The effect of ICS withdrawal and baseline inhaled treatment on exacerbations in the IMPACT study

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Online Data Supplement

Supplement Table 1. Baseline characteristics by ICS use at screening

	Prior ICS use			No prior ICS use		
	FF/UMEC/VI n=2971	**FF/VI n=2908**	**UMEC/VI n=1481**	**FF/UMEC/VI n=1180**	**FF/VI n=1226**	**UMEC/VI n=589**
Age, mean (SD) years	65.3 (8.2)	65.3 (8.3)	65.3 (8.2)	65.3 (8.4)	65.2 (8.3)	65.2 (8.4)
Male, n (%)	1955 (66)	1895 (65)	963 (65)	811 (69)	853 (70)	393 (67)
BMI, mean (SD) kg/m^2*	26.6 (6.2)	26.7 (6.1)	26.7 (6.0)	26.6 (6.4)	26.5 (6.1)	26.4 (5.6)
Smoking status, n (%)						
Current smoker	978 (33)	937 (32)	493 (33)	458 (39)	486 (40)	235 (40)
Former smokers	1993 (67)	1971 (68)	988 (67)	722 (61)	740 (60)	354 (60)
Lung function at screening, mean (SD)						
Pre-bronchodilator FEV_1, L	n=2968 1.13 (0.45)	n=2907 1.13 (0.46)	n=1480 1.14 (0.45)	n=1178 1.26 (0.50)	n=1226 1.24 (0.48)	n=589 1.22 (0.49)
Pre-bronchodilator FEV_1, % predicted	n=2966 40.9 (14.2)	n=2907 40.7 (14.3)	n=1480 41.2 (14.3)	n=1178 44.6 (15.3)	n=1226 43.6 (14.6)	n=588 43.4 (14.5)
Post-bronchodilator FEV_1, L	n=2967 1.24 (0.47)	n=2907 1.24 (0.48)	n=1481 1.25 (0.47)	n=1178 1.37 (0.51)	n=1226 1.35 (0.50)	n=588 1.32 (0.50)
Post-bronchodilator FEV_1, % predicted	n=2967 44.7 (14.7)	n=2907 44.6 (14.6)	n=1481 44.8 (14.7)	n=1178 48.3 (15.3)	n=1226 47.6 (15.0)	n=588 46.9 (14.6)
Post-bronchodilator FEV_1 % predicted <50%, n (%)	n=2967 1946 (66)	n=2907 1934 (67)	n=1481 981 (66)	n=1178 654 (56)	n=1226 736 (60)	n=588 355 (60)
Percent reversibility, %	n=2966 10.53 (12.28)	n=2907 10.96 (12.42)	n=1480 10.11 (12.08)	n=1178 9.93 (12.60)	n=1226 10.45 (12.85)	n=588 9.32 (11.94)
Exacerbation history in the prior year, n (%)						
Moderate/severe exacerbations 0 1 ≥2	 1 (<1) 1343 (45) 1627 (55)	 3 (<1) 1351 (46) 1554 (53)	 1 (<1) 666 (45) 814 (55)	 1 (<1) 510 (43) 669 (57)	 2 (<1) 556 (45) 668 (54)	 1 (<1) 265 (45) 323 (55)
Severe exacerbations 0 1	 2153 (72) 701 (24)	 2114 (73) 680 (23)	 1076 (73) 344 (23)	 911 (77) 239 (20)	 951 (78) 241 (20)	 479 (81) 95 (16)

≥2	117 (4)	114 (4)	61 (4)	30 (3)	34 (3)	15 (3)
SGRQ total score at baseline, mean (SD)	n=2942 51.7 (16.83)	n=2876 51.7 (16.88)	n=1467 50.9 (16.79)	n=1166 48.6 (16.57)	n=1216 48.5 (17.15)	n=583 48.5 (16.32)
Geographic region, n (%)						
Western Europe	799 (27)	822 (28)	405 (27)	453 (38)	452 (37)	233 (40)
Eastern Europe	199 (7)	198 (7)	96 (6)	83 (7)	72 (6)	37 (6)
Asia	479 (16)	452 (16)	247 (17)	175 (15)	208 (17)	83 (14)
North America	852 (29)	793 (27)	415 (28)	219 (19)	253 (21)	107 (18)
South America	479 (16)	475 (16)	241 (16)	205 (17)	205 (17)	103 (17)
Other	163 (5)	168 (6)	77 (5)	45 (4)	36 (3)	26 (4)

