC/VI therapy compared with both dual therapies specifically including a reduction in moderate/severe exacerbations and COPD hospitalizations, and improved lung function and health-related quality of life. The safety profile of triple therapy was like that of the known profiles of the individual molecules.

IMPACT also demonstrated a potentially clinically relevant mortality difference including reduction in the risk of on-treatment all-cause mortality, and all-cause mortality including

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off-treatment data in the intent-to-treat (ITT) population, comparing FF/UMEC/VI with UMEC/VI. However, 574 (5.5%) subjects were censored from the original Week 52 analysis that included off-treatment data because of incomplete vital status information, as not all investigators provided vital status data for their subjects at Week 52 after discontinuation of assigned therapy or withdrawal from the study (10). Due to the amount of missing data in the previous results we felt caution was warranted in the interpretation of the all-cause mortality finding. We now report robust findings of all-cause mortality following collection of additional vital status data at nominal Week 52 representing 99.6% of the study population. In addition, the IMPACT trial design allowed participants to remain on their current COPD therapies prior to randomization, rather than have an artificial “stabilization” or withdrawal of therapy during the run-in period. This was done to mimic therapeutic switch and step down performed in routine clinical practice, thereby improving the generalizability of the trial results. This design affords the opportunity to understand outcomes for participants who entered the trial on differing therapies. We also report on outcomes of patients who entered the trial on inhaled triple therapy and on regimens containing an ICS to understand outcomes of patients who undergo step down or switch in therapy. Some of these data have been previously presented in the form of an abstract (11).

METHODS

Patient population

IMPACT randomized 10,355 patients in a 2:2:1 fashion to FF/UMEC/VI 100/62.5/25µg, FF/VI 100/25µg, and UMEC/VI 62.5/25µg, respectively, and were included in the ITT

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population. Eligible participants had symptomatic COPD with a forced expiratory volume in 1 second (FEV_1) <50% of predicted and a history of ≥1 moderate or severe (hospitalized) exacerbation, or FEV_1 of 50% to <80% of predicted and ≥2 moderate or 1 severe exacerbation in the previous year. A current diagnosis of asthma was exclusionary (10).

The total study duration consisted of a 2-week run-in period where participants remained on their own medication, a 52-week treatment period, and a 1-week safety follow-up.

Patients who permanently discontinued study treatment before the end of the 52-week treatment period but agreed to continue in the study were followed by the investigator until the end of the patients' planned 52-week participation to capture important efficacy and safety assessments, including adverse events, exacerbations, and vital status. Those who discontinued their medications and withdrew from the study were expected to have vital status recorded at the 52-week post-randomization date. All serious adverse reports and deaths within the study were independently adjudicated to determine the primary cause of death.

The study was performed in 37 countries between June 2014 and July 2017 in accordance with Good Clinical Practice and the Declaration of Helsinki. The study received local Institutional Review Board/Independent Ethics Committee approval and all participants provided signed informed consent.

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Definition of all-cause mortality

Time to ACM (on-treatment and on/off treatment) were pre-specified 'Other' efficacy endpoints in the IMPACT protocol and have previously been reported (10). Here we also include *post hoc* analyses of time to ACM including a near complete vital status dataset following a challenging global collection of data.

A death was defined as "on-treatment" if the actual date of death occurred up to 7 days after the last day of treatment and considered to be "off-treatment" if the actual date of death occurred more than 7 days after the last day of treatment and before the projected Week 52 date (Supplement Figure E1).

Statistical considerations and tipping point analyses

To control for the Type I error in the IMPACT trial, the truncated Hochberg method was used in a closed testing hierarchy across the co-primary and key secondary treatment comparisons. Since all tests within the prespecified statistical hierarchy achieved statistical significance ($P<0.001$), significance is inferred for all other endpoints and treatment comparisons with a P-value <0.05 as stated in the IMPACT protocol.

Time to ACM was analyzed using a Cox proportional hazards model with covariates of treatment group, age (at screening), and gender. Kaplan–Meier figures showing probability of patients with an event over time for each treatment group are presented.

To assess the impact of missing vital status data at Week 52 (n=42 of 10,355), tipping point analyses were conducted for the treatment comparison of FF/UMEC/VI compared with UMEC/VI by using multiple imputation for the time to first event in participants

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censored prior to Week 52 using the methods proposed by Jackson et al. (12) (Supplement Figure E2A and B) and by imputing all possible combinations of outcomes for the logistic regression methodology (Supplement Figure E2C).

RESULTS

Participants (N=10,355) with symptomatic COPD and a history of exacerbations were randomized into the ITT population and received study medication. In total, 9087 (88%) completed the trial with 7991 (77%) completing the trial on investigational therapy.

Baseline study demographics are shown in Table 1. Most participants (66%) were male, and the mean age was 65.3 years. There were no clinically relevant differences in participant characteristics between the overall treatment groups. However, participants who entered the study on a triple therapy or an ICS-containing regimen had lower lung function and greater history of hospitalization in the previous 12 months, and were less likely to be a current smoker compared with those who entered on a dual or monotherapy, or non-ICS containing regimen (Table 2). The participants who entered on triple therapy or ICS-containing therapy also had greater rates of exacerbation during the study suggesting they carried greater risk (Table 3).

On-treatment all-cause mortality

As originally reported (10), there were 50 (1.20%) on-treatment deaths in the FF/UMEC/VI arm (n=4151), 49 (1.19%) in the FF/VI arm (n=4134), and 39 (1.88%) in the UMEC/VI arm (n=2070). The hazard ratio (HR) for on-treatment ACM was 0.58 (95% confidence interval [CI]: 0.38, 0.88; P=0.011) for the comparison of FF/UMEC/VI with UMEC/VI, and 0.61 (95% CI: 0.40, 0.93; P=0.022) for the comparison of FF/VI with

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UMEC/VI (Figure 1a). Additional data collection which gathered off-treatment vital status information does not impact the pre-specified on-treatment all-cause mortality analyses and findings.

Independent adjudication of the primary cause of death confirmed lower rates of cardiovascular death, respiratory death, and death associated with the patient's underlying COPD when on either randomized ICS-containing arm compared with UMEC/VI. Similar findings were observed when off treatment adjudicated data were included. (Supplement Table E1).

On/off-treatment all-cause mortality including additional vital status data

Additional post hoc data collection now provides vital status at Week 52 for 99.6% of the ITT population with 42 subjects censored in the analyses because of missing data. Twenty-seven additional off-treatment deaths were identified in the post hoc collection of vital status information (9 on FF/UMEC/VI, 12 on FF/VI, and 6 on UMEC/VI). In total, there were 98 (2.36%) deaths on FF/UMEC/VI, 109 (2.64%) on FF/VI, and 66 (3.19%) on UMEC/VI. Time to ACM, including off-treatment data with the additional vital status collection, demonstrated a HR for ACM of 0.72 for patients treated with FF/UMEC/VI compared with UMEC/VI (95% CI: 0.53, 0.99, P=0.042). The HR for FF/VI versus UMEC/VI was 0.82 (95% CI: 0.60, 1.11, P=0.190). (Figure 1b).

Figure 2 illustrates the results of the various presented analyses including the originally reported findings.

