Effect of co-trimoxazole (trimethoprim-sulfamethoxazole) vs placebo on death, lung transplant, or hospital admission in patients with moderate and severe idiopathic pulmonary fibrosis

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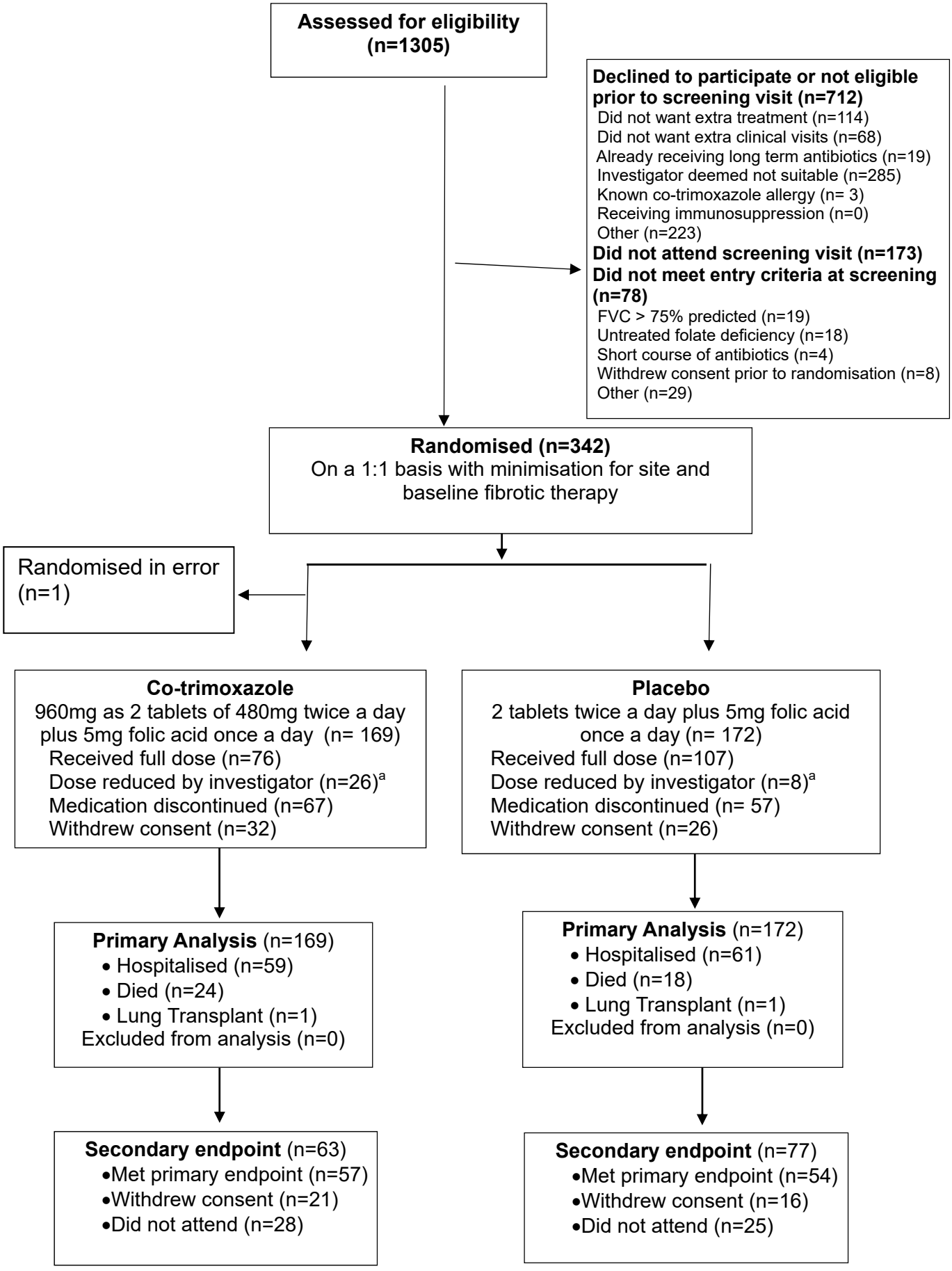
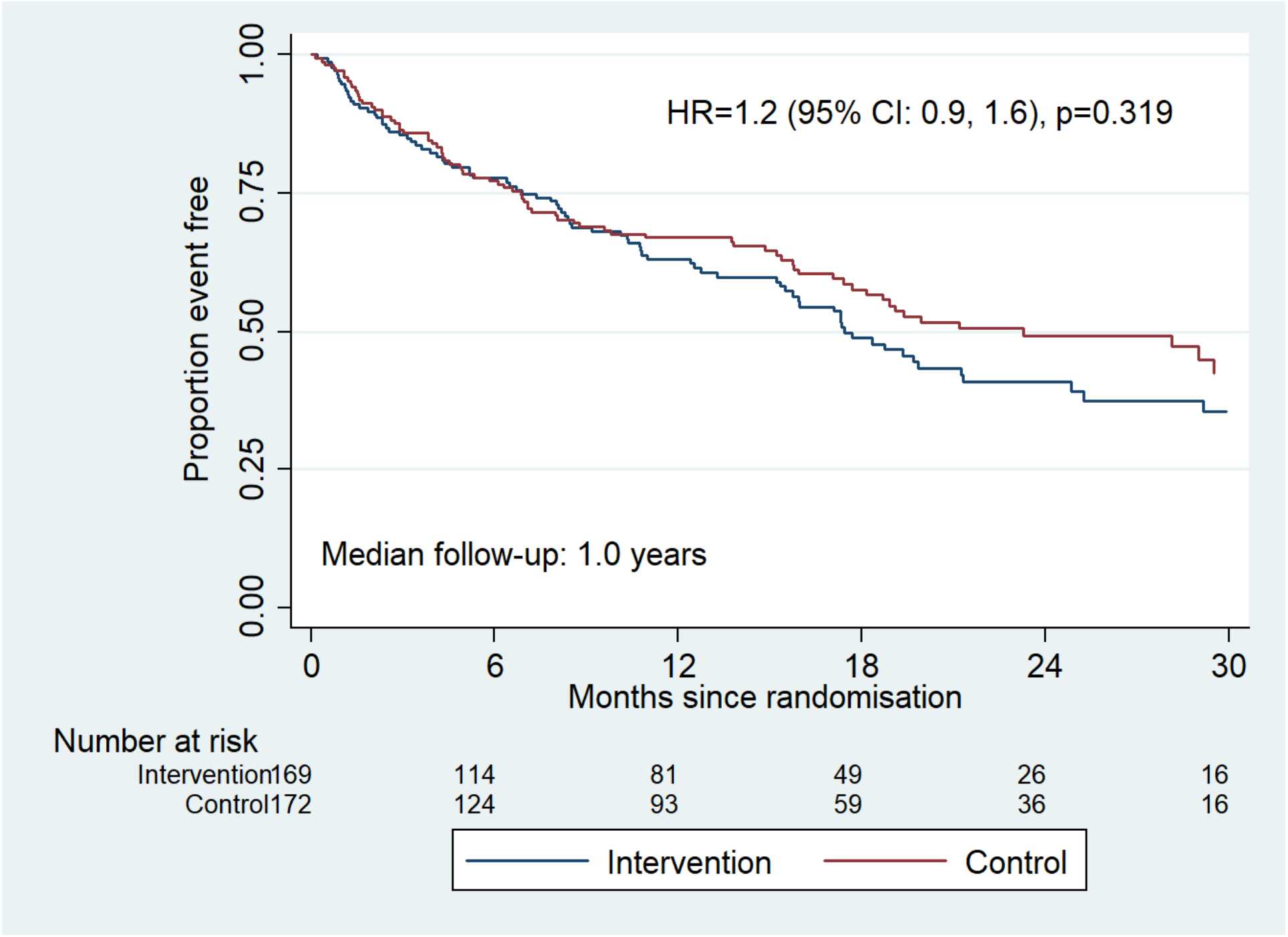
DOI:
10.1001/jama.2020.22960