*FF/UMEC/VI, n=2968. BMI, body mass index; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

Supplement Table 2. Change from baseline in trough FEV_1 and SGRQ total score at Week 52 by ICS use at screening

	ICS use: Yes			ICS use: No		
	FF/UMEC/VI	**FF/VI**	**UMEC/VI**	**FF/UMEC/VI**	**FF/VI**	**UMEC/VI**
Trough FEV_1 at Week 52, mL	**n=2386**	**n=2111**	**n=1028**	**n=980**	**n=949**	**n=462**
LS mean change from baseline (95% CI)	86 (76, 95)	-9 (-19, 1)	36 (22, 50)	115 (98, 132)	11 (-6, 28)	51 (26, 75)
FF/UMEC/VI vs column, difference (95% CI)	–	95 (81, 108); p<0.001	50 (33, 67); p<0.001	–	104 (80, 128); p<0.001	64 (34, 94); p<0.001
SGRQ total score at Week 52	**n=2344**	**n=2091**	**n=1017**	**n=974**	**n=935**	**n=453**
LS mean change from baseline (95% CI)	-5.3 (-5.9, -4.8)	-3.5 (-4.1, -2.9)	-3.7 (-4.5, -2.9)	-5.8 (-6.7, -5.0)	-4.1 (-5.0, -3.3)	-3.7 (-4.9, -2.4)
FF/UMEC/VI vs column, difference (95% CI)	–	-1.8 (-2.6, -1.0); p<0.001	-1.6 (-2.6, -0.6); p=0.001	–	-1.7 (-2.9, -0.5); p=0.006	-2.2 (-3.7, -0.7); p=0.005

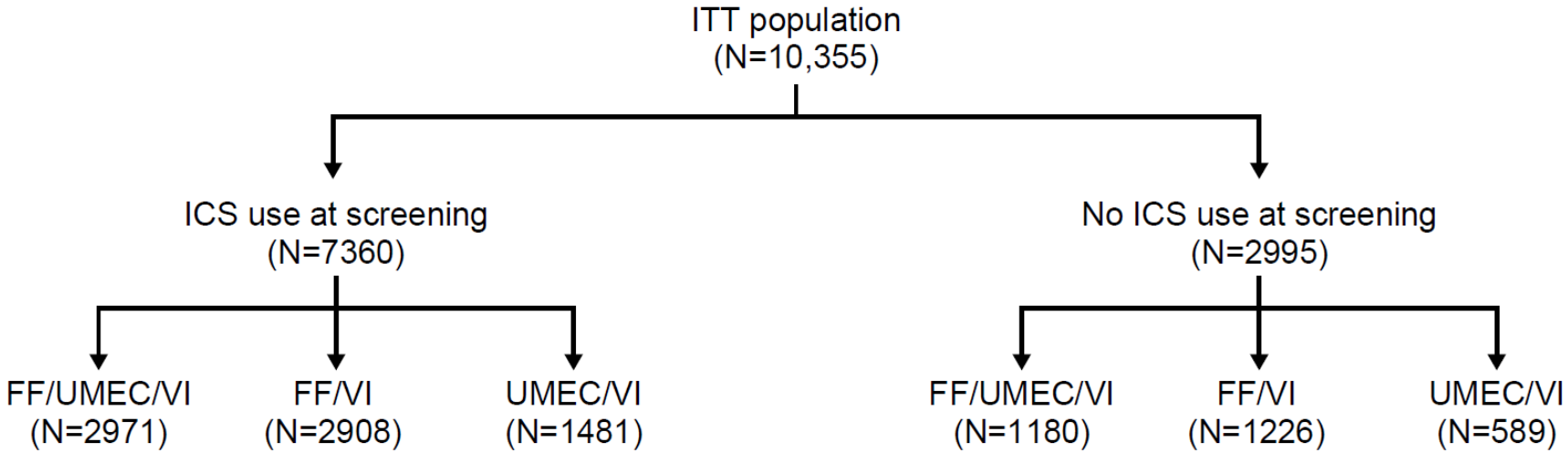
CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ICS, inhaled corticosteroid; n, number of patients with analyzable data at the current timepoint; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

