Supplementary materials

Efficacy assessments

The efficacy assessments used in this study have been described previously;[1, 2] in summary, patients completed an electronic diary (eDiary) each morning to record their symptoms and were alerted to contact their trial investigator if symptoms suggestive of an exacerbation worsened over the course of 2 consecutive days. The investigator confirmed the presence or absence of an exacerbation and determined the severity according to the treatment required. Spirometry was performed at baseline and at Weeks 4, 16, 28, 40 and 52, according to the American Thoracic Society/European Respiratory Society criteria[3]. The SGRQ for patients with COPD was completed by patients using an eDiary at randomisation and at Weeks 4, 28 and 52.

References

1. Pascoe SJ, Lipson DA, Locantore N, Barnacle H, Brealey N, Mohindra R, Dransfield MT, Pavord I, Barnes N. A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol. Eur Respir J 2016; 48: 320-330.

2. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, Singh D, Tabberer M, Wise RA, Pascoe SJ, Investigators I. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018; 378: 1671-1680.

3. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. Standardisation of spirometry. Eur Respir J 2005; 26: 319-338.

Supplementary Table 1. Baseline demographics according to exacerbation history in the year prior to screening in patients receiving FF/UMEC/VI, FF/VI or UMEC/VI

	Single moderate subgroup			Frequent moderate subgroup			Severe subgroup		
	FF/UMEC/VI (n=1198)	**FF/VI (n=1242)**	**UMEC/VI (n=616)**	**FF/UMEC/VI (n=1866)**	**FF/VI (n=1823)**	**UMEC/VI (n=939)**	**FF/UMEC/VI (n=1087)**	**FF/VI (n=1069)**	**UMEC/VI (n=515)**
Age (years), mean (SD)	65.3 (7.91)	65.0 (7.96)	65.1 (80.2)	65.3 (8.52)	65.2 (8.41)	65.3 (8.44)	65.4 (8.13)	65.6 (8.48)	65.3 (8.25)
Sex (male), n (%)	800 (67)	844 (68)	425 (69)	1207 (65)	1142 (63)	573 (61)	759 (70)	762 (71)	358 (70)
Race (white), n (%)	962 (80)	969 (78)	477 (77)	1452 (78)	1415 (78)	737 (78)	786 (72)	795 (74)	390 (76)
Former smoker, n (%)	766 (64)	806 (65)	392 (64)	1218 (65)	1192 (65)	604 (64)	731 (67)	713 (67)	346 (67)
BMI (kg/m^2), mean (SD)	26.17 (6.11)	26.08 (6.07)	26.00 (5.88)	26.93 (5.99)	27.12 (5.74)	27.05 (5.69)	26.55 (6.67)	26.54 (6.58)	26.41 (6.13)
Lung function (post-bronchodilator)									
At screening FEV_1 (L), mean (SD)	1.036 (0.3149)	1.051 (0.3183)	1.056 (0.3294)	1.442 (0.4998)	1.435 (0.5116)	1.430 (0.4960)	1.254 (0.5108)	1.249 (0.4983)	1.226 (0.5001)
FEV_1 % predicted, mean (SD)	36.9 (8.86)	37.1 (8.86)	37.0 (8.83)	51.9 (14.81)	51.7 (14.76)	52.0 (14.74)	44.7 (15.56)	44.5 (15.28)	43.4 (14.49)
FEV_1/FVC ratio, mean (SD)	0.418 (0.1018)	0.422 (0.1032)	0.424 (0.1041)	0.510 (0.1144)	0.508 (0.1151)	0.512 (0.1214)	0.452 (0.1196)	0.450 (0.1193)	0.449 (0.1201)
Baseline concomitant COPD medication at screening* (alone or in combination), n (%)									
LAMA	80 (7)	117 (9)	46 (7)	144 (8)	151 (8)	80 (9)	80 (7)	97 (9)	36 (7)
LABA	31 (3)	35 (3)	18 (3)	66 (4)	71 (4)	29 (3)	21 (2)	13 (1)	7 (1)
LAMA + LABA	131 (11)	119 (10)	77 (13)	167 (9)	145 (8)	80 (9)	91 (8)	85 (8)	39 (8)
ICS + LABA	362 (30)	371 (39)	173 (28)	679 (36)	687 (38)	328 (35)	313 (29)	282 (26)	146 (28)
ICS + LAMA + LABA	505 (42)	492 (40)	261 (42)	662 (35)	638 (35)	351 (37)	505 (46)	517 (48)	252 (49)

