Supplementary Materials

Appendix 1

The incremental shuttle walk test (ISWT) was demonstrated to patients at Visit 1. At Visit 2 participants watched a video of the ISWT and then performed the test to determine the walking speed for the endurance shuttle walk test (ESWT) during the first treatment period (**Figure S1**). Following this the ESWT was demonstrated to all patients. At Visit 3, and at all visits where the ESWT was performed, patients first viewed a video of the ESWT before performing the actual test. At randomization (Visit 4), patients performed a pre-dose ESWT for baseline for the first treatment period. Specific randomisation criteria were included to minimise variability by ensuring that the difference between ESWT at visits 3 and 4 was less than 120s, and that the patients carried out the test correctly and overall walked less than 15 minutes during the test. At Visits 5, 6, and 7, the ESWT was performed 3 hours post dose. After Visit 7, there was a washout of 10–12 days before Visit 8. At Visit 8, patients watched a video of the ISWT and then performed an ISWT to determine the walking speed of the ESWT for the second treatment period. Visit 9 occurred 2–5 days from Visit 8 and represented Day 1 of the second treatment period during which a pre-dose ESWT was performed for baseline. At Visits 10, 11, and 12, the ESWT was performed 3 hours post dose.

Optimisation of test standardisation was ensured using a single standard operating practice across all sites. A site visit by an external expert in the conduct of the ISWT/ESWT was performed to ensure all sites were trained in the implementation of the test.

Figure S1. Study design schema

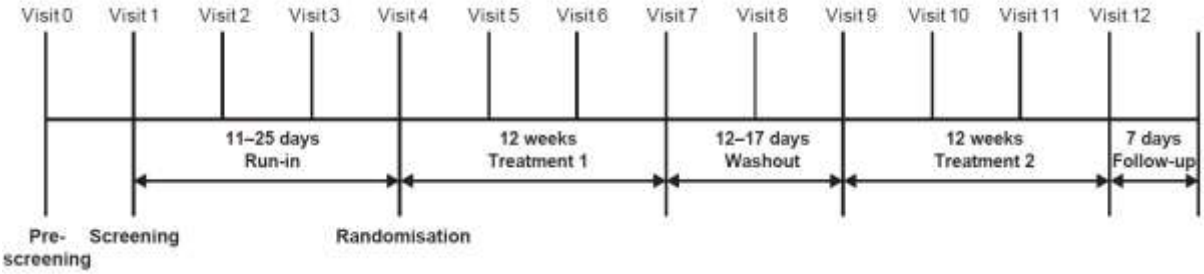
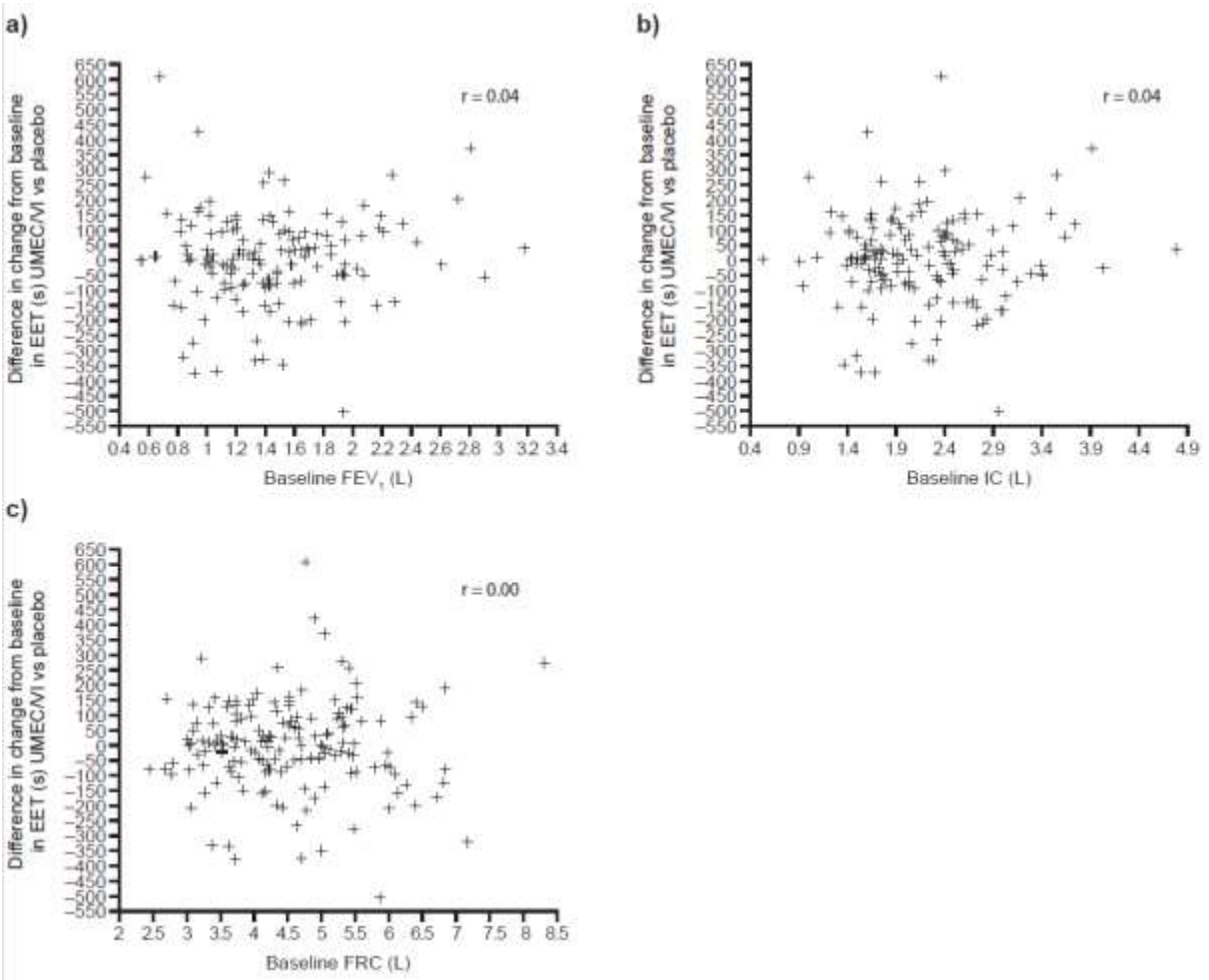


