Reduction in the Risk of All-Cause Mortality With Fluticasone Furoate/Umeclidinium/Vilanterol Compared to Umeclidinium/Vilanterol in IMPACT Including Previously Missing or Censored Vital Status Data

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Introduction

- Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality worldwide and is projected to be the fourth leading cause of death by 2030.[1,2] The increase in mortality due to COPD over recent years has been driven by several factors including the lack of effective therapies that impact mortality.[2]
- The recent InforMing the PAthway of COPD Treatment (IMPACT) study demonstrated that once-daily single-inhaler triple therapy with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) resulted in a lower rate of moderate/severe exacerbations and improved lung function and health-related quality of life compared with dual therapy with FF/VI (inhaled corticosteroids [ICS]/long-acting β_2-agonist [LABA]) or UMEC/VI (long-acting muscarinic antagonist [LAMA]/LABA) in patients with symptomatic COPD and a history of exacerbations.[3]
- Pre-specified analyses from the IMPACT trial demonstrated a statistically significant and clinically relevant reduction for FF/UMEC/VI versus UMEC/VI in the risk of on-treatment all-cause mortality (42.1% [*P*=0.011]) and all-cause mortality including off-treatment data (28.6% [*P*=0.043]).[3]
- However, 574 (5.5%) patients were censored from the original pre-specified analysis including off-treatment data due to incomplete vital status information at Week 52, suggesting that the observed reduction in the risk all-cause mortality may be fragile. These post hoc analyses of IMPACT evaluated all-cause mortality following the collection of additional vital status data.

Methods

- IMPACT (GSK study CTT116855; NCT02164513) was a Phase III, double-blind, parallel-group, 52-week, multicenter study in patients ≥40 years of age with symptomatic COPD and ≥1 moderate/severe exacerbation in the prior year. Patients were randomized 2:2:1 to single-inhaler triple therapy with FF/UMEC/VI 100/62.5/25 mcg, or dual therapy with FF/VI 100/25 mcg or UMEC/VI 62.5/25 mcg, all once-daily via the ELLIPTA inhaler.[3]
- The primary study endpoint was the annual rate of on-treatment moderate/severe exacerbations. Other pre-specified efficacy endpoints included time to on-treatment all-cause mortality and all-cause mortality including off-treatment data.
- On- and off-treatment deaths were defined as those which occurred between study treatment start date and the latest of: the last day of treatment + 7 days, or the projected Week 52 date + 7 days (inclusive). Deaths were based on the actual date of death rather than the start date of an event that had a fatal outcome. Additional vital status data were collected post hoc.
- Using these additional vital status data, this post hoc analysis evaluated time to all-cause mortality using a Cox proportional hazards model with covariates of treatment group, age and gender for FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI. Hazard ratios (HR) and 95% confidence intervals (CI) are reported.
- Sensitivity analyses were performed using a tipping point approach, imputing post-withdrawal hazards for patients censored prior to the end of the study.

Results

Patients

- Baseline demographic and clinical characteristics for the intent-to-treat (ITT) population are presented in **Table 1**.
- Collection of additional vital status data provided data for 99.6% of the study population (42 censored patients) and resulted in available data for an additional 27 off-treatment deaths, which are included in the all-cause mortality analyses presented here. In this additional collection of vital status data, 505 patients were found to be alive at the end of the 52-week period.

Time to all-cause mortality including additional vital status data

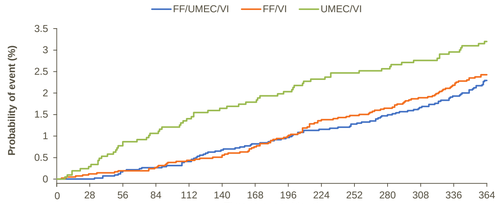
- The on-treatment findings in the original pre-specified analysis of the IMPACT study[3] were not affected by the additional post hoc data collection and subsequent analyses.
- When including off-treatment data, there were 98 deaths (2.4%) with FF/UMEC/VI, 109 (2.6%) with FF/VI and 66 (3.2%) with UMEC/VI.
  - For patients randomized to FF/UMEC/VI, the risk of dying was reduced by 11.3% (HR: 0.89 [95% CI: 0.67, 1.16]; *P*=0.387) compared with FF/VI, and by 27.7% (HR: 0.72 [95% CI: 0.53, 0.99]; *P*=0.042) compared with UMEC/VI (Kaplan–Meier plot: **Figure 1**).
- The post hoc findings including off-treatment data for time to all-cause mortality were consistent with the pre-specified analysis results (**Figure 2**).