The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (≥2 moderate/no severe exacerbations in the prior year) and severe (≥1 severe/any moderate exacerbation in the prior year). *Between day of screening −3 days and date of screening (inclusive). BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

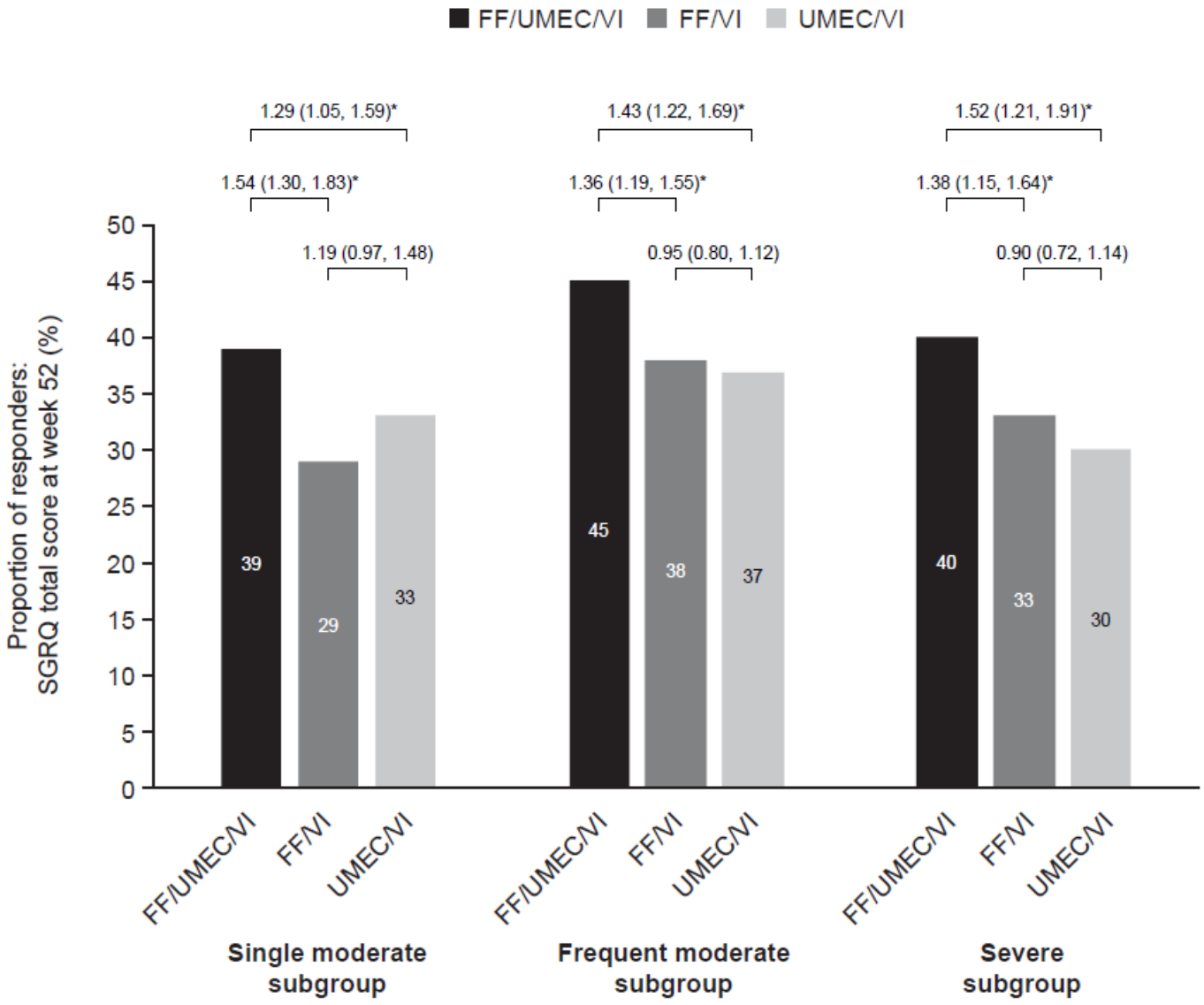
Supplementary Table 2. Annual exacerbation rates by exacerbation history in the year prior to screening and by quintiles of baseline blood eosinophil counts in patients treated with FF/UMEC/VI, FF/VI or UMEC/VI