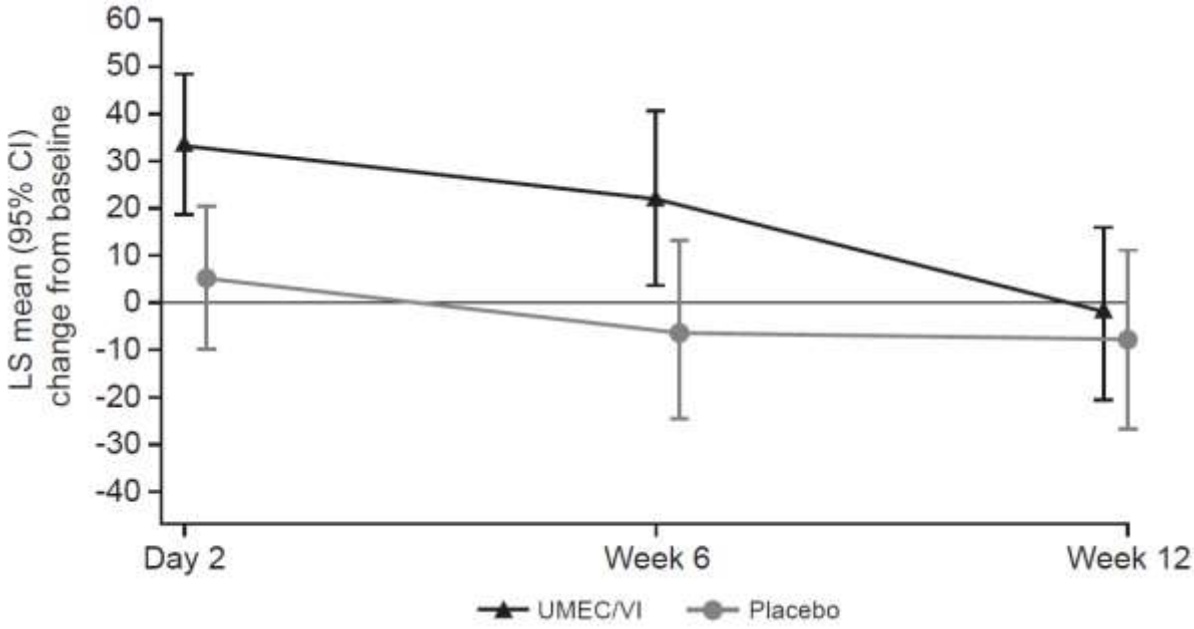
Figure S2 Post hoc analysis of correlations between EET and (a) baseline FEV_1; (b) baseline IC; (c) baseline FRC[#]



