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All-cause Mortality by Subgroup in Patients With Chronic Obstructive Pulmonary Disease: Post Hoc Analysis of the IMPACT Trial

Mammen MJ[1], Carr TF[2], Criner GJ[3], Dransfield MT[4], Halpin DMG[5], Han MK[6], Jain RG[7], Kaul V[8,9], Kaye MG[10], Kraft M[2], Mapel D[11], Midwinter D[12], Scanlon PD[13], Singh D[14], Wells JM[4], Wise R[15], Lipson DA[16,17]

[1]Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA; [2]Department of Medicine and Asthma and Airway Disease Research Center, University of Arizona College of Medicine, Tucson, AZ, USA; [3]Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA; [4]Division of Pulmonary, Allergy, and Critical Care Medicine, Lung Health Center, University of Alabama at Birmingham, Birmingham, AL, USA; [5]University of Exeter Medical School, University of Exeter, Exeter, UK; [6]University of Michigan, Pulmonary & Critical Care, Ann Arbor, MI, USA; [7]GSK, Research Triangle Park, NC, USA; [8]State University of New York Upstate Medical, Syracuse, NY, USA; [9]Crouse Health, Syracuse, NY, USA; [10]Minnesota Lung Center, Minneapolis, MN, USA; [11]University of New Mexico College of Pharmacy, Albuquerque, NM, USA; [12]GSK, Brentford, UK; [13]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA; [14]University of Manchester, Manchester University NHS Foundation Trust, Manchester, UK; [15]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [16]GSK, Collegeville, PA, USA; [17]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Recording by Manoj J Mammen

IMPACT TRIAL

American Thoracic Society
Annual Meeting 2021
May 14–19, 2021

DISCLOSURES

- This study was funded by GlaxoSmithKline (GSK; CTT116855; NCT02164513).
- On behalf of all authors, an audio recording of this poster was prepared by Manoj J Mammen, who did not receive any payment for this recording.
- The presenting author, Manoj J Mammen declares no real or perceived conflicts of interest during the last 24 months in relation to this presentation.
- Editorial support (in the form of writing assistance, including preparation of the initial draft under the direction and guidance of the authors, collating and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing, and referencing) was provided by Eloise Morecroft, PhD, of Fishawack Indicia Ltd, UK, part of Fishawack Health, and was funded by GSK.

Objectives

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- COPD is a leading cause of death worldwide; various factors including smoking history, patient age, FEV_1, comorbidities, exacerbations, and BMI have all been investigated as predictive factors of COPD-related mortality.[1,2]
- A post hoc analysis of the IMPACT trial demonstrated a significant 28% reduction in the risk of on-/off-treatment ACM risk with FF/UMEC/VI versus UMEC/VI in patients with symptomatic COPD and a history of exacerbations.[3]
- To identify whether this mortality benefit finding was associated with specific patient characteristics, the time to on-/off- treatment ACM by patient subgroups was investigated.

ACM, all-cause mortality; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol

1. GOLD report 2021. Available at: https://goldcopd.org/gold-reports/. Accessed March 15, 2021; 2. Soler-Cataluña JJ, et al. Thorax 2005;60:925–31; 3. Lipson DA, et al. Am J Respir Crit Care Med 2020;201:1508–16. Mammen MJ, et al. All-cause Mortality by Subgroup in Patients With Chronic Obstructive Pulmonary Disease:Post Hoc Analysis of the IMPACT Trial.

Methods

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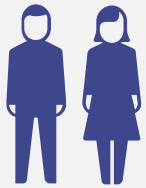
Study[1]

Randomized | Double-blind | Multicenter

Phase III

(CTT116855 [NCT02164513])

Patients[1]



- ≥40 years of age
- Symptomatic COPD: CAT score ≥10 at screening
- FEV_1 <50% predicted at screening and ≥1 moderate/severe exacerbation in prior 12 months

OR

- FEV_1 50–<80% at screening and ≥2 moderate or ≥1 severe exacerbation in prior 12 months

Treatments[1]