Tipping point analyses conducted for the treatment comparison of FF/UMEC/VI compared with UMEC/VI using multiple imputation for the time to first event in

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participants censored prior to Week 52 demonstrated that if all patients on UMEC/VI with censored data are imputed as alive at the end of 52 weeks the post-withdrawal hazard for FF/UMEC/VI would need to be approximately 10 times higher than the pre-withdrawal hazard before losing statistical significance. Similarly, if the patients on UMEC/VI with censored data are assumed to have a post-withdrawal hazard the same as the pre-withdrawal hazard (i.e. it is assumed that the missing data for UMEC/VI is missing at random) then the post-withdrawal hazard for FF/UMEC/VI would need to be approximately 14 times higher than the pre-withdrawal hazard before losing statistical significance. These extreme assumptions are unlikely and support the conclusion that the observed survival finding is robust to missing data. (Supplement Figure E2).

Effect of step down from triple and switch of therapy

Supplement Table E2 summarizes ACM by the patients' COPD medication at study entry. Forty per-cent of participants (n=4183) entered the study on a triple therapy (ICS+LAMA+LABA) regimen. Because of the randomization scheme, approximately 40% of these patients were maintained on triple therapy, 40% were stepped down to ICS/LABA (removal of the LAMA component) and 20% were stepped down to a LAMA/LABA (removal of the ICS component).

In the analysis including the additional follow up data in participants who entered the study on a triple therapy, the study suggested a reduced risk of on/off-treatment death for patients maintained on a triple therapy compared with those who underwent step down to either dual therapy (Figure 3a) with a HR of 0.71 (95% CI: 0.46, 1.10, P=0.124) compared with patients stepped down to ICS/LABA, and a HR of 0.62 (95% CI: 0.38,

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1.00, P=0.051) compared with patients stepped down to LAMA/LABA, though these reductions did not achieve statistical significance.

In those patients who entered the study on medications other than a triple regimen, risk of all-cause mortality was numerically lower for patients who were randomized to either triple therapy or to ICS/LABA compared with those randomized to LAMA/LABA. (Figure 3b). For participants in this subgroup randomized to triple therapy the HR for risk of ACM was 1.03 (95% CI: 0.72, 1.47, P=0.870) compared with ICS/LABA and 0.80 (95% CI: 0.53, 1.21, P=0.285) compared with LAMA/LABA. (Figure 3E).

Effect of previous ICS use on all-cause mortality

Most participants (76.9%, n=7960) who entered the study were on a medication regimen that contained an ICS. In these patients, mortality was lower if they were maintained on an ICS-containing regimen compared with LAMA/LABA (Figure 3c). The HR for risk of ACM in this subgroup was 0.82 (95% CI: 0.60, 1.13, P=0.229) for patients randomized to triple therapy compared with ICS/LABA and 0.63 (95% CI: 0.44, 0.89, P=0.009) compared with LAMA/LABA (Figure 3E). There was no apparent difference in mortality in the smaller number of participants (23.1%, n=2395) who entered the study on a non-ICS containing medication regimen (Figure 3d), although interpretation is limited given the relatively smaller size of this group and lower numbers of deaths.

Analysis of all-cause mortality by time intervals after randomization

Analysis of ACM by time interval (death within 30 days, 60 days, or 180 days after randomization) demonstrated a statistically significant benefit for FF/UMEC/VI compared with UMEC/VI within 60 and 180 days after randomization. There were no

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deaths in the FF/UMEC/VI arm, 5 in the FF/VI arm, and 7 in the UMEC/VI arm within 30 days of randomization; no analysis was performed due to the small numbers of events. (Supplement Figures E3 and E4).

DISCUSSION

We demonstrate that treatment of symptomatic patients with COPD and a history of exacerbation with FF/UMEC/VI significantly reduced the risk of all-cause mortality compared with the dual bronchodilator UMEC/VI. This finding was consistently observed in the on-treatment analyses, the analyses that included off-treatment data, and in sensitivity tipping point analyses. These data extend previous studies that suggested a reduction in mortality using ICS-containing medications in patients with COPD (5,6,8,13,14).

We confirm a survival benefit to ICS-containing therapy in a pre-defined, prospective analysis. The survival benefit has been previously suggested in other studies, but either did not reach pre-determined levels of statistical significance or were performed post hoc. The TORCH study (5) demonstrated a 17.5% (95% CI: −0.2, 31.9) reduction in the hazard of death in the combination group using salmeterol/fluticasone propionate (SFC) compared with placebo (P=0.052) and only missed statistical significance due to an interim analysis that raised the threshold for significance. The INSPIRE study (6) demonstrated a 52% reduction in the hazard of on-treatment ACM with SFC compared with tiotropium (HR: 0.48; 95% CI: 0.27, 0.85; P=0.012), though this analysis was performed post hoc on a safety endpoint with incomplete follow-up. The SUMMIT study (8) demonstrated a 12.2% reduction in the hazard of ACM for FF/VI compared with

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placebo (HR: 0·88 [95% CI: 0·74, 1·04]; P=0·137) in a milder COPD population with either the presence or high risk of cardiovascular disease. The endpoint did not reach statistical significance in the study, though that may be because that study was powered assuming a 30% reduction in mortality in a much milder patient population. A post-hoc, stratified, safety pooled analysis of fatal adverse events of ICS-containing therapy in three 52-week studies suggested a 29% reduction in mortality, although this did not reach statistical significance (HR 0.71, 95% CI 0.50-1.02, p=0.066) (13). Interestingly, a recent Bayesian network meta-analysis of 219 trials found that both ICS/LAMA/LABA and ICS/LABA were associated with a statistically significantly higher probability of reducing mortality compared with placebo (OR 0.74, 95% Credible Interval [CrI] 0.59–0.93, posterior probability of OR >1 P[OR > 1] 0.004; and OR 0.86, 95% CrI 0.76–0.98, P[OR > 1] 0.015; respectively (14). Thus, to put these data into perspective, IMPACT has now prospectively confirmed a survival benefit with ICS-containing therapy that had previously been suggested in patients with COPD.

It is likely that the finding of reduction in the risk of all-cause mortality was confirmed in IMPACT because of the clinical severity of the population in the study, and the significant efficacy observed with the addition of the ICS FF in a highly symptomatic group of patients with frequent moderate or severe exacerbations. In IMPACT we observed a 25% reduction in the rate of on-treatment moderate and severe COPD exacerbations comparing FF/UMEC/VI with UMEC/VI as well as a 34% reduction in COPD hospitalizations for this comparison (10). The reduction in recurrent exacerbation events likely led to improved patient well-being and reduced hospitalization. Reduction in hospitalization likely reduced the known morbidity and mortality associated with

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hospitalization in patients with COPD (15-18). This is supported by the independently adjudicated findings of reduced cardiovascular death, respiratory death, and death associated with the patient's underlying COPD compared to an efficacious active-comparator.

