Supplemental Online Content

Wilson AM, Clark AB, Cahn T, Chilvers ER, Fraser W, Hammond M, Livermore DM, Maher TM, Parfrey H, Swart AM, Stirling S, Thickett DR, Whyte M, . Effect of Co-Trimoxazole (Trimethoprim-Sulfamethoxazole) vs Placebo on Death, Lung Transplant, or Hospital Admission in Patients With Moderate and Severe Idiopathic Pulmonary Fibrosis. *JAMA.* Published online December 8, 2020. doi:10.1001/jama.2020.22960

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1 Dose modifications[a]

	Co-trimoxazole		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 (cumulative incidence)	Total exposure time (years)	Number of events to date (cumulative 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=0.18
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
Lung transplant	185.6	1	209.1	1	Not analysed.
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 cause)	132.6	45	132.0	51	Unadjusted 1.1 (0.7 to 1.7) p=0.58 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	92.5	10	123.7	11	Unadjusted 1.2 (0.5 to 2.9) p=0.63

time of primary event)					Adjusted[1] 1.2 (0.5 to 2.9) p=0.62
Non-elective hospital admissions (all cause)	92.5	32	123.7	49	Unadjusted 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 lung function and 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
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 (mmol/min/KPa)	39	3.37 (1.92)	40	3.69 (1.47)	0.28 (-0.47, 1.03)	0.46	0.45 (-0.24, 1.15)	0.20
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
Medical Research Council dyspnea score[b], Median (IQR)	55	3.00 (2.00, 4.00)	56	3.00 (2.00, 4.00)		0.84		0.45
EQ-5D-5L utiliy[c]	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
Cough score, mean (mm)[d]	55	44.80 (28.76)	55	49.56 (26.77)	4.42 (-5.92, 14.75)	0.40	0.40	0.86
Leicester Cough Questionnaire, mean (SD)[e]								
LCQ total	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	0.07	-0.4	0.04

					(-1.1, 0.0)		(-0.9, -0.0)	
King's Brief Interstitial Lung Disease questionnaire[f]								
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

[a]This is defined as people who adhered to at least 80% of the study medication. [b]Medical Research Council dyspnea score is a 5 point scale ranging between 1 and 5 (higher values represent increasing breathlessness) a value of 3 represents walking slower than contemporaries or having to stop when walking at own pace, [c]EQ-5D-5L utility ranges from−0.59 to 1 (higher score indicates better health utility) a value of 0.75 represents that the quality of life adjusted years has been reduced by a slight amount. Utilities are calculated by mapping to standard health state valuations. [d]The cough score is a cough severity visual analogue score between 0 and 100 (higher score represents greater cough severity) a value of 40 represents coughing is two-fifths of their maximum perceived cough severity. [e]The Leicester Cough Questionnaire is a cough related quality of life score and ranges from 3 to 21 - domain scores range from 1 to 7 - (higher values represent better cough related quality of life) a value of 15 suggests a cough that has affected life activities a little bit of the time over the preceding 2 weeks. It is calculated as the sum of the individual domains. [f]The King's Brief Interstitial Lung Disease questionnaire total and domain scores range between 0 and 100 (higher values represent better health status) a value of 50

suggest that IPF has affect life activities some of the time over the last 2 weeks. It is calculated using the logit-scoring method. 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 lung function and questionnaire outcomes at 12 months

Outcome	Co-trimoxazole		Placebo		Unadjusted		Adjusted	
	N	Mean (SD)	N	Mean (SD)	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
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

[b]Medical Research Council dyspnea score Median (IQR)[b]	38	3.0 (2.0, 4.0)	54	3.0 (2.0, 4.0)		0.66		0.49
EQ5D[c]	60	0.40 (0.37)	81	0.40 (0.37)	-0.03 (-0.14,0.09)	0.66	-0.01 (-0.12,0.10)	0.84
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
Leicester Cough Questionnaire, mean (SD)[e]								
LCQ total	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
Kings Brief Interstitial Lung Disease questionnaire[f]								
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 (-5.4,4.2)	0.81	-1.4 (-5.3,2.5)	0.49