2 : 2 : 1 randomization
FF/UMEC/VI : FF/VI : UMEC/VI

FF/UMEC/VI Once daily		**Fluticasone furoate 100 mcg** **Umeclidinium 62.5 mcg** **Vilanterol 25 mcg**
FF/VI Once daily		**Fluticasone furoate 100 mcg** **Vilanterol 25 mcg**
UMEC/VI Once daily		**Umeclidinium 62.5 mcg** **Vilanterol 25 mcg**

 **52 weeks**

Post hoc analysis

Time to on-/off-treatment ACM for FF/UMEC/VI versus UMEC/VI including additional vital status data

- Analyzed using a Cox proportional hazards model with covariates of treatment group, age (at screening), and sex
- On-/off-treatment deaths were defined as those occurring between study treatment start date and the latest of study treatment stop date or projected Week 52 date (based on treatment start date) +7 days, inclusive

Subgroup analyses conducted for:

- **Pneumonia history**
- **CV risk factors** (0, 1, ≥2)
- **Smoking status**
- **Age** (<65 years, ≥65 years)
- **Sex**
- **BMI** (<25 kg/m^3, ≥25 kg/m^3)
- **Race**
- **Geographical region**
- **Exacerbation history in the prior year*** (<2 moderate/severe; ≥2 moderate/severe)

- The ITT population comprised 10,355 patients (FF/UMEC/VI, n=4151; FF/VI n=4134; UMEC/VI, n=2070); vital status at Week 52 was obtained for 99.6% of the ITT population.

*Moderate exacerbation, any exacerbation requiring antibiotics and/or oral/systemic corticosteroids; severe exacerbation, any exacerbation leading to hospitalization or death.
ACM, all-cause mortality; BMI, body mass index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disorder; CV, cardiovascular; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ITT, intent-to-treat; UMEC, umeclidinium; VI, vilanterol

1. Lipson DA, et al. N Engl J Med 2018;378:1671–80.
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Baseline characteristics and demographics were similar between the treatment groups (ITT population)

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	FF/UMEC/VI (N=4151)	FF/VI (N=4134)	UMEC/VI (N=2070)	Total (N=10,355)
Sex (male), n (%)	2766 (67)	2748 (66)	1356 (66)	6870 (66)
Age, years, mean (SD)	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)	65.3 (8.3)
BMI*, mean (SD) kg/m²	26.6 (6.2)	26.7 (6.1)	26.6 (5.9)	26.6 (6.1)
Race†, n (%)				
White	3231 (78)	3224 (78)	1628 (79)	8083 (78)
Asian	668 (16)	676 (16)	335 (16)	1679 (16)
Black or African American	122 (3)	99 (2)	43 (2)	264 (3)
Other	130 (3)	134 (3)	64 (3)	328 (3)
Geographical region, n (%)				
Western Europe	1252 (30)	1274 (31)	638 (31)	3164 (31)
Eastern Europe	282 (7)	270 (7)	133 (6)	685 (7)
Asia	654 (16)	660 (16)	330 (16)	1644 (16)
North America	1071 (26)	1046 (25)	522 (25)	2639 (25)
South America	684 (16)	680 (16)	344 (17)	1708 (16)
Other	208 (5)	204 (5)	103 (5)	515 (5)

*FF/UMEC/VI, n=4148; FF/VI, n=4134; UMEC/VI, n=2070; total, n=10,352; †FF/UMEC/VI, n=4151; FF/VI, n=4133; UMEC/VI, n=2070; total, n=10,354.
FF, fluticasone furoate; ITT, intent-to-treat; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol
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	FF/UMEC/VI (N=4151)	FF/VI (N=4134)	UMEC/VI (N=2070)	Total (N=10,355)
Exacerbation history in prior 12 months, n (%)				
<2 moderate/severe exacerbations	1855 (45)	1912 (46)	933 (45)	4700 (45)
≥2 moderate/severe exacerbation	2296 (55)	2222 (54)	1137 (55)	5655 (55)
CV risk factors*, n (%)				
0	1365 (33)	1322 (32)	656 (32)	3343 (32)
1	1147 (28)	1158 (28)	580 (28)	2885 (28)
≥2	1639 (39)	1654 (40)	834 (40)	4127 (40)
Smoking status, n (%)				
Former smoker	2715 (65)	2711 (66)	1342 (65)	6768 (65)
Current smoker	1436 (35)	1423 (34)	728 (35)	3587 (35)
Past history of pneumonia†, n (%)	916 (22)	951 (23)	476 (23)	2343 (23)
Post-bronchodilator FEV_1 % predicted‡, mean (SD)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)	45.5 (14.8)