Our time interval data refutes the premise that the difference in all-cause mortality was due to acute ICS withdrawal, as evidenced by the continued reduction in mortality throughout the trial; not only in the first 30 days when the effect of acute ICS withdrawal would be expected to be greatest. These data suggest acute step down of medication did not drive the overall findings; rather, they demonstrate the overall benefit of ICS for this population. The observation of the statistically significant and clinically relevant reduction of on-treatment mortality with FF/VI compared with UMEC/VI further supports that the ICS component drives the survival benefit. The findings of triple compared with FF/VI, and the triple step-down data, demonstrate an additional contribution of the LAMA component to survival when using triple-inhaled therapy in this population.

The survival benefit was observed in participants who entered the trial on ICS. This is not unexpected as these patients appeared at greater risk with lower lung function and higher rates of previous hospitalization at study entry, despite being on ICS. As this population is sicker, as evidenced by higher rates of exacerbations during the trial, and most likely to be hospitalized, one might expect that this is the population that would derive the greatest benefit in the study. Only a minority of patients entered the study not taking an ICS, so we are less able to determine if there is a survival benefit in this smaller subgroup with lower risk at study entry.

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Differential response based on prior treatment has been observed in other trials. For example, post hoc analyses of patients who were previously treated with ICS in the SUMMIT trial demonstrated a beneficial effect on mortality differing from those who had not been previously treated with ICS (19). Additionally, both LABA and ICS use predicted a higher rate of health-care utilized exacerbation in the TIOSPIR study (20). Perhaps this should be expected as patients were on their previous medications for a reason, and would likely have different clinical characteristics that would have prompted their physician to use these medications in the first place (19). This also suggests that there is something inherently different about these patients, rather than an effect of withdrawal or switch of medication in IMPACT and in these trials.

The data from patients who entered the trial on an “open” triple of ICS + LAMA + LABA suggest that maintenance on a triple therapy is associated with a trend towards lower risk of death than step down to either dual therapy in a symptomatic patient population at risk for further exacerbation. This supports the benefit of both ICS and LAMA in this population, and is of importance as international treatment guidelines suggest consideration of step down of therapy in stable patients (21). However, our findings suggest that physicians should use caution when considering step down in therapy in patients with characteristics that mirror those enrolled in IMPACT.

A limitation of the study was that it was only of 52 weeks in duration. Previous mortality studies have been a minimum of 2–3 years in length to ensure enough events to demonstrate a mortality difference. However, we were able to demonstrate a difference despite being only 1 year in length, likely due to the high-risk nature of this population. Mortality studies of longer length have shown that the mortality curves between arms

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generally continue to widen over time, though this is dependent on disease stage and the mode of action of a drug (5,8). The mortality finding in IMPACT would not be expected to be different from previous longer studies as there is no suggestion from the data, or the study population, that the benefit would wane over time. Strengths of the study include the large sample size of well-characterized participants with substantial follow-up information. An additional strength is that we evaluated both on-treatment mortality (vital status of subjects while taking assigned therapy), and the mortality of subjects including off-treatment data (including vital status of subjects even after discontinuation of assigned therapy, as ITT). On-treatment data is clinically relevant because it demonstrates expected outcomes related to use of a chronic therapy while the subject is taking the medication; ACM including off-treatment data is important for understanding treatment policy and the impact of differential dropout.

In summary, we have now prospectively confirmed for the first time a reduction in the risk of death using pharmacologic therapy with once-daily inhaled FF/UMEC/VI in symptomatic patients at risk for future exacerbations. We believe that these data are important to healthcare providers and to patients with COPD.

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Declaration of interests

NC Day, C Crim, CE Jones, S Kilbride, S Lettis, P Manchester, N Martin, D Midwinter, A Morris and DA Lipson are employees of GSK and hold stocks/shares in GSK. SJ Pascoe was an employee of GSK at the time of the study and holds stocks/shares in GSK. He is currently an employee of CSL Behring. MT Dransfield has received personal fees from AstraZeneca, Boehringer Ingelheim, PneumRx/BTG, Quark Pharmaceuticals and GSK, grant support from the American Lung Association, Department of Defense, Department of Veterans Affairs, and NIH, and contracted clinical trial support from Boehringer Ingelheim, Novartis, AstraZeneca, Yungjin, PneumRx/BTG, Pulmonx, Boston Scientific, Gala, Nuvaira, and GSK. GJ Criner has received personal fees from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Broncus Medical, Chiesi, CSA Medical, Eolo, Gala Therapeutics, GSK, Helios Medical, Medtronic, Merck, Mereo BioPharma, NGM Pharmaceuticals, Novartis, Nuvaira, Olympus, Philips Respironics, Pulmonx, Respivant Sciences, The Implementation Group, and Verona. He also has ownership interest in HGE Technologies. DMG Halpin has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer and Sanofi, and non-financial support from Boehringer Ingelheim and Novartis. MK Han has received personal fees from AstraZeneca, GSK, Mylan, and Boehringer Ingelheim and research support from Novartis and Sunovion. P Lange has received personal fees from GSK, AstraZeneca, and Boehringer Ingelheim, and grant support from Boehringer Ingelheim and GSK. DA Lomas has received grant income, honoraria, and consultancy fees from

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AstraZeneca/MedImmune, Boehringer Ingelheim, Pearl Therapeutics, GSK, and Sanofi-Aventis.

Data sharing statement

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

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Figure legends

Figure 1. Kaplan–Meier plots of time to ACM for (A) on-treatment deaths and (B) on-/off-treatment deaths

ACM, all-cause mortality; FF, fluticasone furoate; ICS, inhaled corticosteroid; UMEC, umeclidinium; VI, vilanterol.

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A, B, C and D: Kaplan–Meier plots of ACM including off-treatment data (with additional vital status follow-up). ACM, all-cause mortality; FF, fluticasone furoate; ICS, inhaled corticosteroid; UMEC, umeclidinium; VI, vilanterol. *Medication taken between date of screening -3 days and date of screening (inclusive).

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Table 1. Baseline patient demographics (ITT population)

	FF/UMEC/VI (n=4151)	FF/VI (n=4134)	UMEC/VI (n=2070)	Overall (N=10,355)
Age (years), mean (SD)	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)	65.3 (8.3)
Sex (male), %	2766 (67)	2748 (66)	1356 (66)	6870 (66)
Former smoker, n (%)	2715 (65)	2711 (66)	1342 (65)	6768 (65)
Post-bronchodilator FEV_1 % predicted, mean (SD)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)	45.5 (14.8)
COPD exacerbations in prior year, n (%)				
<2 moderate and no severe	1198 (29)	1242 (30)	616 (30)	3056 (30)
≥2 moderate or ≥ 1 severe	2953 (71)	2892 (70)	1454 (70)	7299 (70)
≥2 severe	147 (4)	148 (4)	76 (4)	371 (4)
Baseline COPD medications at screening*, n (%)				
ICS + LABA + LAMA	1672 (40)	1647 (40)	864 (42)	4183 (40)
ICS + LABA	1354 (33)	1340 (32)	647 (31)	3341 (32)
LAMA + LABA	389 (9)	349 (8)	196 (9)	934 (9)
LAMA	304 (7)	365 (9)	162 (8)	831 (8)

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SD, standard

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deviation; UMEC, umeclidinium; VI, vilanterol. *Medication taken between date of screening -3 days and date of screening (inclusive).

