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

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Online Data Supplement

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

data

	FF/UMEC/VI		FF/VI (N=4134)		UMEC/VI (N=2070)	
	(N=	4151)				
	n (%)	Rate [#]	n (%)	Rate [#]	n (%)	Rate [#]
Total duration	4088.3		4030.1		1999.3	
at risk (subject-						
years)						
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 associate	ed with CO	PD				
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	9 (<1)	2.2 [9]	14 (<1)	3.5 [14]	12 (<1)	6.0 [12]
information						
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

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

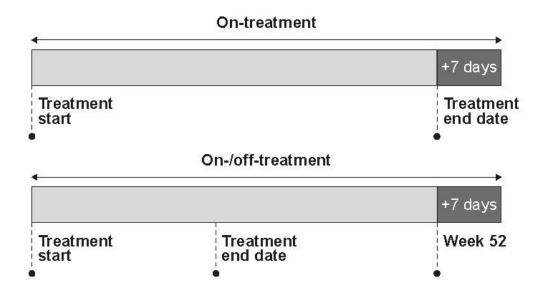
COPD	FF/UMEC/VI		FF/VI (N=4134)		UMEC/VI (N=2070)		
medication	(N=4151)						
	n/N (%)	Rate [#]	n/N (%)	Rate [#]	n/N (%)	Rate [#]	
ICS + LABA +	36/1672	0.0214	49/1647	0.0297	30/864	0.0351	
LAMA	(2.15)		(2.98)		(3.47)		
ICS + LABA	29/1354	0.0213	30/1340	0.0222	22/647	0.0343	
without LAMA	(2.14)		(2.24)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

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.

Supplement Figures

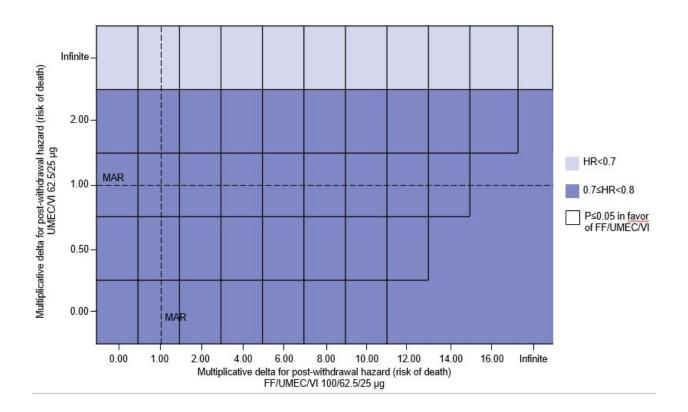
Supplement Figure E1. Definitions of on- and off-treatment deaths

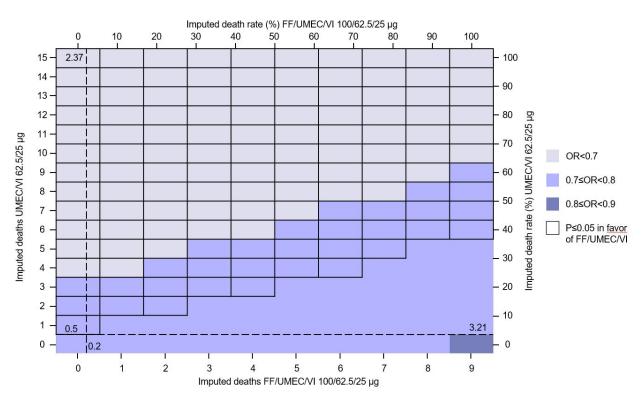


Supplement Figure E2. Tipping point analyses of ACM including off-treatment data for FF/UMEC/VI versus UMEC/VI. A: Analysis with imputation P-value for hazard ratio; B: Analysis with imputation hazard ratio and P-value; C: Analysis with imputation odds ratio and P-value

Infinite Multiplicative delta for post-withdrawal hazard (risk of death) UMEC/VI 62.5/25 µg 2.00-P≤0.001 0.001<P≤0.01 MAR 1.00 0.01<P≤0.05 P>0.05 0.50-0.00-MAR 0.00 6.00 12.00 1.00 2.00 4.00 8.00 10.00 14.00 16.00 Infinite Multiplicative delta for post-withdrawal hazard (risk of death) FF/UMEC/VI 100/62.5/25 µg

Α





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

С

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.