Treatment and blood eosinophil quintile	n	Rate (95% CI)	FF/UMEC/VI vs dual therapy rate ratio (95% CI)	FF/VI vs UMEC/VI rate ratio (95% CI)
Single moderate subgroup				
<90 cells/µL				
FF/UMEC/VI	272	0.77 (0.63, 0.93)		
FF/VI	271	1.00 (0.83, 1.22)	0.76 (0.58, 1.00)	
UMEC/VI	132	1.06 (0.81, 1.38)	0.73 (0.52, 1.01)	0.95 (0.69, 1.32)
90–<140 cells/µL				
FF/UMEC/VI	242	0.78 (0.63, 0.95)		
FF/VI	253	1.06 (0.88, 1.28)	0.73 (0.55, 0.96)	
UMEC/VI	104	0.74 (0.53, 1.03)	1.05 (0.72, 1.54)	1.44 (0.99, 2.10)
140–<200 cells/µL				
FF/UMEC/VI	238	0.88 (0.73, 1.05)		
FF/VI	250	1.04 (0.88, 1.24)	0.84 (0.66, 1.08)	
UMEC/VI	127	0.95 (0.74, 1.22)	0.93 (0.68, 1.25)	1.10 (0.81, 1.49)
200–<310 cells/µL				
FF/UMEC/VI	240	0.76 (0.64, 0.92)		
FF/VI	242	1.09 (0.92, 1.30)	0.70 (0.54, 0.90)	
UMEC/VI	136	1.03 (0.81, 1.30)	0.74 (0.55, 1.00)	1.07 (0.80, 1.42)
≥310 cells/µL				
FF/UMEC/VI	202	1.08 (0.89, 1.32)		
FF/VI	222	1.01 (0.83, 1.24)	1.07 (0.80, 1.42)	
UMEC/VI	115	1.21 (0.93, 1.57)	0.90 (0.64, 1.25)	0.84 (0.60, 1.17)
Frequent moderate subgroup				
<90 cells/µL				
FF/UMEC/VI	399	0.77 (0.66, 0.89)		
FF/VI	376	0.97 (0.83, 1.13)	0.79 (0.64, 0.98)	
UMEC/VI	203	0.80 (0.64, 0.99)	0.96 (0.74, 1.26)	1.22 (0.93, 1.58)
90–<140 cells/µL				
FF/UMEC/VI	340	0.85 (0.73, 0.99)		
FF/VI	319	0.95 (0.82, 1.11)	0.89 (0.72, 1.10)	
UMEC/VI	170	1.11 (0.90, 1.36)	0.77 (0.60, 0.99)	0.86 (0.67, 1.11)
140–<200 cells/µL				
FF/UMEC/VI	358	0.92 (0.80, 1.07)		
FF/VI	330	1.00 (0.85, 1.17)	0.93 (0.75, 1.15)	
UMEC/VI	154	0.89 (0.70, 1.12)	1.04 (0.79, 1.38)	1.12 (0.85, 1.49)
200–<310 cells/µL				
FF/UMEC/VI	389	0.85 (0.73, 0.98)		
FF/VI	386	0.93 (0.81, 1.08)	0.91 (0.74, 1.11)	
UMEC/VI	209	1.25 (1.04, 1.51)	0.68 (0.53, 0.86)	0.75 (0.59, 0.95)
≥310 cells/µL				
FF/UMEC/VI	374	0.87 (0.75, 1.01)		
FF/VI	411	0.91 (0.79, 1.06)	0.95 (0.77, 1.17)	
UMEC/VI	201	2.05 (1.70, 2.49)	0.42 (0.33, 0.54)	0.44 (0.35, 0.56)