Document Version
Peer reviewed version

Citation for published version (Harvard):
EME-TIPAC team 2020, 'Effect of co-trimoxazole (trimethoprim-sulfamethoxazole) vs placebo on death, lung transplant, or hospital admission in patients with moderate and severe idiopathic pulmonary fibrosis: the EME-TIPAC randomized clinical trial', *JAMA The Journal of the American Medical Association*, vol. 324, no. 22, pp. 2282-2291. https://doi.org/10.1001/jama.2020.22960


Assessed for eligibility (n=1305)
Declined to participate or not eligible prior to screening visit (n=712)
Did not want extra treatment (n=114)
Did not want extra clinical visits (n=68)
Already receiving long term antibiotics (n=19)
Investigator deemed not suitable (n=285)
Known co-trimoxazole allergy (n= 3)
Receiving immunosuppression (n=0)
Other (n=223)
Did not attend screening visit (n=173)
Did not meet entry criteria at screening (n=78)
FVC > 75% predicted (n=19)
Untreated folate deficiency (n=18)
Short course of antibiotics (n=4)
Withdrew consent prior to randomisation (n=8)
Other (n=29)
Randomised (n=342)
On a 1:1 basis with minimisation for site and baseline fibrotic therapy
Randomised in error (n=1)
Co-trimoxazole
960mg as 2 tablets of 480mg twice a day plus 5mg folic acid once a day (n= 169)
Received full dose (n=76)
Dose reduced by investigator (n=26)a
Medication discontinued (n=67)
Withdrew consent (n=32)
Placebo
2 tablets twice a day plus 5mg folic acid once a day (n= 172)
Received full dose (n=107)
Dose reduced by investigator (n=8)a
Medication discontinued (n= 57)
Withdrew consent (n=26)
Primary Analysis (n=169)
• Hospitalised (n=59)
• Died (n=24)
• Lung Transplant (n=1)
Excluded from analysis (n=0)
Primary Analysis (n=172)
• Hospitalised (n=61)
• Died (n=18)
• Lung Transplant (n=1)
Excluded from analysis (n=0)
Secondary endpoint (n=63)
•Met primary endpoint (n=57)
•Withdrew consent (n=21)
•Did not attend (n=28)
Secondary endpoint (n=77)
•Met primary endpoint (n=54)
•Withdrew consent (n=16)
•Did not attend (n=25)


HR=1.2 (95% CI: 0.9, 1.6), p=0.319
Median follow-up: 1.0 years
Proportion event free
0.00
0.25
0.50
0.75
1.00
0
6
12
18
24
30
Months since randomisation
Number at risk
Intervention 169 114 81 49 26 16
Control 172 124 93 59 36 16
Intervention
Control

Supplement 2

eTable 1 Dose modifications[a]

	Active Treatment		Placebo	
	Number of participants*	Number (%) of dose modifications	Number of participants*	Number (%) of dose modifications
3 month visit	114	19 (16.7%)	137	10 (7.3%)
6 month visit	96	7 (7.3%)	113	6 (5.3%)
12 month visit	61	4 (6.6%)	78	0
18 month visit	38	1 (2.6%)	46	0
24 month visit	20	0	28	0
30 month visit	10	0	10	0
36 month visit	2	0	3	0
Any dose change		31 (19%)		16 (9%)

[a]This represents the reduction of study drug from 2 tablets twice a day, to 2 tablets once a day 3 times a week

eTable 2 Primary outcome and secondary outcomes for individual components of primary outcome

	Co-trimoxazole (N=169)		Placebo (N=172)		
	Total exposure time (years)	Number of events to date (incidence)	Total exposure time (years)	Number of events to date (incidence)	Hazard Ratio (comparing co-trimoxazole to Placebo)
Randomized group allocation analysis[a]					
Composite primary outcome	185.6	84	209.1	80	Unadjusted 1.2 (0.9 to 1.6) p=0.33 Adjusted[1] 1.2 (0.9 to 1.6) p=0.32
Deaths censored at date of primary event (if primary not death)	185.6	24	209.1	18	Unadjusted 1.5 (0.8 to 2.8) p=0.17 Adjusted 1.5 (0.8 to 2.8) p=0.179
Respiratory-related death (censored at time of primary event)	185.6	20	209.1	17	Unadjusted 1.4 (0.7 to 2.6) p=0.34 Adjusted 1.4 (0.7 to 2.6) p=0.35
Non-elective hospital admissions (all cause)	185.6	59	209.1	61	Unadjusted 1.1 (0.7 to 1.5) p=0.75 Adjusted