Supplement Table 3. AESI incidence by ICS use at screening and by treatment

AESI incidence, n (%)	Prior ICS use				No prior ICS use			
	FF/UMEC/VI N=2971	FF/VI N=2908	UMEC/VI N=1481	Total N=7360	FF/UMEC/VI N=1180	FF/VI N=1226	UMEC/VI N=589	Total N=2995
Anticholinergic syndrome (SMQ)	138 (5)	104 (4)	51 (3)	293 (4)	46 (4)	36 (3)	19 (3)	101 (3)
Asthma/bronchospasm (SMQ)	23 (<1)	25 (<1)	15 (1)	63 (<1)	4 (<1)	9 (<1)	1 (<1)	14 (<1)
Cardiovascular effects	331 (11)	308 (11)	165 (11)	804 (11)	119 (10)	122 (10)	59 (10)	300 (10)
Decreased BMD and associated fractures	66 (2)	61 (2)	23 (2)	150 (2)	32 (3)	24 (2)	14 (2)	70 (2)
Effects on potassium	31 (1)	18 (<1)	2 (<1)	51 (<1)	3 (<1)	7 (<1)	6 (1)	16 (<1)
Gastrointestinal obstruction (SMQ)	7 (<1)	6 (<1)	1 (<1)	14 (<1)	2 (<1)	4 (<1)	1 (<1)	7 (<1)
Hyperglycemia/new onset DM (SMQ)	107 (4)	84 (3)	52 (4)	243 (3)	45 (4)	33 (3)	21 (4)	99 (3)
Hypersensitivity	140 (5)	151 (5)	65 (4)	356 (5)	56 (5)	44 (4)	30 (5)	130 (4)
LRTI excluding pneumonia	145 (5)	142 (5)	81 (5)	368 (5)	55 (5)	57 (5)	27 (5)	139 (5)
Local steroid effects	229 (8)	205 (7)	77 (5)	511 (7)	108 (9)	96 (8)	31 (5)	235 (8)
Ocular effects	43 (1)	37 (1)	17 (1)	97 (1)	12 (1)	8 (<1)	9 (2)	29 (1)
Pneumonia	227 (8)	219 (8)	68 (5)	514 (7)	90 (8)	73 (6)	29 (5)	192 (6)
Tremor	4 (<1)	3 (<1)	4 (<1)	11 (<1)	4 (<1)	1 (<1)	2 (<1)	7 (<1)
Urinary retention	6 (<1)	11 (<1)	7 (<1)	24 (<1)	2 (<1)	1 (<1)	2 (<1)	5 (<1)