*CV risk factors included past or current history of: angina pectoris; coronary artery disease; myocardial infarction; arrhythmia; congestive heart failure; hypertension; cerebrovascular accident; carotid or aorto-femoral vascular disease; diabetes mellitus; hypercholesterolemia; †any history of pneumonia; ‡FF/UMEC/VI, n=4145; FF/VI, n=4133; UMEC/VI, n=2069; total, n=10,347.
CV, cardiovascular; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ITT, intent-to-treat; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol
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The mortality reduction with FF/UMEC/VI versus UMEC/VI was generally consistent across all subgroups

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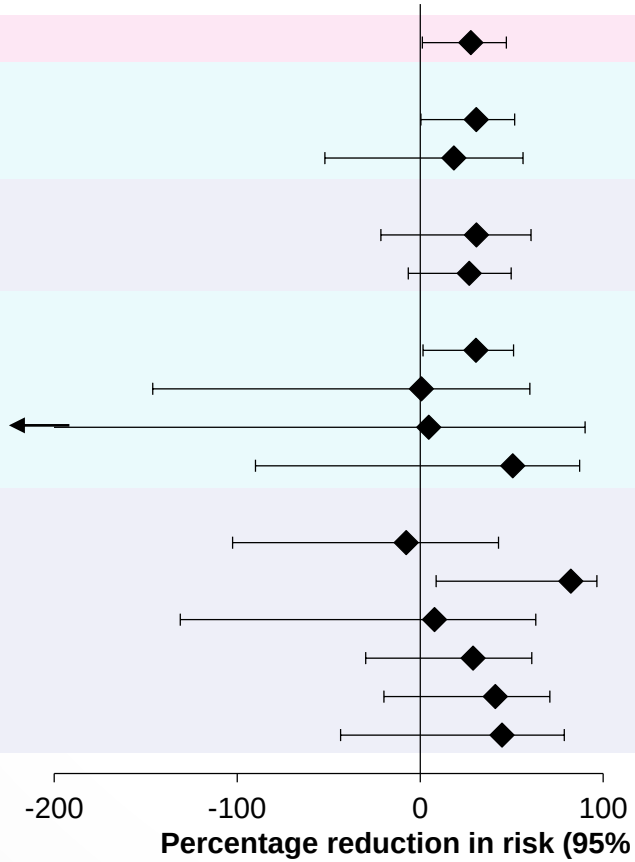
- FF/UMEC/VI demonstrated a significant reduced risk of on-/off-treatment ACM compared with UMEC/VI in some subgroups.



	Reduction in risk, % (95% CI), *P*-value	FF/UMEC/VI (N=4151)	UMEC/VI (N=2070)
		Number (%) of patients with event	
Overall (N=6221)	27.7 (1.2, 47.1), 0.042	98 (2.36)	66 (3.19)
Sex			
Male (n=4122)	30.6 (0.4, 51.6), 0.047	72 (2.60)	50 (3.69)
Female (n=2099)	18.4 (-52.1, 56.2), 0.522	26 (1.88)	16 (2.24)
Age group			
<65 years (n=2848)	30.7 (-21.5, 60.5), 0.200	29 (1.54)	21 (2.18)
≥65 years (n=3373)	26.8 (-6.5, 49.7), 0.103	69 (3.05)	45 (4.06)
Race			
White (n=4859)	30.5 (1.5, 51.0), 0.041	76 (2.35)	54 (3.32)
Asian (n=1003)	0.6 (-146.2, 59.9), 0.989	14 (2.10)	7 (2.09)
Black or African American (n=165)	4.7 (-816.4, 90.1), 0.966	3 (2.46)	1 (2.33)
Other (n=194)	50.6 (-90.0, 87.1), 0.305	5 (3.85)	4 (6.25)
Geographical region			
Western Europe (n=1890)	-7.7 (-102.5, 42.8), 0.819	31 (2.48)	14 (2.19)
Eastern Europe (n=415)	82.3 (8.7, 96.6), 0.039	2 (0.71)	5 (3.76)
Asia (n=984)	7.8 (-131.1, 63.2), 0.862	13 (1.99)	7 (2.12)
North America (n=1593)	28.9 (-29.8, 61.0), 0.267	26 (2.43)	18 (3.45)
South America (n=1028)	41.0 (-19.8, 70.9), 0.144	17 (2.49)	14 (4.07)
Other (n=311)	44.7 (-43.5, 78.7), 0.223	9 (4.33)	8 (7.77)