Table 1. Baseline characteristics (ITT population)

	FF/UMEC/VI (N=4151)	FF/VI (N=4134)	UMEC/VI (N=2070)
Age, mean (SD) years	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)
Gender, % male	67	66	66
BMI, mean (SD) kg/m²	26.6 (6.2)	26.7 (6.1)	26.6 (5.9)
Smoking status, n (%)			
Former smoker	2715 (65)	2711 (66)	1342 (65)
Current smoker	1436 (35)	1423 (34)	728 (35)
Exacerbation history in prior 12 months, n (%)			
≥2 moderate exacerbations	1967 (47)	1921 (46)	989 (48)
≥1 severe exacerbation	1087 (26)	1069 (26)	515 (25)
Post-bronchodilator FEV_1 % predicted, mean (SD)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)
CV risk factor,* n (%)			
0	1365 (33)	1322 (32)	656 (32)
1	1147 (28)	1158 (28)	580 (28)
≥2	1639 (39)	1654 (40)	834 (40)

*Includes past or current medical conditions recorded at screening. CV risk factors include hypertension, hypercholesterolemia, diabetes mellitus, coronary artery disease, arrhythmia, angina pectoris, myocardial infarction, congestive heart failure, cerebrovascular accident and vascular disease (carotid or aorto-femoral).
BMI, body mass index; CV, cardiovascular; SD, standard deviation

Figure 1. Kaplan–Meier plot of time to all-cause mortality including off-treatment data (with additional vital status follow-up)



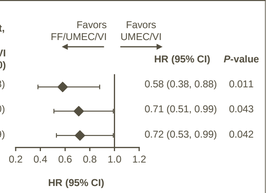
Number of patients at risk														
FF/UMEC/VI	4151	4150	4142	4137	4131	4119	4113	4107	4097	4092	4082	4073	4062	3919
FF/VI	4134	4129	4123	4118	4111	4106	4095	4082	4065	4060	4050	4040	4027	3848
UMEC/VI	2070	2063	2052	2045	2037	2030	2027	2021	2013	2008	2004	1999	1995	1914

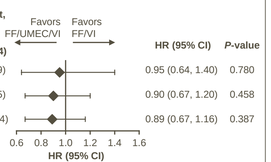
Post hoc analysis

Sensitivity analyses of all-cause mortality including additional vital status data

- At Week 52, complete vital status data was missing for 42 patients.
- Tipping-point analyses show that if all missing patients on UMEC/VI were imputed as alive at Week 52 (ie, their pre-withdrawal hazard is multiplied by 0 [0.00 on Figure 3 y-axis]), the post-withdrawal hazard for FF/UMEC/VI would need to be approximately 10 times higher than the pre-withdrawal hazard before statistical significance is lost for the reduction in the risk of death with FF/UMEC/VI versus UMEC/VI (**Figure 3**).
- If missing post-withdrawal hazards are assumed to be the same as the pre-withdrawal hazard for UMEC/VI (1.00 on Figure 3 y-axis), the post-withdrawal hazard for FF/UMEC/VI would need to be approximately 14 times higher than the pre-withdrawal hazard before statistical significance is lost (**Figure 3**).
- Regardless of the assumption made about the post-withdrawal hazard for either treatment arm, at least a 20% reduction in the risk of death (hazard ratio <0.8) was observed in patients treated with FF/UMEC/VI versus UMEC/VI (**Figure 4**).
- These results are supportive of the main analyses.