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

UMEC/VI

			Favors FF/UMEC/VI	Favors UMEC/VI		
	Patients with an event, n/N (%) FF/UMEC/VI UMEC/VI		•		→ Hazard ratio (95% CI)	p-value
Overall						
On-treatment ACM	50/4151 (1.20)	39/2070 (1.88)	⊢♦ −−1		0.58 (0.38, 0.88)	0.011
ACM including off-treatment data	89/4151 (2.14)	60/2070 (2.90)	⊢.		0.71 (0.51, 0.99)	0.043
ACM including off-treatment data (With additional vital status follow-up)	98/4151 (2.36)	66/2070 (3.19)	⊢ ♦		0.72 (0.53, 0.99)	0.042
Within 30 days						
On-treatment ACM	0/4151(0)	7/2070 (0.34)			NA	
ACM including off-treatment data	0/4151(0)	7/2070 (0.34)			NA	
ACM including off-treatment data (With additional vital status follow-up) Within 60 days	0/41551(0)	7/2070 (0.34)			NA	
On-treatment ACM	8/4151 (0.19)	15/2070 (0.72)	⊢♦ −−−−		0.26 (0.11, 0.61)	0.002
ACM including off-treatment data	9/4151 (0.22)	17/2070 (0.82)			0.26 (0.12, 0.59)	0.001
ACM including off-treatment data (With additional vital status follow-up) Within 180 days	9/4151 (0.22)	18/2070 (0.87)			0.25 (0.11, 0.55)	<0.001
On-treatment ACM	23/4151 (0.55)	27/2070 (1.30)			0.40 (0.23, 0.69)	0.001
ACM including off-treatment data	35/4151 (0.84)	38/2070 (1.84)	⊢♦ −−1		0.45 (0.28, 0.71)	<0.001
ACM including off-treatment data (With additional vital status follow-up)	36/4151 (0.87)	40/2070 (1.93)	⊢♦ −−1		0.44 (0.28, 0.69)	<0.001
			0.0 0.5 1	.0 1.5 2.0 2.5 3.0 Hazard ratio (95% Cl)	3.5 4.0	

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).

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

FF/VI

			Favors FF/UMEC/VI	Favors FF/VI			
	Patients with an event, n/N (%) FF/UMEC/VI FF/VI		•		→	Hazard ratio (95% CI)	p-value
Overall							
On-treatment ACM	50/4151 (1.20)	49/4134 (1.19)	⊢●			0.95 (0.64, 1.40)	0.780
ACM including off-treatment data	89/4151 (2.14)	97/4134 (2.35)	⊢.			0.90 (0.67, 1.20)	0.458
ACM including off-treatment data (With additional vital status follow-up)	98/4151 (2.36)	109/4134(2.64)	⊢◆			0.89 (0.67, 1.16)	0.387
Within 30 days							
On-treatment ACM	0/4151(0)	5/4134 (0.12)				NA	
ACM including off-treatment data	0/4151(0)	5/4134 (0.12)				NA	
ACM including off-treatment data (With additional vital status follow-up) Within 60 days	0/4151(0)	5/4134 (0.12)				NA	
On-treatment ACM	8/4151 (0.19)	6/4134 (0.15)	H	•		1.30 (0.45, 3.74)	0.628
ACM including off-treatment data	9/4151 (0.22)	8/4134 (0.19)		•		1.12 (0.43, 2.89)	0.822
ACM including off-treatment data (With additional vital status follow-up) Within 180 days	9/4151 (0.22)	8/4134 (0.19)	 	•		1.12 (0.43, 2.90)	0.818
On-treatment ACM	23/4151 (0.55)	19/4134 (0.46)	H	•		1.15 (0.63, 2.12)	0.647
ACM including off-treatment data	35/4151 (0.84)	34/4134 (0.82)	H	♦		1.02 (0.63, 1.63)	0.946
ACM including off-treatment data (With additional vital status follow-up)	36/4151 (0.87)	35/4134 (0.85)	⊢	↓ ◆↓		1.02 (0.64, 1.63)	0.931
			0.0 0.5 1	.0 1.5 2.0 2.5 Hazard ratio (9		4.0	

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).