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Table 2. Baseline characteristics of subjects entering the trial on a triple therapy or an ICS-containing regimen

Baseline characteristic	On triple-therapy at screening* (N=4183)	No triple-therapy at screening* (N=6172)	ICS use at screening* (N=7960)	No ICS use at screening* (N=2395)
Age, n	4183	6172	7960	2395
Mean (SD)	65.6 (8.1)	65.1 (8.4)	65.2 (8.3)	65.4 (8.2)
Gender, n	4183	6172	7960	2395
Male, n (%)	2733 (65)	4137 (67)	5207 (65)	1663 (69)
Female, n (%)	1450 (35)	2035 (33)	2753 (35)	732 (31)
Smoking status, n	4183	6172	7960	2395
Current smoker, n (%)	1294 (31)	2293 (37)	2597 (33)	990 (41)
Former smoker, n (%)	2889 (69)	3879 (63)	5363 (67)	1405 (59)
Post-bronchodilator % predicted FEV_1, n	4182	6165	7955	2392
Mean (SD)	42.9 (14.1)	47.4 (15.1)	44.8 (14.7)	47.9 (14.9)
GOLD grade, n	4182	6165	7955	2392
GOLD 1, n (%)	3 (<1)	19 (<1)	12 (<1)	10 (<1)
GOLD 2, n (%)	1206 (29)	2513 (41)	2729 (34)	990 (41)
GOLD 3, n (%)	2173 (52)	2809 (46)	3886 (49)	1096 (46)
GOLD 4, n (%)	800 (19)	824 (13)	1328 (17)	296 (12)
Exacerbation history, n	4183	6172	7960	2395

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<2 moderate and no severe exacerbations in the past year, n (%)	1258 (30)	1798 (29)	2301 (29)	755 (32)
≥2 moderate or ≥1 severe exacerbation in the past year, n (%)	2925 (70)	4374 (71)	5659 (71)	1640 (68)
≥1 severe exacerbation, n (%)	1274 (30)	1397 (23)	2120 (27)	551 (23)

FEV_1, forced expiratory volume in 1 second, GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; SD, standard deviation.

*Medication taken between date of screening -3 days and date of screening (inclusive).

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Table 3. Rates of on-treatment (95% CI) moderate/severe exacerbations in IMPACT by medication at study entry

Baseline medication*	FF/UMEC/VI	FF/VI	UMEC/VI
Overall	0.91 (0.87, 0.95)	1.07 (1.02, 1.12)	1.21 (1.14, 1.29)
ICS/LAMA/LABA	1.21 (1.13, 1.28)	1.43 (1.35, 1.53)	1.72 (1.58, 1.87)
ICS/LABA	0.70 (0.64, 0.77)	0.85 (0.78, 0.92)	0.94 (0.83, 1.06)
LAMA/LABA	0.84 (0.73, 0.98)	1.11 (0.95, 1.29)	1.05 (0.86, 1.29)
LAMA	0.65 (0.54, 0.78)	0.75 (0.64, 0.89)	0.61 (0.47, 0.80)

CI, confidence interval; FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; UMEC, umeclidinium; VI, vilanterol. Note: Medication classes are mutually exclusive. *Medication taken between date of screening -3 days and date of screening (inclusive).

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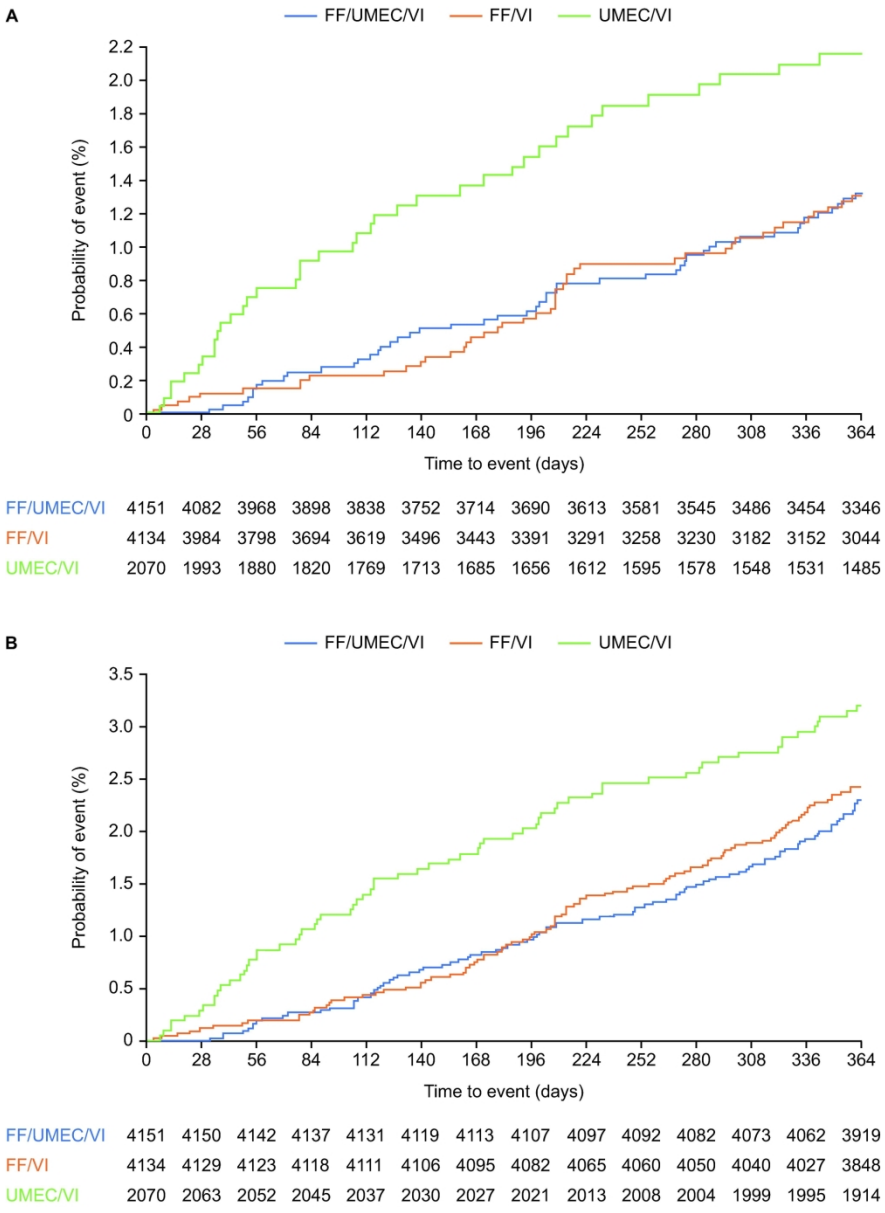