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

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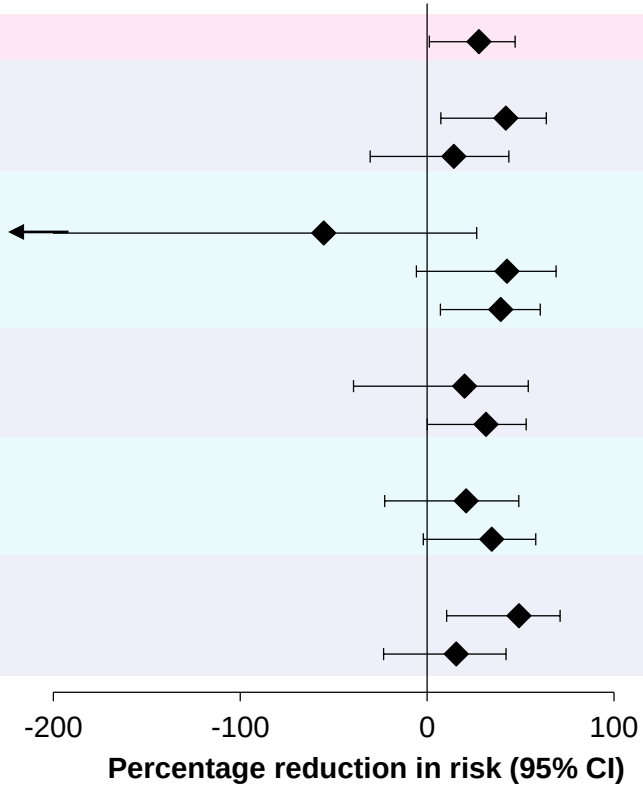

	Reduction in risk, % (95% CI), *P*-value	FF/UMEC/VI (N=4151)	UMEC/VI (N=2070)
		Number (%) of patients with event	
Overall (N=6221)	27.7 (1.2, 47.1), 0.042	98 (2.36)	66 (3.19)
Exacerbation history, prior year*			
<2 Moderate/Severe (n=2788)	42.1 (7.3, 63.8), 0.023	38 (2.05)	32 (3.43)
≥2 Moderate/Severe (n=3433)	14.3 (-30.5, 43.7), 0.472	60 (2.61)	34 (2.99)
CV risk factors†			
No risk factors (n=2021)	-55.3 (-228.1, 26.5), 0.249	29 (2.12)	9 (1.37)
1 risk factor (n=1727)	42.7 (-5.8, 69.0), 0.075	22 (1.92)	19 (3.28)
≥2 risk factors (n=2473)	39.4 (7.1, 60.5), 0.022	47 (2.87)	38 (4.56)
Smoking status			
Current smoker (n=2164)	20.0 (-39.4, 54.1), 0.431	33 (2.30)	20 (2.75)
Former smoker (n=4057)	31.5 (0.1, 53.0), 0.050	65 (2.39)	46 (3.43)
BMI			
<25 kg/m^2 (n=2758)	20.9 (-22.7, 49.0), 0.296	53 (2.86)	32 (3.55)
≥25 kg/m^2 (n=3460)	34.6 (-2.1, 58.1), 0.062	45 (1.96)	34 (2.91)
Pneumonia history‡			
Past history of pneumonia (n=1392)	49.1 (10.4, 71.1), 0.019	24 (2.62)	24 (5.04)
No past history of pneumonia (n=4819)	15.6 (-23.3, 42.2), 0.382	74 (2.29)	42 (2.64)