					1.1 (0.7 to 1.3) p=0.73
Respiratory-related hospitalisation (censored at time of primary event)	185.6	40	209.1	42	Unadjusted 1.0 (0.7 to 1.6) p=0.86 Adjusted 1.0 (0.7 to 1.6) p=0.83
Per protocol analysis[b]					
Composite primary outcome	132.6	59	132.0	64	Unadjusted 0.9 (0.7 to 1.3) p=0.70 Adjusted[1] 0.9 (0.7 to 1.3) p=0.76
Deaths censored at date of primary event (if primary not death)	132.6	13	132.0	12	Unadjusted 1.1 (0.5 to 2.4) p=0.82 Adjusted[1] 1.1 (0.5 to 2.4) p=0.81
Respiratory-related death (censored at time of primary event)	132.7	12	132	11	Unadjusted 1.1 (0.5 to 2.5) p=0.82 Adjusted[2] 1.1 (0.5 to 2.5) p=0.82
Non-elective hospital admissions (all	132.6	45	132.0	51	Unadjusted 1.1 (0.7 to 1.7) p=0.58

cause)					Adjusted[1] 0.9 (0.6 to 1.4) p=0.64
Respiratory-related hospitalisation (censored at time of primary event)	132.6	29	132.0	35	Unadjusted 0.8 (0.5 to 1.3) p=0.45 Adjusted[2] 0.8 (0.5 to 1.4) p=0.49
Modified per protocol analysis[c]					
Composite primary outcome	92.5	44	123.7	62	Unadjusted 0.9 (0.6 to 1.4) p=0.41 Adjusted[1] 0.9 (0.6 to 1.4) p=0.77
Deaths censored at date of primary event (if primary not death)	92.5	11	123.7	12	Unadjusted 1.2 (0.5 to 2.8) p=0.60 Adjusted[1] 1.3 (0.6 to 2.9) p=0.59
Respiratory-related death (censored at time of primary event)	92.5	10	123.7	11	Unadjusted 1.2 (0.5 to 2.9) p=0.63 Adjusted[1] 1.2 (0.5 to 2.9) p=0.62
Non-elective	92.5	32	123.7	49	Unadjusted

hospital admissions (all cause)					0.9 (0.5 to 1.3) p=0.49 Adjusted[1] 0.9 (0.6 to 1.3) p=0.51
Respiratory-related hospitalisation (censored at time of primary event)	92.5	23	123.7	34	Unadjusted 0.9 (0.5 to 1.5) p=0.64 Adjusted[2] 0.9 (0.5 to 1.5) p=0.66

[a] This is defined as all participants analysed in the group to which they were randomized [b]This is defined as people who adhered to at least 80% of the study medication [c] This is defined as people who adhered to at least 80% of the high dose regimen

eTable 3 Per-protocol[a] analysis of the questionnaire outcomes at 12 months.

Outcome	*Co-trimoxazole*		*Placebo*		*Adjusted for site and baseline anti-fibrotic therapy*		*Adjusted for site, baseline anti-fibrotic therapy and baseline value*	
	N	*Mean (SD)*	*N*	*Mean (SD)*	*Mean difference (95% CI)*	*p-value*	*Mean difference (95% CI)*	*p-value*
LCQ total[b]	*53*	*15.9 (3.9)*	*46*	*14.3 (4.1)*	*-1.5 (-3.1, 0.04)*	0.06	*-1.2 (-2.4, -0.1)*	0.03
LCQ physical	*53*	*5.1 (1.2)*	*47*	*4.7 (1.2)*	*-0.4 (-0.8, 0.1)*	0.13	*-0.3 (-0.6, 0.1)*	0.14
LCQ psychol	*53*	*5.3 (1.4)*	*49*	*4.8 (1.6)*	*-0.5 (-1.1, 0.1)*	0.07	*-0.5 (-0.9, -0.1)*	0.02
LCQ Social	*53*	*5.5 (1.5)*	*49*	*5.0 (1.5)*	*-0.5 (-1.1, 0.0)*	0.07	*-0.4 (-0.9, -0.0)*	0.04
MRC Score, median (IQR)	*55*	*3.00 (2.00, 4.00)*	*56*	*3.00 (2.00, 4.00)*		*0.84*		*0.45*
Cough score,	*55*	*44.80*	*55*	*49.56 (26.77)*	*4.42 (-5.92,*	*0.40*	0.40	*0.86*