Severe subgroup				
<90 cells/µL				
FF/UMEC/VI	227	1.03 (0.86, 1.22)		
FF/VI	218	1.11 (0.92, 1.34)	0.92 (0.71, 1.19)	
UMEC/VI	102	1.06 (0.81, 1.40)	0.97 (0.70, 1.34)	1.05 (0.75, 1.46)
90–<140 cells/µL				
FF/UMEC/VI	204	1.01 (0.83, 1.22)		
FF/VI	189	1.41 (1.17, 1.70)	0.71 (0.55, 0.93)	
UMEC/VI	82	1.14 (0.85, 1.52)	0.89 (0.63, 1.25)	1.24 (0.88, 1.75)
140–<200 cells/µL				
FF/UMEC/VI	205	1.11 (0.93, 1.33)		
FF/VI	199	1.30 (1.08, 1.56)	0.86 (0.66, 1.10)	
UMEC/VI	99	1.28 (0.98, 1.68)	0.86 (0.63, 1.19)	1.01 (0.73, 1.40)
200–<310 cells/µL				
FF/UMEC/VI	205	0.89 (0.73, 1.07)		
FF/VI	229	1.35 (1.14, 1.59)	0.66 (0.51, 0.84)	
UMEC/VI	111	1.42 (1.11, 1.80)	0.62 (0.46, 0.85)	0.95 (0.71, 1.27)
≥310 cells/µL				
FF/UMEC/VI	242	1.20 (1.01, 1.43)		
FF/VI	229	1.20 (1.00, 1.44)	1.00 (0.78, 1.29)	
UMEC/VI	119	2.02 (1.59, 2.58)	0.59 (0.44, 0.80)	0.59 (0.44, 0.80)