*Moderate exacerbation, any exacerbation requiring antibiotics and/or oral/systemic corticosteroids; severe exacerbation, any exacerbation leading to hospitalization or death; †CV risk factors included past or current history of: angina pectoris; coronary artery disease; myocardial infarction; arrhythmia; congestive heart failure; hypertension; cerebrovascular accident; carotid or aorto-femoral vascular disease; diabetes mellitus; hypercholesterolemia; ‡any history of pneumonia. ACM, all-cause mortality; BMI, body mass index; CI, confidence interval; CV, cardiovascular; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol

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Conclusions

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- This post hoc analysis examined multiple patient subgroups in the IMPACT trial representing predefined demographics and baseline disease characteristics.
- The mortality reduction with FF/UMEC/VI versus UMEC/VI was generally consistent across all subgroups with no subgroups disproportionately contributing to the overall on-/off-treatment ACM benefits for FF/UMEC/VI seen in the IMPACT trial.
  - The small number of events in some patient subgroups limits the interpretation of these findings.

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CO-AUTHORS' DISCLOSURES

- V Kaul and MG Kaye have nothing to disclose. TF Carr received personal fees from Aimmune, AstraZeneca, GSK, Novartis, Sanofi Genzyme, and Regeneron; grant support from NIH, Aimmune, AstraZeneca, and Novartis. GJ Criner 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, and has ownership interest in HGE Technologies. MT Dransfield 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; contracted clinical trial support from Boehringer Ingelheim, Novartis, AstraZeneca, Yungjin, PneumRx/BTG, Pulmonx, Boston Scientific, Gala, Nuvaira, and GSK. DMG Halpin received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer, and Sanofi; nonfinancial support from Boehringer Ingelheim and Novartis. MK Han has received personal fees from AstraZeneca, GSK, Mylan, and Boehringer Ingelheim; research support from Novartis and Sunovion. RG Jain, D Midwinter, and DA Lipson are employees of GSK and holds stocks/shares in GSK. M Kraft received personal fees for consulting in asthma from AstraZeneca, Sanofi, Genentech, and Chiesi; research support from NIH, ALA, AstraZeneca, Sanofi, and Chiesi, and is cofounder of RaeSedo, LLC, a company that studies peptidomimetics for treatment of asthma. D Mapel has received research grant funding from AstraZeneca, Boehringer Ingelheim, Endo Pharmaceuticals, GSK, Sunovian, and Pfizer Pharmaceuticals; personal fees from Mylan/Theravance Biopharma. PD Scanlon has served as an investigator for clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Forest, GSK, Novartis, Pearl, and Pfizer, as well as studies funded by the National Heart, Lung and Blood Institute and the Department of Defense. He has served on scientific advisory panels for GSK and Boehringer Ingelheim. D Singh has received personal fees from GSK, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, Glenmark, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Theravance, and Verona; grant support from AstraZeneca, Boehringer Ingelheim, Chiesi, Glenmark, Menarini, Mundipharma, Novartis, Pfizer, Pulmatrix, Theravance, and Verona. JM Wells received personal fees from AstraZeneca, Boehringer Ingelheim, Takeda, and GSK; grant support from the NIH, and contracted research support from Bayer AG, ARCUS-Med, Vertex Pharmaceuticals, Mereo BioPharma, and Verona. R Wise has received personal fees from AstraZeneca/MedImmune, Boehringer Ingelheim, ContraFect, Pulmonx, Roche, Spiration, Sunovion, Merck, Circassia, Pneuma, Verona, Bonti, Denali, Aradigm, Mylan/Theravance, Propeller Health, AbbVie, and GSK; grant support from AstraZeneca/MedImmune, Boehringer Ingelheim, Pearl Therapeutics, GSK, and Sanofi-Aventis.