mean (mm)		*(28.76)*			*14.75)*			
KBILD[e]								
Psychol	*54*	*51.4 (16.7)*	*55*	*52.3 (16.6)*	*1.0 (-5.3, 7.3)*	0.76	*-0.4 (-5.8, 4.9)*	0.88
Breathless	*55*	*35.2 (17.6)*	*56*	*35.1 (15.4)*	*0.6 (-5.6, 6.8)*	0.85	*-1.7 (-6.6, 3.2)*	0.50
Chest	*55*	*62.5 (18.8)*	*56*	*54.6 (21.9)*	*-8.4 (-16.1, -0.8)*	0.03	*-6.9 (-13.3, 0.4)*	0.04
Total	*54*	*51.5 (11.8)*	*55*	*50.8 (11.0)*	*-0.7 (-5.0, 3.7)*	0.77	*-1.6 (-5.1,1.9)*	0.37
EQ5D[f]	*77*	*0.43 (0.37)*	*84*	*0.40 (0.37)*	*-0.03 (-0.14,0.09)*	*0.66*	*-0.03 (-0.13,0.06)*	*0.49*
Lung Function								
Absolute								
FVC (L)	*48*	*2.21 (0.49)*	*50*	*2.27 (0.52)*	*0.05 (-0.16, 0.25)*	0.65	*0.04 (0.06, 0.14)*	*0.42*
FEV1 (L)	*48*	*1.83 (0.39)*	*50*	*1.90 (0.42)*	*0.08 (-0.08, 0.25)*	0.33	*0.03 (-0.05, 0.12)*	*0.44*
DLCO	*39*	*3.37*	*40*	*3.69 (1.47)*	*0.28*	0.46	*0.45*	*0.20*

(mmol/min/ KPa)		*(1.92)*			*(-0.47, 1.03)*		*(-0.24, 1.15)*	
Percent predicted								
FVC (%)	*48*	*52.8 (8.7)*	*50*	*54.0 (9.4)*	*0.9 (-2.7, 4.5)*	0.63	*0.6 (-1.8, 3.0)*	*0.62*
FEV1 (%)	*48*	*56.5 (9.2)*	*50*	*59.2 (11.1)*	*2.7 (-1.4, 6.8)*	*0.20*	*1.0 (-1.7, 3.6)*	*0.48*
DLCO (%)	*39*	*38.5(19.0)*	*40*	*42.2 (14.8)*	*3.5 (-4.1, 11.0)*	*0.37*	*5.8 (-1.7, 13.4)*	*0.13*

[a]This is defined as people who adhered to at least 80% of the study medication. . [b] The Leicester Cough Questionnaire score ranges from 3 (lowest quality of life) to 21 (highest quality of life) and the domain scores range from 1 (lowest quality of life) to 7 (highest quality of life), [c] The King's Brief Interstitial Lung Disease questionnaire total and domain scores ranges between 0 (worse health status) and 100 (best heath status),[d] The MRC dyspnea score is a 5 point scare ranging from 1 (Not troubled by breathlessness except on strenuous exercise) to 5 (Too breathless to leave the house or breathlessness on dressing or undressing), [e] Cough score was a visual analogue score between 0 (I have not been bothered by my cough at all) to 100 (My cough has been the worst it can be). [f]EuroQol 5-Dimension 5-Level utility ranges between 0 (death) and 1 (perfect health). There data was incomplete for some patients as they did not complete the questionnaires or attend for lung function assessments

n = number, SD = standard deviation, CI = confidence interval, MRC = medical research council, IQR = inter-quartile range, psychol: psychological FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide. L: Liters, mmol/min/KPa: millimoles per minute per kilopascal %: percent