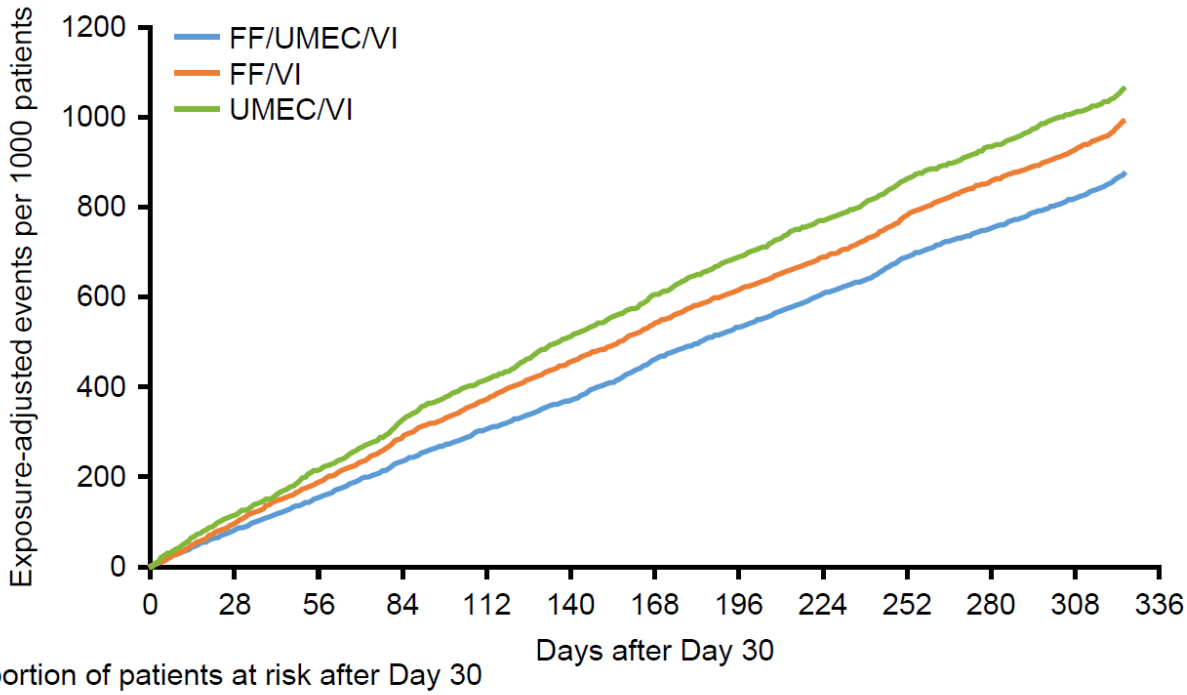
AESI, adverse event of special interest; BMD, bone mineral density; DM, diabetes mellitus; FF, fluticasone furoate; LRTI, lower respiratory tract infection; SMQ, Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query; UMEC, umeclidinium; VI, vilanterol.

Supplement Figure 1. Patients disposition according to COPD medications at screening



COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; ICS, inhaled corticosteroid; ITT, intent-to-treat; UMEC, umeclidinium; VI, vilanterol.

Supplement Figure 2. Cumulative number of moderate/severe exacerbations removing the first 30 days.