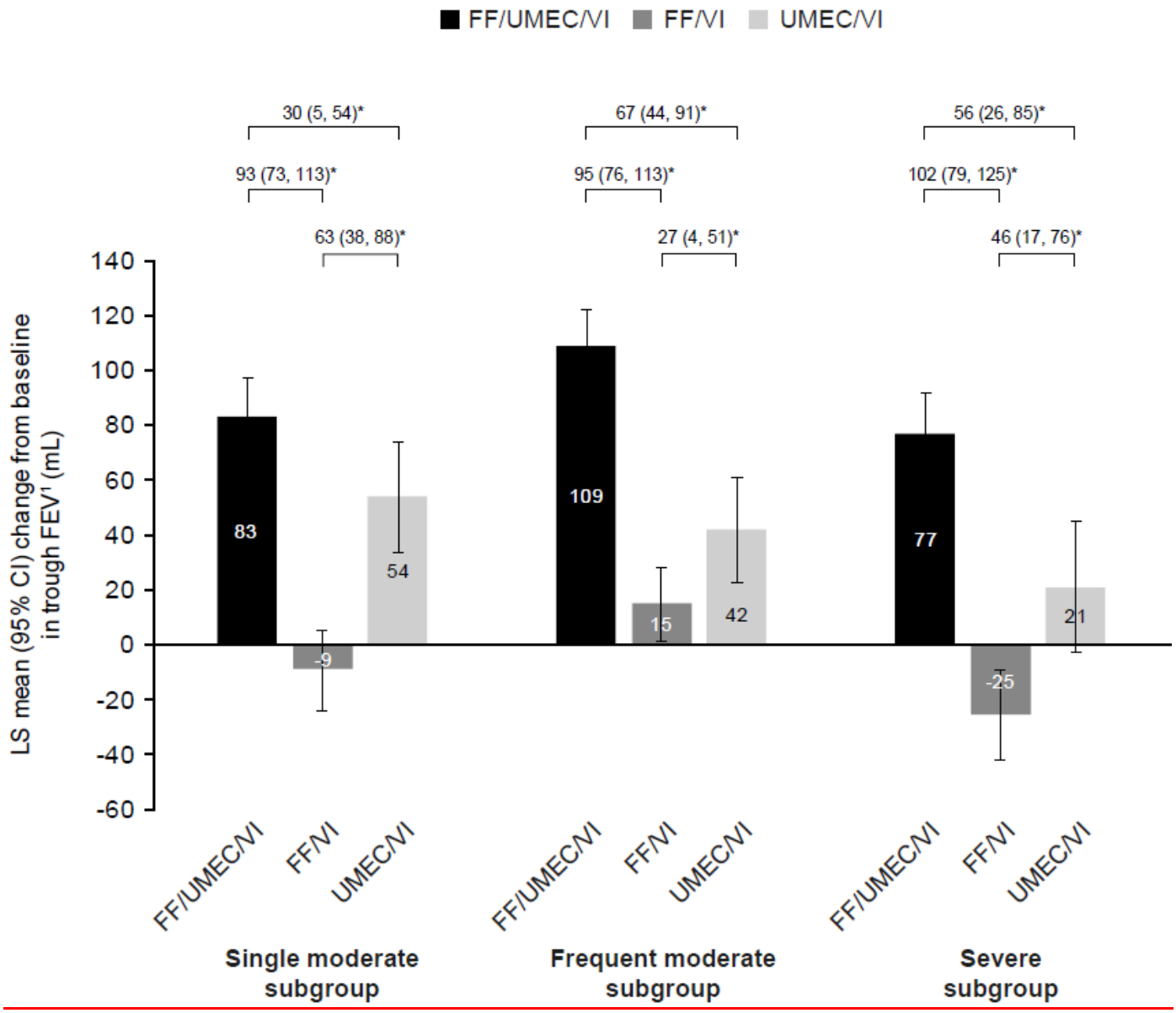
The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (≥2 moderate/no severe exacerbations in the prior year) and severe (≥1 severe/any moderate exacerbation in the prior year). CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

Supplementary Figure 1. Proportion of patients achieving a 4-unit change in SGRQ compared with baseline at Week 52 (odds ratio [95% CI]) by prior exacerbation subgroup



The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (≥2 moderate/no severe exacerbations in the prior year) and severe (≥1 severe/any moderate exacerbation in the prior year). Post hoc analysis. Numbers above the brackets indicate the between-treatment difference (95% CI) in the proportion of SGRQ responders for FF/UMEC/VI versus UMEC/VI, FF/UMEC/VI versus FF/VI and UMEC/VI versus FF/VI. *p<0.05. CI, confidence interval; FF, fluticasone furoate; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

Supplementary Figure 2. LS mean (95% CI) change in trough FEV_1 (mL) at Week 52 by prior exacerbation subgroup



The exacerbation history subgroups are defined as single moderate (1 moderate/no severe exacerbation in the prior year), frequent moderate (≥2 moderate/no severe exacerbations in the prior year) and severe (≥1 severe/any moderate exacerbation in the prior year). Post hoc analysis. Numbers above the brackets indicate the between-treatment difference (95% CI) in LS mean change from baseline at Week 52 in trough FEV_1 (mL) for FF/UMEC/VI vs UMEC/VI, FF/UMEC/VI vs FF/VI and UMEC/VI vs FF/VI. *p<0.05. CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; LS, least squares; UMEC, umeclidinium; VI, vilanterol.