Figure 1. Kaplan–Meier plots of time to ACM for (A) on-treatment deaths and (B) on-/off-treatment deaths
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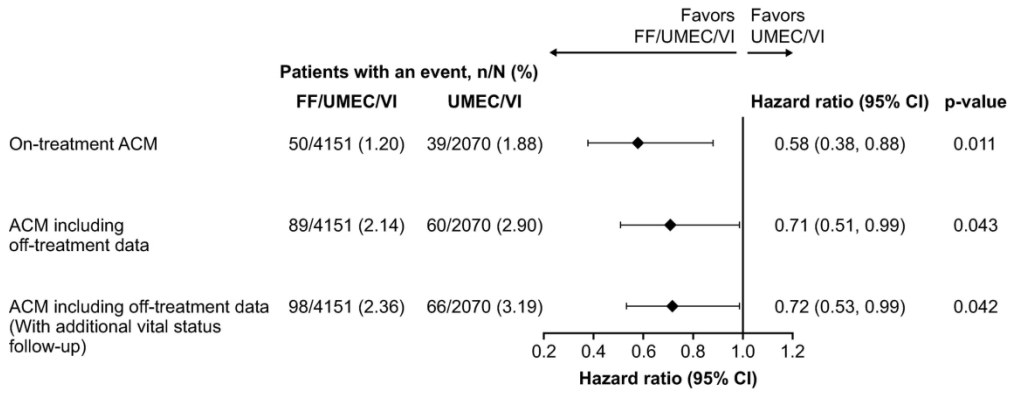

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ACM, all-cause mortality; CI, confidence interval; FF, fluticasone furoate; ICS, inhaled corticosteroid; UMEC, umeclidinium; VI, vilanterol.

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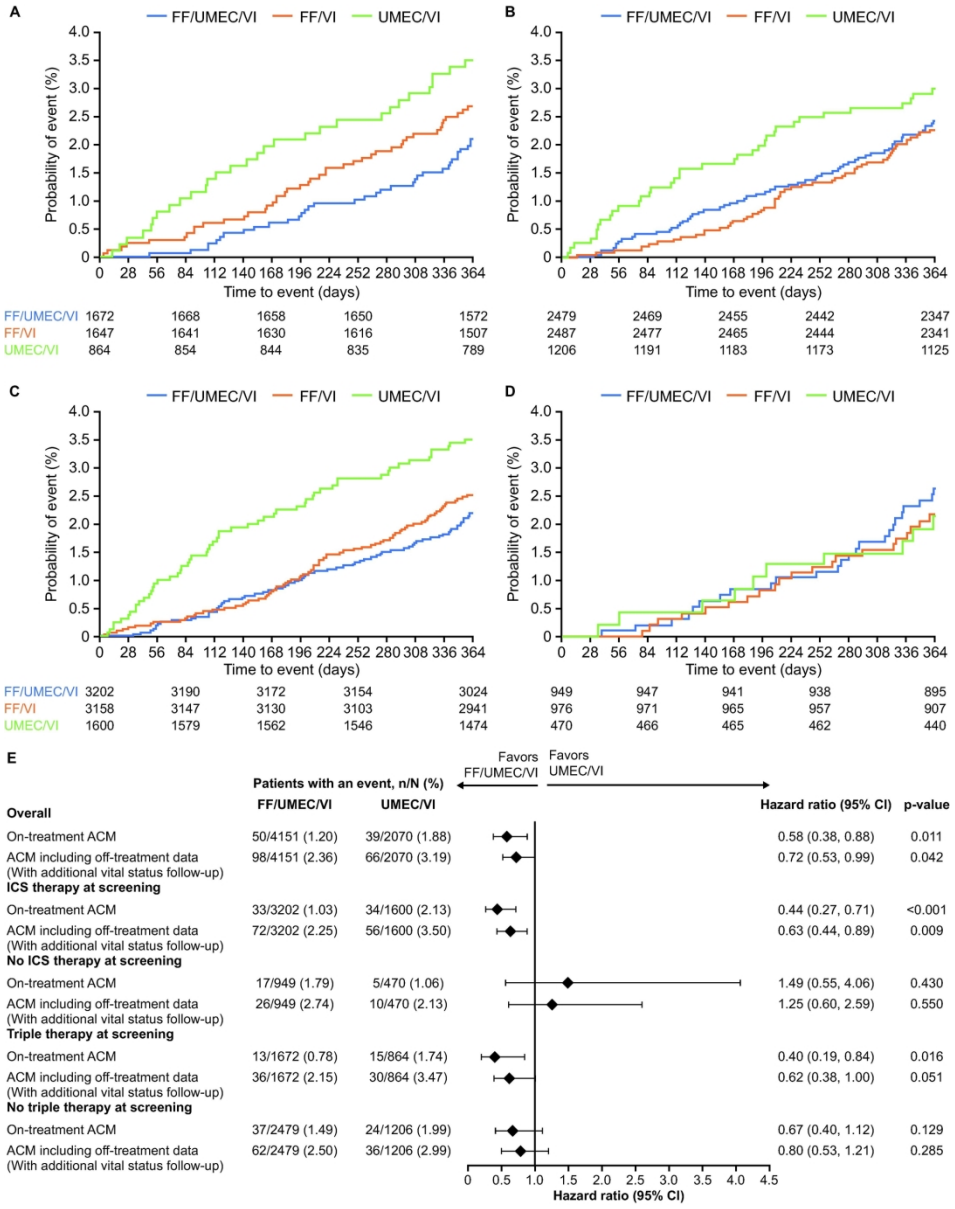

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A, B, C and D: Kaplan–Meier plots of ACM including off-treatment data (with additional vital status follow-up). ACM, all-cause mortality; FF, fluticasone furoate; ICS, inhaled corticosteroid; UMEC, umeclidinium; VI, vilanterol. *Medication taken between date of screening -3 days and date of screening (inclusive).

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Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in COPD patients

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Online Data Supplement

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Supplement Table E1. Summary of adjudicated deaths including off-treatment data

	FF/UMEC/VI (N=4151)		FF/VI (N=4134)		UMEC/VI (N=2070)	
	n (%)	**Rate [#]**	**n (%)**	**Rate [#]**	**n (%)**	**Rate [#]**
Total duration at risk (subject-years)	4088.3		4030.1		1999.3	
Primary cause of death						
Total	88 (2)	21.5 [88]	92 (2)	22.8 [92]	58 (3)	29.0 [58]
Cardiovascular	26 (<1)	6.4 [26]	31 (<1)	7.7 [31]	20 (<1)	10.0 [20]
Respiratory	25 (<1)	6.1 [25]	26 (<1)	6.5 [26]	18 (<1)	9.0 [18]
Cancer	13 (<1)	3.2 [13]	7 (<1)	1.7 [7]	6 (<1)	3.0 [6]
Unknown	14 (<1)	3.4 [14]	14 (<1)	3.5 [14]	11 (<1)	5.5 [11]
Other	10 (<1)	2.4 [10]	14 (<1)	3.5 [14]	3 (<1)	1.5 [3]
Death associated with COPD						
Yes	34 (<1)	8.3 [34]	36 (<1)	8.9 [36]	25 (1)	12.5 [25]
No	40 (<1)	9.8 [40]	37 (<1)	9.2 [37]	16 (<1)	8.0 [16]
Inadequate information	9 (<1)	2.2 [9]	14 (<1)	3.5 [14]	12 (<1)	6.0 [12]
Indeterminate	5 (<1)	1.2 [5]	5 (<1)	1.2 [5]	5 (<1)	2.5 [5]

COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol. Note: n = Number of subjects, # = Number of events, Rate

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is event rate per 1000 subject-years, calculated as the number of events x 1000, divided by the total duration at risk. Previously missing data were not re-adjudicated.