[#]ITT population including on-treatment data only.

FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; ITT, intent-to-treat

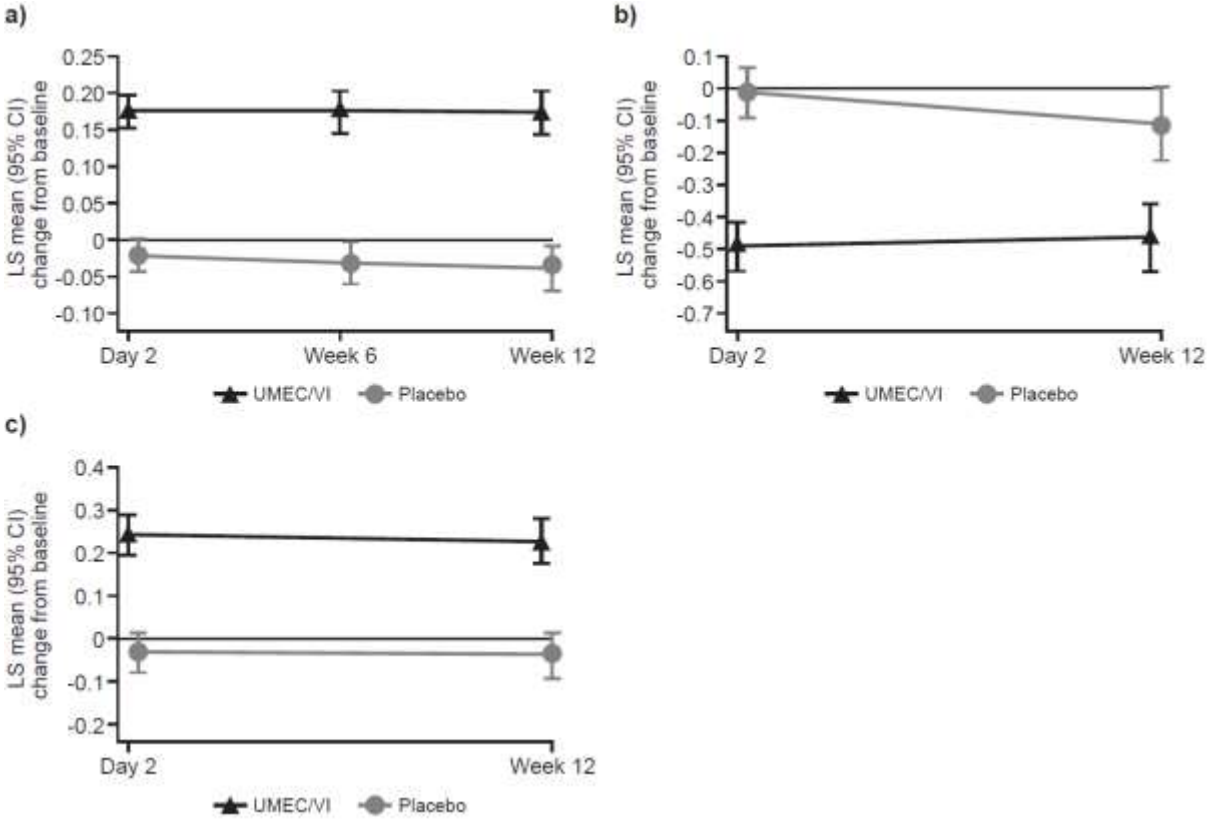
Figure S3 LS mean change (95% CI) from baseline in 3-h post-dose EET (s)[#]



[#]ITT population including on-treatment data only.

