










Web appendices

Sub-group analysis from a parallel arm, randomised, placebo controlled clinical trial with multiple imputation for missing values: Forest plot of treatment reporting odds ratios for visual analogue scores of mean breathlessness response at days 5-7 compared to baseline by sub-group on an intention to treat basis. (n=284)

Appendix 1:

Domain: Intensity. Threshold for difference: 15% relative difference mean days 5-7 over baseline Measure 0-100mm visual analogue scale (VAS) - <i>best breathlessness</i> in the previous 24 hours.	Number			Odds ratio (OR)	95% CI		p value
	Total	Observed	Imputed		Lower	Upper	
Overall	241	214	27	1.06	0.81	1.38	0.695
COPD - Yes	140	120	20	1.16	0.57	2.35	0.688
COPD - No	101	94	7	1.06	0.46	2.41	0.893
Baseline mMRC - 1 or 2	76	67	9	1.52	0.58	3.97	0.395
Baseline mMRC - 3 or 4	158	141	17	1.02	0.52	1.99	0.949
COPD - Yes; Baseline mMRC - 1 or 2	46	39	7	1.88	0.53	6.67	0.330
COPD - Yes; Baseline mMRC - 3 or 4	92	80	12	0.92	0.39	2.18	0.849
COPD - No; Baseline mMRC - 1 or 2	30	28	2	1.04	0.24	4.53	0.963
COPD - No; Baseline mMRC - 3 or 4	66	61	5	1.20	0.42	3.41	0.737

CI - confidence intervals; mMRC - modified Medical Research Council breathless scale; COPD – chronic obstructive pulmonary disease.

Domain: Intensity. Threshold for difference: 8.9mm absolute difference mean days 5-7 over baseline Measure 0-100mm visual analogue scale (VAS) - <i>best breathlessness</i> in the previous 24 hours.		Number			Odds ratio (OR)	95% CI		p value
		Total	Observed	Imputed		Lower	Upper	
Overall		241	214	27	1.14	0.87	1.49	0.356
COPD - Yes		140	120	20	1.50	0.73	3.05	0.266
COPD - No		101	94	7	1.04	0.45	2.41	0.923
Baseline mMRC - 1 or 2		76	67	9	1.36	0.52	3.59	0.529
Baseline mMRC - 3 or 4		158	141	17	1.07	0.54	2.14	0.841
COPD - Yes; Baseline mMRC - 1 or 2		46	39	7	2.18	0.60	7.84	0.235
COPD - Yes; Baseline mMRC - 3 or 4		92	80	12	1.15	0.47	2.84	0.760
COPD - No; Baseline mMRC - 1 or 2		30	28	2	0.59	0.12	2.89	0.512
COPD - No; Baseline mMRC - 3 or 4		66	61	5	0.97	0.34	2.79	0.956

CI - confidence intervals; mMRC - modified Medical Research Council breathless scale; COPD – chronic obstructive pulmonary disease.

Appendix 2

Domain: Intensity. Threshold for difference: 15% relative difference mean days 5-7 over baseline Measure 0-100mm visual analogue scale (VAS) – <i>breathlessness (intensity) now.</i>	Number			Odds ratio (OR)	95% CI		p value
	Total	Observed	Imputed		Lower	Upper	
Overall	264	233	31	0.97	0.75	1.25	0.814
COPD - Yes	155	133	22	0.68	0.35	1.32	0.259
COPD - No	109	100	9	1.50	0.68	3.29	0.317
Baseline mMRC - 1 or 2	77	68	9	1.02	0.40	2.62	0.968
Baseline mMRC - 3 or 4	167	148	19	0.93	0.49	1.77	0.817
COPD - Yes; Baseline mMRC - 1 or 2	46	39	7	0.72	0.21	2.47	0.607
COPD - Yes; Baseline mMRC - 3 or 4	99	86	13	0.53	0.23	1.23	0.141
COPD - No; Baseline mMRC - 1 or 2	31	29	2	1.72	0.39	7.57	0.475
COPD - No; Baseline mMRC - 3 or 4	68	62	6	2.12	0.76	5.91	0.151

CI - confidence intervals; mMRC - modified Medical Research Council breathless scale; COPD – chronic obstructive pulmonary disease.