eTable 4

Modified per-protocol analysis[a] of the questionnaire outcomes at 12 months

Outcome		Active Treatment		Placebo	Unadjusted		Adjusted	
	N	Mean (SD)	N	Mean (SD)	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
LCQ total[b]	37	15.7 (3.8)	44	14.1 (4.1)	-1.5 (-3.2,0.3)	0.10	-1.4 (-2.7,-0.1)	0.03
LCQ physical	37	5.0 (1.2)	45	4.6 (1.2)	-0.4 (-0.9,0.2)	0.17	-0.4 (-0.8,0.0)	0.06
LCQ psychol	37	5.4 (1.3)	46	4.8 (1.6)	-0.5 (-1.1,0.2)	0.14	-0.5 (-1.0,-0.1)	0.03
LCQ Social	37	5.4 (1.5)	46	4.9 (1.5)	-0.5 (-1.1,0.2)	0.16	-0.5 (-1.0,0.0)	0.05
MRC Median (IQR)[c]	38	3.0 (2.0, 4.0)	54	3.0 (2.0, 4.0)		0.66		0.49
Cough score (mm)[d]	38	43.1 (28.4)	53	49.8 (27.2)	6.3 (-5.3,18.0)	0.29	2.3 (-8.3,12.9)	0.67
KBILD[e]								
Psychol	38	51.4 (16.2)	53	52.3 (16.7)	1.0 (-6.0,7.9)	0.78	-1.0 (-6.9,4.9)	0.74
Breathless	38	35.3 (17.6)	54	35.0 (15.7)	0.5 (-6.2,7.2)	0.89	-1.0 (-6.3,4.4)	0.73
Chest	38	60.6 (19.2)	54	54.5 (22.1)	-6.8 (-15.5,1.9)	0.13	-6.3 (-13.8,1.1)	0.10
Total	38	51.5 (11.7)	53	50.8 (11.2)	-0.6	0.81	-1.4	0.49

					(-5.4,4.2)		(-5.3,2.5)	
EQ5D[†]	60	0.40 (0.37)	81	0.40 (0.37)	-0.03 (-0.14,0.09)	0.663	-0.01 (-0.12,0.10)	0.836
Lung Function								
Absolute								
FVC (L)	*32*	*2.23 (0.51)*	*48*	*2.26 (0.53)*	*0.03 (-0.21 – 0.26)*	*0.83*	*0.06 (-0.05 – 0.17)*	*0.30*
FEV1 (L)	*32*	*1.84 (0.43)*	*48*	*1.89 (0.43)*	*0.05 (-0.14 – 0.25)*	*0.58*	*0.05 (-0.05 – 0.15)*	*0.70*
DLCO (mmol/L/ Kpa)	*27*	*3.71 (2.19)*	*40*	*3.69 (1.47)*	*0.01 (-0.86 – 0.87)*	*0.99*	*0.36 (-0.43 – 1.14)*	*0.37*
Percent predicted								
FVC (%)	*32*	*52.5 (8.5)*	*48*	*54.0 (9.6)*	*1.5 (-2.6 – 5.6)*	*0.47*	*1.2 (-1.5 – 3.8)*	*0.39*
FEV1 (%)	*32*	*56.2 (9.6)*	*48*	*59.2 (11.2)*	*3.2 (-1.5 – 7.9)*	*0.18*	*1.6 (-1.4 – 4.7)*	*0.29*
DLCO (%)	*27*	*41.4 (21.3)*	*40*	*42.2(14.8)*	*1.3 (-7.4 – 9.9)*	*0.77*	*5.3 (-3.0 – 13.6)*	*0.21*

[a]This is defined as people who adhered to at least 80% of the high dose regimen. [b] The Leicester Cough Questionnaire score ranges from 3 (lowest quality of life) to 21 (highest quality of life) and the domain scores range from 1 (lowest quality of life) to 7 (highest quality of life), [c] The King's Brief Interstitial Lung Disease questionnaire total and domain scores ranges between 0 (worse health status) and 100 (best heath status),[d] The MRC dyspnea score is a 5 point scare ranging from 1 (Not troubled by breathlessness except on strenuous exercise) to 5 (Too breathless to leave the house or breathlessness on dressing or undressing), [e] Cough score was a visual analogue score between 0 (I have not been bothered by my cough at all) to 100 (My cough has been the worst it can be). [f]EuroQol 5-Dimension 5-Level utility ranges between 0 (death) and 1 (perfect health). There data was incomplete for some patients as they did not complete the questionnaires or attend for lung function assessments