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Supplement Table E2. Summary of ACM including off-treatment data by COPD medication at study entry*

COPD medication	FF/UMEC/VI (N=4151)		FF/VI (N=4134)		UMEC/VI (N=2070)	
	n/N (%)	Rate [#]	n/N (%)	Rate [#]	n/N (%)	Rate [#]
ICS + LABA + LAMA	36/1672 (2.15)	0.0214	49/1647 (2.98)	0.0297	30/864 (3.47)	0.0351
ICS + LABA without LAMA	29/1354 (2.14)	0.0213	30/1340 (2.24)	0.0222	22/647 (3.40)	0.0343
LAMA + LABA without ICS	12/389 (3.08)	0.0307	10/349 (2.87)	0.0288	3/196 (1.53)	0.0153
ICS + LAMA without LABA	1/47 (2.13)	0.0211	0/40		0/20	
LAMA without LABA or ICS	6/304 (1.97)	0.0195	6/365 (1.64)	0.0164	3/162 (1.85)	0.0185
ICS without LABA or LAMA	6/129 (4.65)	0.0462	6/131 (4.58)	0.0459	4/69 (5.8)	0.0592
LABA without ICS or LAMA	3/118 (2.54)	0.0251	1/119 (0.84)	0.0083	4/54 (7.41)	0.0755
No ICS, LABA or LAMA	5/138 (3.62)	0.0363	7/143 (4.90)	0.0490	0/58	

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ACM, all-cause mortality; FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; UMEC, umeclidinium; VI, vilanterol. Note: Data in the table include additional vital status follow-up.

*Medication taken between date of screening -3 days and date of screening (inclusive).

n: number of subjects with event; N: number of subjects in subgroup. Rate is event rate per subject-year, calculated as the number of events divided by the total duration at risk.

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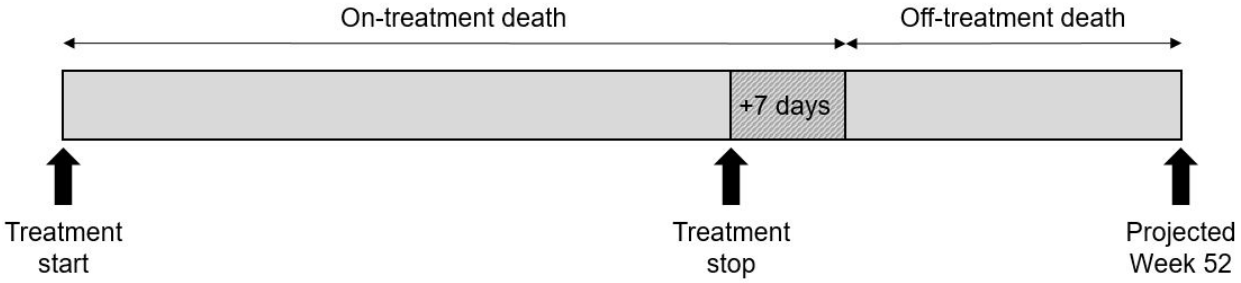
Supplement Figures

Supplement Figure E1. Definitions of on- and off-treatment deaths



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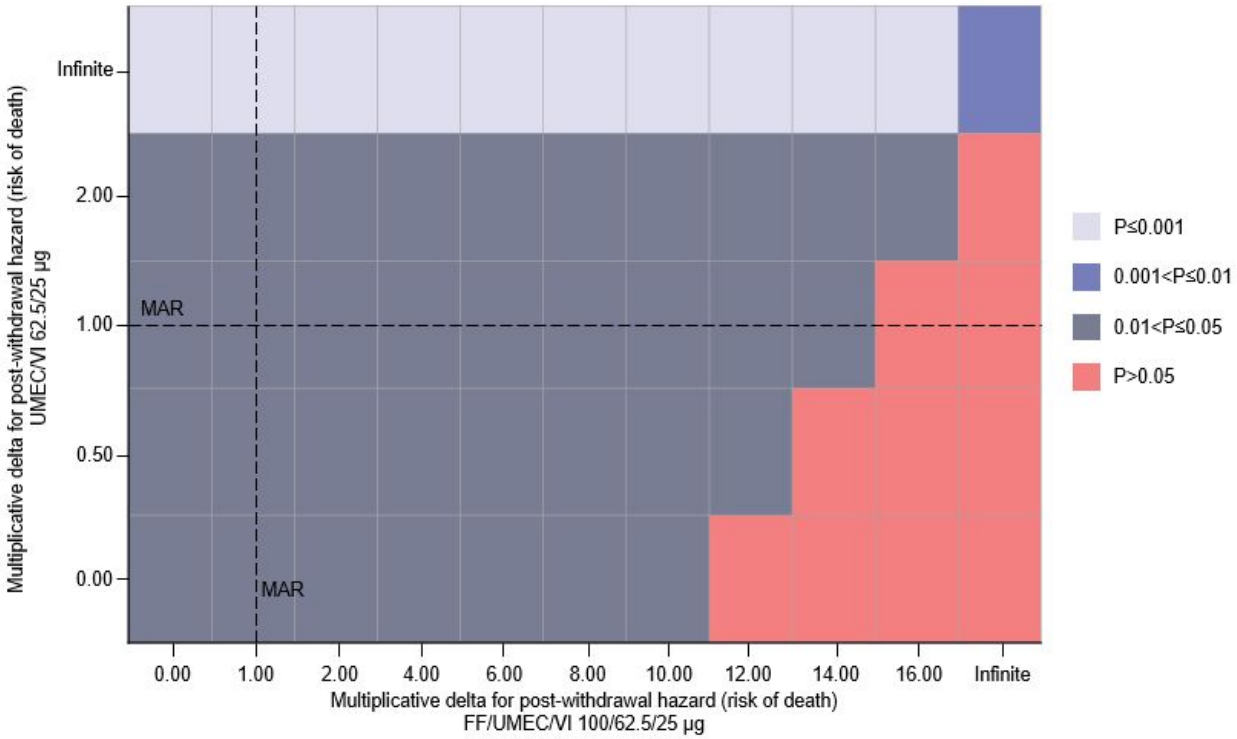
Supplement Figure E2. Tipping point analyses of ACM including off-treatment data for FF/UMEC/VI versus UMEC/VI. A: Analysis with imputation P-value for hazard ratio; B: Analysis with imputation hazard ratio and P-value; C: Analysis with imputation odds ratio and P-value