Domain: Intensity. Threshold for difference: 8.9mm absolute difference mean days 5-7 over baseline Measure 0-100mm visual analogue scale (VAS) – <i>breathlessness (intensity) now</i> .		Number			Odds ratio (OR)	95% CI		p value
		Total	Observed	Imputed		Lower	Upper	
Overall		264	233	31	0.87	0.68	1.13	0.308
COPD - Yes		155	133	22	0.79	0.40	1.55	0.491
COPD - No		109	100	9	0.72	0.33	1.61	0.428
Baseline mMRC - 1 or 2		77	68	9	0.50	0.19	1.34	0.168
Baseline mMRC - 3 or 4		167	148	19	0.75	0.39	1.44	0.382
COPD - Yes; Baseline mMRC - 1 or 2		46	39	7	0.50	0.14	1.78	0.281
COPD - Yes; Baseline mMRC - 3 or 4		99	86	13	0.81	0.35	1.87	0.619
COPD - No; Baseline mMRC - 1 or 2		31	29	2	0.48	0.10	2.20	0.345
COPD - No; Baseline mMRC - 3 or 4		68	62	6	0.67	0.24	1.89	0.451

CI - confidence intervals; mMRC - modified Medical Research Council breathless scale; COPD – chronic obstructive pulmonary disease.

Appendix 3

Domain: Intensity. Threshold for difference: 15% relative difference mean days 5-7 over baseline Measure 0-100mm visual analogue scale (VAS) – <i>breathlessness unpleasantness now.</i>	Number			Odds ratio (OR)	95% CI		p value
	Total	Observed	Imputed		Lower	Upper	
Overall	258	227	31	1.25	0.95	1.63	0.108
COPD - Yes	153	130	23	1.20	0.58	2.46	0.622
COPD - No	105	97	8	2.22	0.97	5.12	0.060
Baseline mMRC - 1 or 2	76	66	10	0.91	0.34	2.45	0.850
Baseline mMRC - 3 or 4	163	145	18	2.09	1.05	4.14	0.035
COPD - Yes; Baseline mMRC - 1 or 2	46	38	8	0.67	0.17	2.64	0.566
COPD - Yes; Baseline mMRC - 3 or 4	97	84	13	1.50	0.62	3.62	0.368
COPD - No; Baseline mMRC - 1 or 2	30	28	2	1.32	0.30	5.81	0.715
COPD - No; Baseline mMRC - 3 or 4	66	61	5	3.41	1.13	10.23	0.029

CI - confidence intervals; mMRC - modified Medical Research Council breathless scale; COPD – chronic obstructive pulmonary disease.

Domain: Intensity. Threshold for difference: 8.9mm absolute difference mean days 5-7 over baseline Measure 0-100mm visual analogue scale (VAS) – <i>breathlessness unpleasantness now.</i>		Number			Odds ratio (OR)	95% CI		p value
		Total	Observed	Imputed		Lower	Upper	
Overall		258	227	31	1.03	0.79	1.34	0.812
COPD - Yes		153	130	23	1.00	0.51	1.96	0.993
COPD - No		105	97	8	1.17	0.52	2.64	0.709
Baseline mMRC - 1 or 2		76	66	10	0.64	0.23	1.73	0.378
Baseline mMRC - 3 or 4		163	145	18	1.18	0.59	2.38	0.640
COPD - Yes; Baseline mMRC - 1 or 2		46	38	8	1.02	0.26	3.95	0.982
COPD - Yes; Baseline mMRC - 3 or 4		97	84	13	0.97	0.40	2.36	0.941
COPD - No; Baseline mMRC - 1 or 2		30	28	2	0.32	0.07	1.60	0.166
COPD - No; Baseline mMRC - 3 or 4		66	61	5	1.58	0.53	4.69	0.406

CI - confidence intervals; mMRC - modified Medical Research Council breathless scale; COPD – chronic obstructive pulmonary disease.