n = number, SD = standard deviation, CI = confidence interval, MRC = medical research council, IQR = inter-quartile range, psychol: psychological FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide. L: Liters, mmol/min/KPa: millimoles per minute per kilopascal %: percent

eTable 5 Cough score over time by randomisation arm

	Co-trimoxazole		Placebo			
	Mean (SD)	n	Mean (SD)	n	Difference	p-value (Bonferoni corrected)
3 months	43.7 (26.8)	122	44.2 (28.3)	139	1.0 (-8.2,10.2)	1.00
6 months	40.1 (26.2)	106	47.5 (28.7)	116	6.8 (-3.0,16.6)	0.44
12 months	44.7 (27.0)	72	49.7 (26.7)	84	4.5 (-6.8,15.7)	1.00
18 months	46.0 (29.7)	42	58.4 (25.0)	51	15.0 (1.2,28.8)	0.02
24 months	39.7 (27.3)	22	48.6 (25.7)	30	11.9 (-5.9,29.6)	0.51
30 months	43.6 (27.2)	13	54.6 (26.8)	12	10.6 (-13.9,35.0)	1.00
36 months	75.0 (7.1)	2	41.3 (38.4)	4	-21.1 (-71.8,29.6)	1.00
Overall Difference					5.7 (0.1,11.2)	0.04

n = number, SD = standard deviation

eTable 6 Summary of safety blood measures at 12 months

	Intervention		Placebo		
	Mean (SD)	N	Mean (SD)	N	p-value
White cell count x 10^9/litre	8.9 (2.3)	68	8.4 (1.9)	87	0.23
Haemoglobin (HB) g/dL	142.8 (13.2)	68	146.5 (14.0)	87	0.10
Red Cell Count (RCC) x 10^{12} /litre	4.7 (0.5)	67	4.8 (0.4)	86	0.09
Mean cell volume (MCV) fL	92.7 (6.9)	68	92.0 (5.6)	86	0.48
Mean cell haemoglobin (MCH) picograms	30.9 (2.8)	68	30.7 (2.1)	86	0.66
Haematocrit (HCT) (%)	0.4 (0.0)	67	0.4 (0.0)	83	0.09
Neutrophils x 10^9 / litre	5.99 (1.94)	67	5.65 (1.65)	86	0.24
Lymphocytes x 10^9 / litre	1.70 (0.75)	68	1.78 (0.69)	86	0.50
Eosinophils x 10^9 / litre	0.29 (0.15)	68	0.25 (0.15)	86	0.11
Basophils x 10^9 / litre	0.06 (0.04)	67	0.05 (0.04)	86	0.24
Monocytes x 10^9 / litre	0.71 (0.22)	68	0.68 (0.21)	86	0.40
Platelets x 10^9 / litre	242.8 (65.4)	68	238.7 (67.0)	87	0.71
Sodium (Na) mmol/litre	138.2 (2.8)	68	138.7 (2.7)	88	0.22
Potassium (K) mmol/litre	4.4 (0.5)	68	4.4 (0.4)	88	0.61
Urea mmol/litre	6.1 (2.4)	68	5.6 (1.7)	88	0.11
Creatinine µmol/litre	96.3 (34.7)	68	83.6 (21.1)	88	0.005
Bilirubin µmol/litre	8.2 (3.8)	65	9.6 (5.0)	86	0.06
Alanine aminotransferase: IU/litre	22.9 (12.6)	68	21.3 (10.3)	85	0.39
Alkaline phosphatase IU/litre	95.5 (53.0)	68	88.1 (29.0)	88	0.27
Albumin g/dL	39.8 (3.8)	67	39.3 (4.6)	88	0.52
Total protein g/dL	74.0 (6.8)	56	73.2 (6.1)	75	0.46
Globulin g/dL	30.2 (9.9)	31	34.0 (6.5)	39	0.06

SD = standard deviation, n = number, g/dL = grams per decilitre, fL = femtoliters, mmol = millimole, µmol = micromole, IU = international unit

Data sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised individual patient data, with appropriate data dictionary, may be granted following review and appropriate data sharing agreements assuming there is appropriate acknowledgement of the data source. There are no restriction on the analyses that may be undertaken using the data.