A



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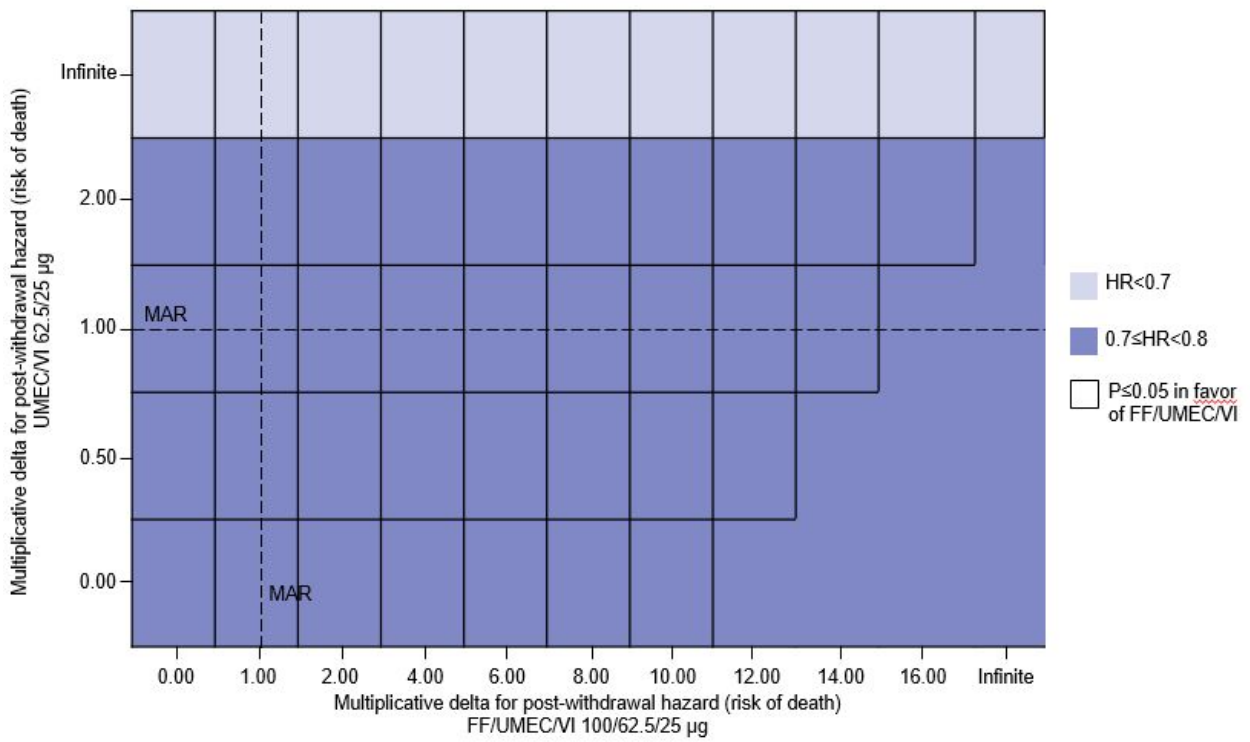

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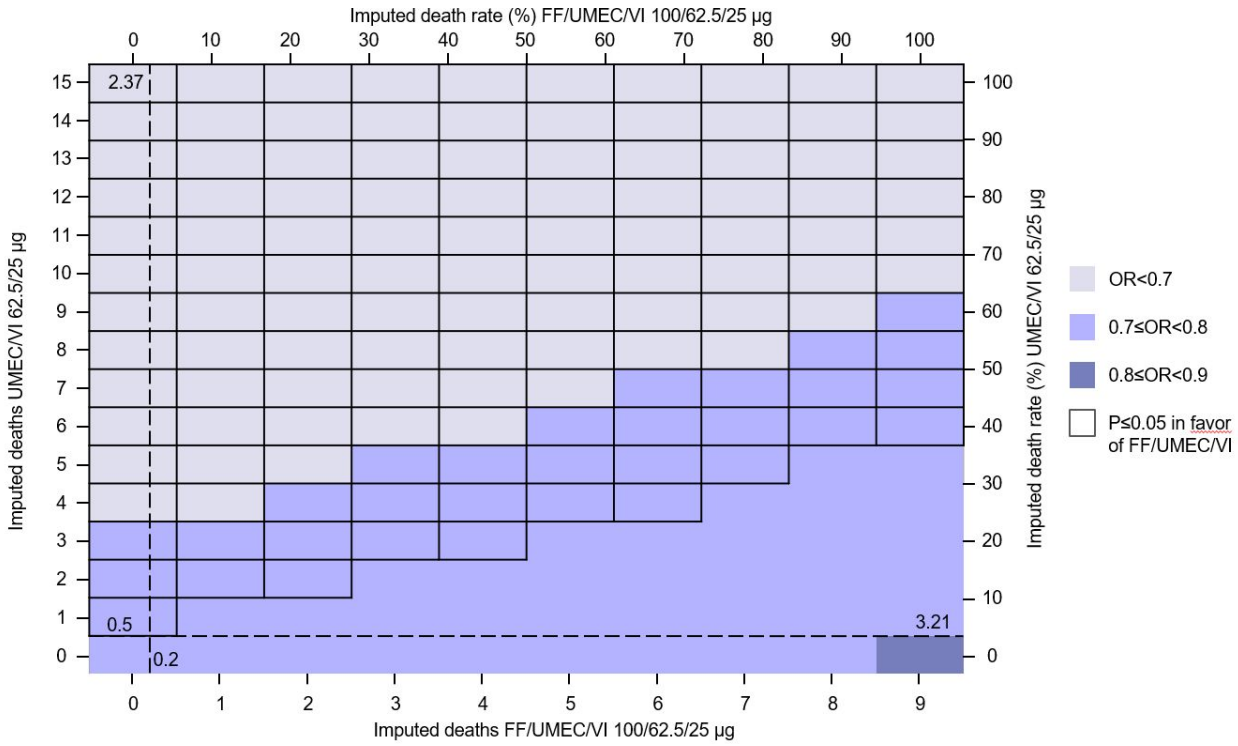
C



A. If all patients on UMEC/VI with censored data are imputed as alive at the end of 52 weeks the post-withdrawal hazard for FF/UMEC/VI would need to be approximately 10 times higher than the pre-withdrawal hazard before losing statistical significance. If the patients on UMEC/VI with censored data are assumed to have a post-withdrawal hazard the same as the pre-withdrawal hazard (i.e., it is assumed that the missing data for UMEC/VI is missing at random) then the post-withdrawal hazard for FF/UMEC/VI would need to be approximately 14 times higher than the pre-withdrawal hazard before losing statistical significance. **B.** Regardless of the assumption made about the post-withdrawal hazard for either treatment arm, there is at least a 20% reduction in the risk of death (HR<0.80) on FF/UMEC/VI compared with UMEC/VI. **C.** Regardless of the number of patients with missing survival status that we impute as dead or alive on either treatment, the OR is always <0.81 (i.e. the odds of dying is at least 19% lower on

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FF/UMEC/VI compared with UMEC/VI [OR=0.803 for all patients on UMEC/VI with censored data imputed as alive and all patients on FF/UMEC/VI with censored data imputed as dead]).

A and **B.** Reference line denotes expected number of deaths under a MAR assumption, i.e. that the hazard for the imputed period is the same as the hazard seen in the observed data. **C.** Reference line denotes expected number of deaths under a missing at random assumption, i.e. that deaths occur at the same rate for patients with a missing survival status at Day 356 as those with a known survival status.
FF, fluticasone furoate; HR, hazard ratio; MAR, missing at random; OR, odds ratio; UMEC, umeclidinium; VI, vilanterol.