CI, confidence interval; EET, exercise endurance time; LS, least squares, ITT, intent-to-treat; UMEC, umeclidinium; VI, vilanterol

Figure S4 (a) LS mean change (95% CI) from baseline in trough FEV_1 (mL); (b) LS mean change (95% CI) from baseline in 3-h post-dose FRC (mL); (c) LS mean change (95% CI) from baseline in 3-h post-dose IC (mL)[#]



[#]ITT population including on-treatment data only.

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; IC, inspiratory capacity; ITT, intent-to-treat; LS, least squares; UMEC, umeclidinium; VI, vilanterol

Table S1. Variability in EET data between patients in the study sites

Study site	Number of patients	Between-patient variance	Within-patient variance	ICC
1	21	177	57.9	0.90
2	20	93.9	37.7	0.86
3	19	109	44.4	0.86
4	37	126	43.6	0.89
5	11	82.5	36.0	0.84
6	11	134	41.6	0.91
7	17	189	41.6	0.95
8	9	212	30.6	0.98
9	16	131	52.7	0.86
10	10	105	46.2	0.84
11	24	71.5	26.8	0.88

Study sites with less than six patient were not included in the analysis. EET, exercise endurance test; ICC, interclass coefficient

Table S2. Exercise capacity, as measured by EET (s), at Day 2, Week 6 and Week 12[#]

		Placebo (N=198)	**UMEC/VI (N=198)**
Week 12		n=153	n=169
	LS mean change from baseline (SE)	-7.5 (9.75)	-2.0 (9.34)
	Difference from placebo (95% CI)	-	5.5 (-19.1, 30.1); p=0.660
Day 2		n=177	n=183
	LS mean change from baseline (SE)	5.0 (7.81)	33.7 (7.66)
	Difference from placebo (95% CI)	-	28.7 (9.6, 47.7); p=0.003
Week 6		n=164	n=177
	LS mean change from baseline (SE)	-6.2 (9.74)	22.3 (9.38)
	Difference from placebo (95% CI)	-	28.5 (3.9, 53.1); p=0.024

[#]ITT population including on-treatment data only.

CI, confidence interval; EET, exercise endurance test; ITT, intent-to-treat; LS, least squares; SE, standard error; UMEC, umeclidinium; VI, vilanterol

Table S3. Lung function and hyperinflation measurements at Week 12[#]

		Placebo (N=198)	UMEC/VI (N=198)
Trough FEV_1, mL		n=159	n=172
	LS mean change from baseline (SE)	-38 (16)	175 (15)
	Difference from placebo (95% CI)	-	213 (174, 252); p<0.001
Trough FVC, mL		n=159	n=172
	LS mean change from baseline (SE)	-34 (25)	239 (24)
	Difference from placebo (95% CI)	-	273 (212, 334); p<0.001
Trough FRC, mL		n=159	n=174
	LS mean change from baseline (SE)	71 (56)	-274 (53)
	Difference from placebo (95% CI)	-	-345 (-490, -200); p<0.001
Trough RV, mL		n=159	n=174
	LS mean change from baseline (SE)	68 (59)	-338 (56)
	Difference from placebo (95% CI)	-	-406 (-560, -252); p<0.001
3-h post-dose RV, mL		n=158	n=175
	LS mean change from baseline (SE)	-75 (58)	-544 (55)
	Difference from placebo (95% CI)	-	-468 (-613, -324); p<0.001
Trough IC, mL		n=159	n=175
	LS mean change from baseline (SE)	-66 (27)	148 (26)
	Difference from placebo (95% CI)	-	214 (148, 280); p<0.001

[#]ITT population including on-treatment data only.

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; ITT, intent-to-treat; LS, least squares; SE, standard error; RV, residual volume; UMEC, umeclidinium; VI, vilanterol