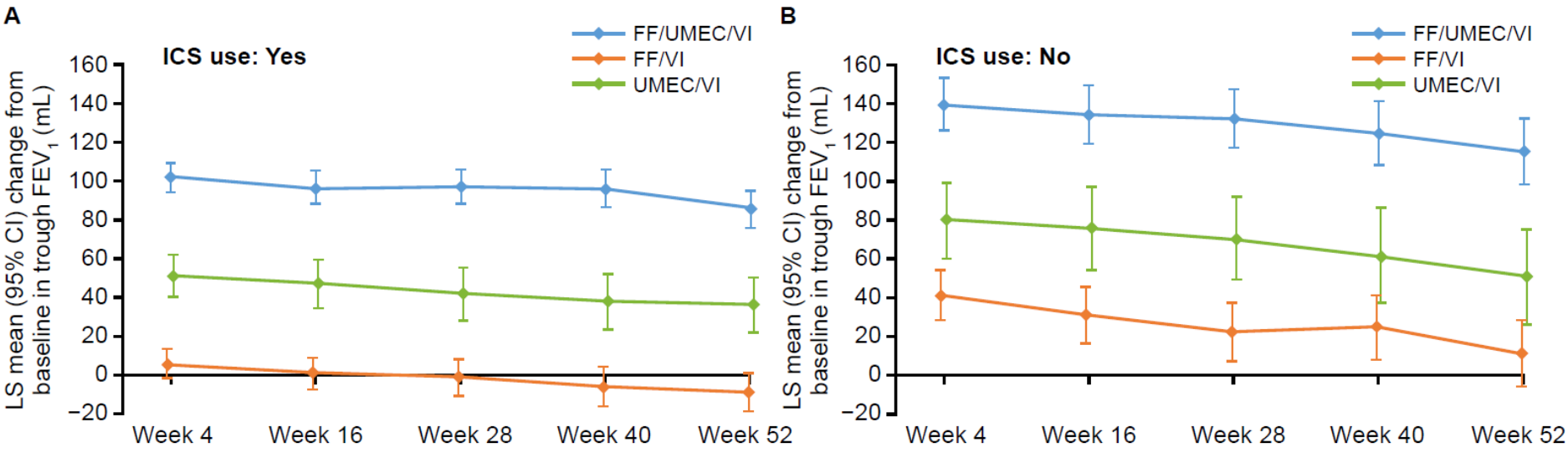


Proportion of patients at risk after Day 30

FF/UMEC/VI	1.00	0.98	0.97	0.95	0.93	0.92	0.91	0.90	0.89	0.88	0.86	0.86
FF/VI	1.00	0.97	0.94	0.92	0.90	0.88	0.87	0.85	0.84	0.83	0.82	0.81
UMEC/VI	1.00	0.96	0.94	0.91	0.88	0.87	0.85	0.83	0.83	0.82	0.80	0.79

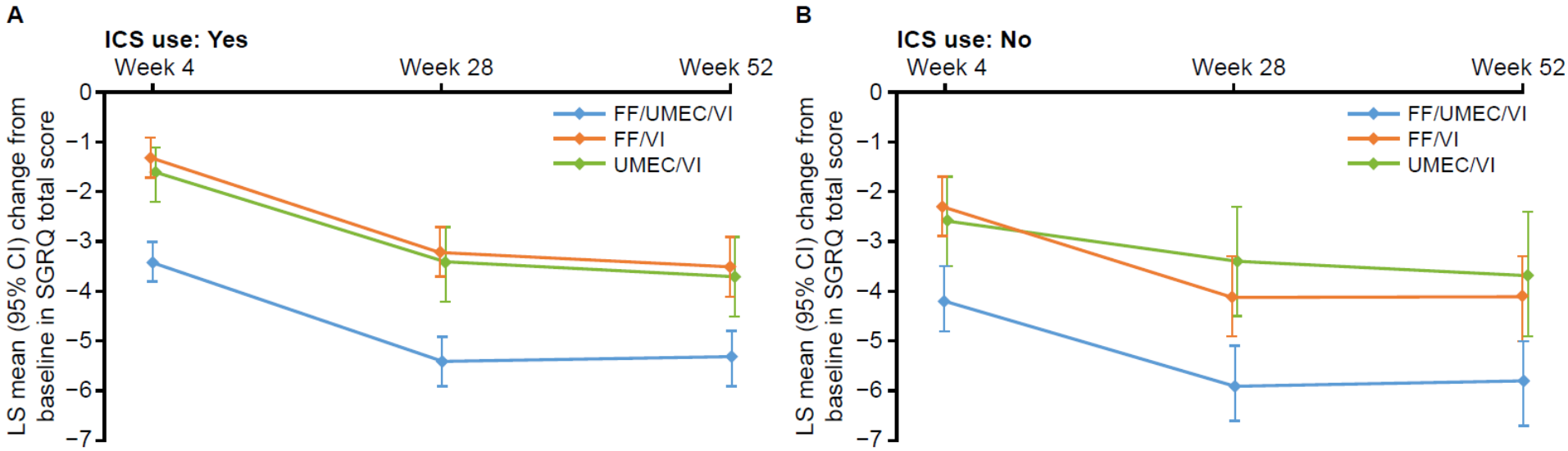
FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

Supplement Figure 3. Change from baseline in trough FEV_1 by ICS use at screening



CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ICS, inhaled corticosteroid; LS, least squares; UMEC, umeclidinium; VI, vilanterol.

Supplement Figure 4. Change from baseline in SGRQ total score by ICS use at screening



CI, confidence interval; FF, fluticasone furoate; ICS, inhaled corticosteroid; LS, least squares; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.