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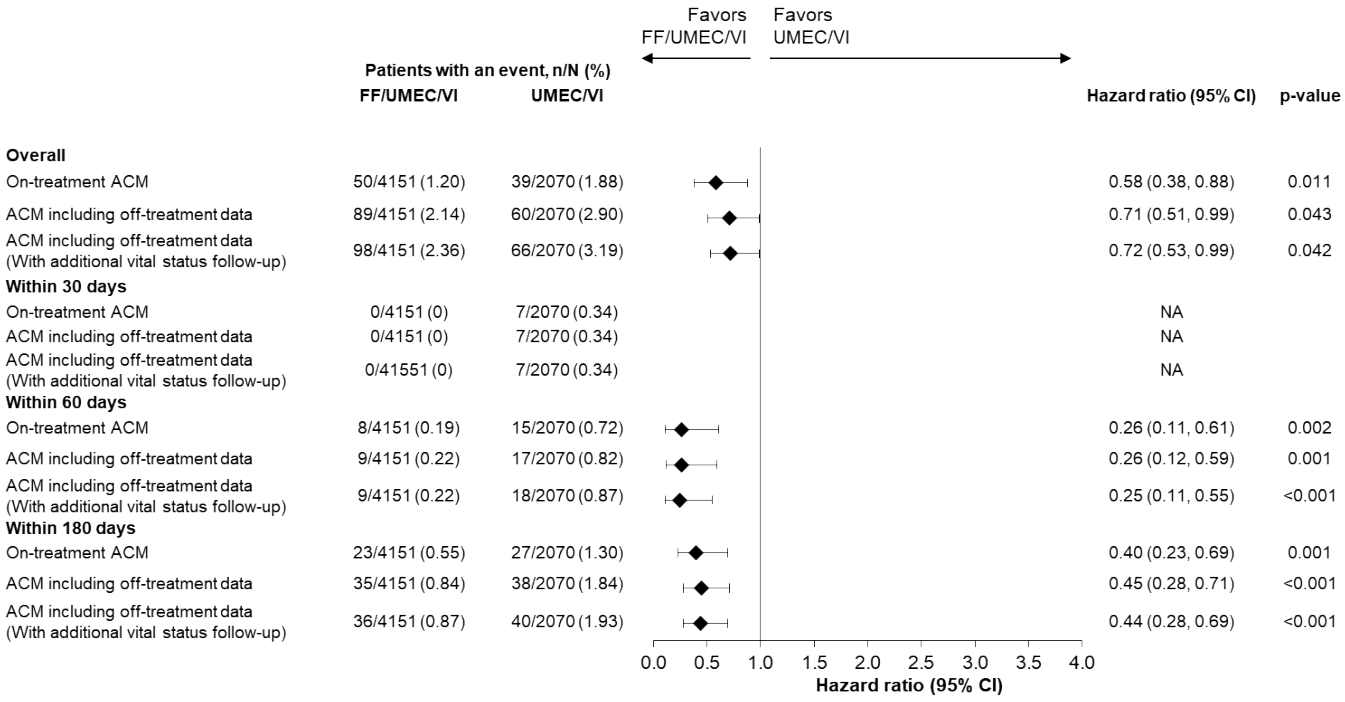
Supplement Figure E3. Forest plot of ACM by time interval for FF/UMEC/VI versus UMEC/VI



ACM, all-cause mortality; CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol. Note: Analysis was not performed if there were zero events in one or more of the three treatment arms (FF/UMEC/VI, FF/VI or UMEC/VI).

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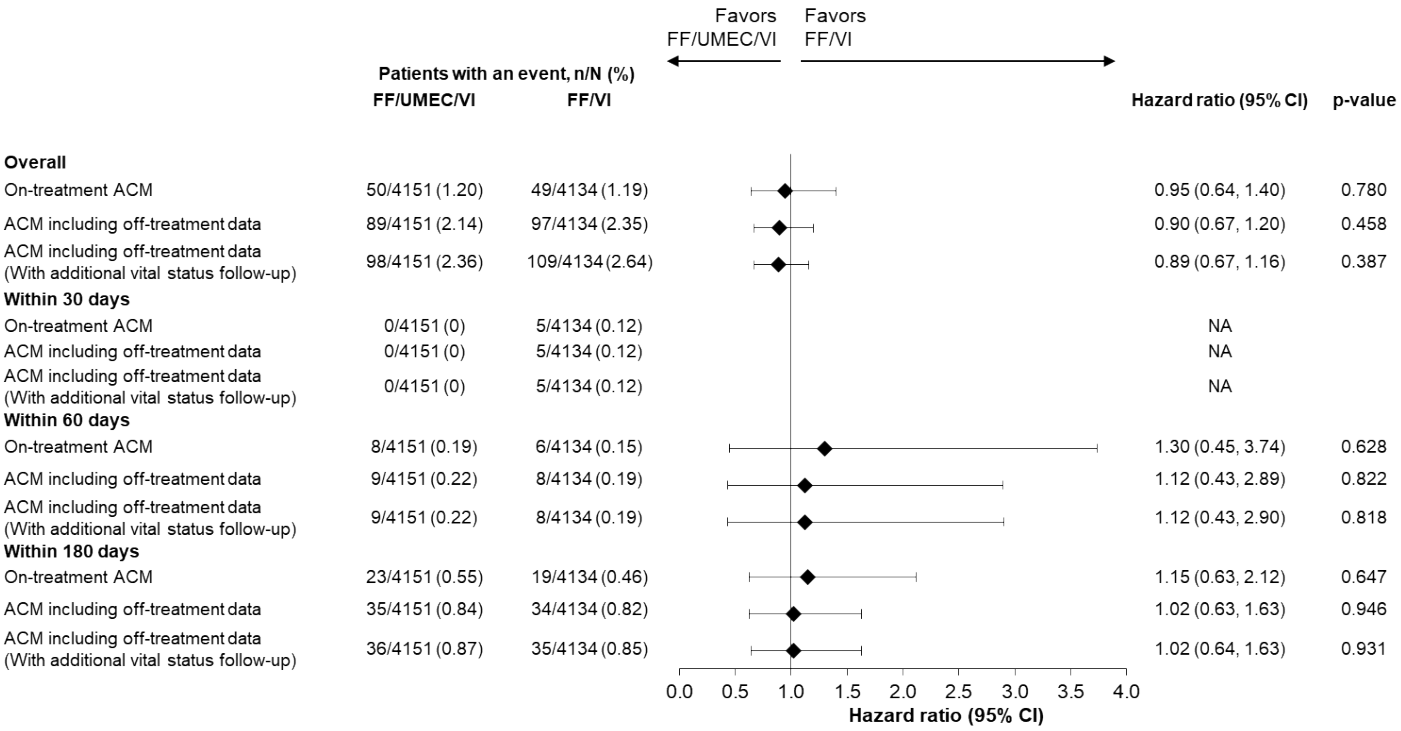
Supplement Figure E4. Forest plot of ACM by time interval for FF/UMEC/VI versus FF/VI



ACM, all-cause mortality; CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol. Note: Analysis was not performed if there were zero events in one or more of the three treatment arms (FF/UMEC/VI, FF/VI or UMEC/VI).

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