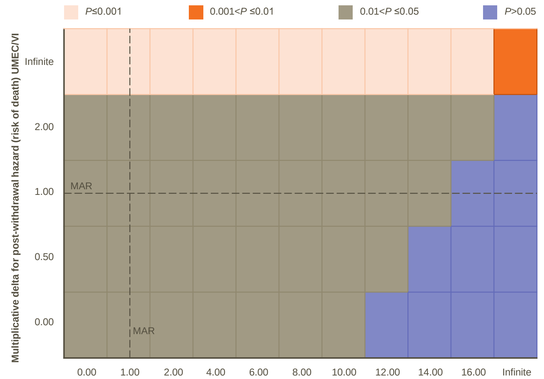
Figure 2. Pre-specified and post hoc analyses of all-cause mortality for (A) FF/UMEC/VI versus UMEC/VI and (B) FF/UMEC/VI versus FF/VI





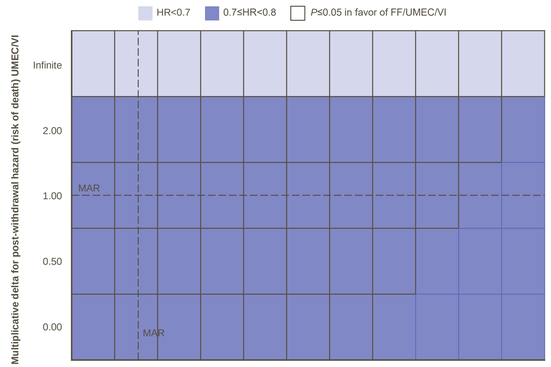
*Post hoc analysis

Figure 3. Sensitivity analysis: Tipping point heat plot of all-cause mortality including off-treatment data with imputation *P*-value for hazard ratio (FF/UMEC/VI vs UMEC/VI)



The dotted reference line denotes the expected number of deaths under a missing at random (MAR) assumption, ie, that the hazard for the imputed period is the same as the hazard seen in the observed data.

Figure 4. Sensitivity analysis: Tipping point heat plot of all-cause mortality including off-treatment data with imputation hazard ratio and *P*-value (FF/UMEC/VI vs UMEC/VI)



The dotted reference line denotes the expected number of deaths under a missing at random (MAR) assumption, ie, that the hazard for the imputed period is the same as the hazard seen in the observed data.

Conclusions

- Once-daily single-inhaler triple therapy with FF/UMEC/VI reduced the risk of all-cause mortality compared with UMEC/VI in a large patient population with symptomatic COPD and a history of exacerbations.
- The results from these post hoc analyses of the IMPACT study, which include additional vital status data, are consistent with pre-specified analyses and confirm the robustness of the originally reported findings.

References

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Disclosures

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- DALi, NCD, CEJ, SK, PM, DM, and ANM are employees of GSK and hold stocks and shares in GSK. SJP was a GSK employee at the time of the study and holds stocks and shares in GSK. GC has received personal fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, CSA Medical, Eolo, GSK, HGE Technologies, Novartis, Nuvaira, Olympus, Pulmonx, and Verona. MTD has received personal fees from AstraZeneca, GSK, and Mereo, and contracted clinical trial support from AstraZeneca, Boehringer Ingelheim, and GSK. DMGH has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, and Pfizer. MKH has received personal fees from and has consulted for AstraZeneca, Boehringer Ingelheim, and GSK, and research support from Novartis and Sunovion. PL has received personal fees and research grants from GSK, and personal fees from AstraZeneca, Boehringer Ingelheim, and Chiesi. DALo has received personal fees and grant income from GSK. FJM has taken part in advisory boards for AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Sunovion, and Teva, steering committees for AstraZeneca and GSK, DSMB for Genentech/Roche, and GSK and has been an advisor for ProTerrix Bio. DS has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, Glenmark, GSK, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Theravance, and Verona. RAW has been a consultant for AstraZeneca, Boehringer Ingelheim, Contrafect, GSK, Novartis and Merck, has received research grants from AstraZeneca, Boehringer Ingelheim, and GSK, and has taken part in advisory boards for Mylan/Theravance, Propeller Health, Sunovion, and Verona.
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