Abbreviations: 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

[a]This is defined as people who adhered to at least 80% of the high dose regimen. [b]Medical Research Council dyspnea score is a 5 point scale ranging between 1 and 5 (higher values represent increasing breathlessness) a value of 3 represents walking slower than contemporaries or having to stop when walking at own pace, [c]EQ-5D-5L utility ranges from−0.59 to 1 (higher score indicates better health utility) a value of 0.75 represents that the quality of life adjusted years has been reduced by a slight amount. Utilities are calculated by mapping to standard health state valuations. [d]The cough score is a cough severity visual analogue score between 0 and 100 (higher score represents greater cough severity) a value of 40 represents coughing is two fifths as much as it could possibly be. [e]The Leicester Cough Questionnaire is a cough related quality of life score and ranges from 3 to 21 - domain scores range from 1 to 7 - (higher values represent better cough related quality of life) a value of 15 suggests a cough that has affected life activities a little bit of the time over the preceding 2 weeks. It is calculated as the sum of the individual domains. [f]The King's Brief Interstitial Lung Disease questionnaire total and domain scores range between 0 and 100 (higher values represent better health status) a value of 50 suggest that IPF has affect life activities some of the time over the last 2 weeks. It is calculated using the logit-scoring method. There data was incomplete for some patients as they did not complete the questionnaires or attend for lung function assessments

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 Adverse events

Adverse event	Co-trimoxazole: total events	Co-trimoxazole number of people with at least one event (%)	Placebo: number of events	Placebo: number of people with at least one event (%)
		N = 169		N = 172
Blood and lymphatic system disorders	3	3 (2%)	3	3 (2%)
Cardiac disorders	6	6 (4%)	4	3 (2%)
Ear and labyrinth disorders	3	2 (1%)	0	0
Eye disorders	5	5 (3%)	6	5 (3%)
Gastrointestinal disorders	216	92 (54%)	224	81 (47%)
- Nausea	89	53 (31%)	67	42 (24%)
- Diarrhoea	52	36 (21%)	84	53 (31%)
- Vomiting	28	20 (12%)	20	16 (9%)
- Constipation	11	10 (6%)	5	5 (3%)
General disorders and administration site conditions	36	25 (15%)	20	17 (10%)
- Fatigue	15	15 (9%)	11	10 (6%)
- Chest pain	8	7 (4%)	6	5 (3%)
- Edema peripheral	5	4 (2%)	0	0
Immune system disorders	1	1 (1%)	1	1(1%)
Infections and infestations	110	57 (33%)	127	70 (41%)
- Lower Respiratory Tract Infection	63	35 (20%)	66	42 (24%)
Injury, poisoning and procedural complications	7	5 (3%)	10	10 (6%)0
Investigations	44	34 (20%)	22	16 (9%)

- Weight decrease	24	21 (12%)	16	14 (8%)
Metabolism and nutrition disorders	57	38 (22%)	27	19 (11%)
- Decreased appetite	26	18 (11%)	9	6 (3%)
- Hyperkalemia	24	18 (11%)	14	11 (6%)
Musculoskeletal and connective tissue disorders	21	18 (11%)	20	14 (8%)
Neoplasm/s benign, malignant and unspecified (incl cysts and polyps)	3	2 (1%)	1	1 (1%)
Nervous system disorders	41	29 (17%)	32	24 (14%)
- Headache	22	16 (9%)	14	11 (6%)
Psychiatric disorders	5	4 (2%)	2	2 (1%)
Renal and urinary disorders	14	12 (7%)	7	7 (4%)
Reproductive system and breast disorders	0	0	2	2 (2%)
Respiratory, thoracic and mediastinal disorders	77	46 (27%)	95	61 (35%)
- Cough	27	23 (14%)	33	30 (17%)
- Dyspnoea	31	25 (15%)	34	30 (17%)
Skin and subcutaneous tissue disorders	46	29 (17%)	30	23 (13%)
- Rash	31	23 (14%)	20	15 (9%)
Surgical and medical procedures	1	1 (1%)	2	2 (1%)
Vascular disorders	0	0	5	3 (2%)
Total adverse events	696		640	
Number with at least one adverse event		146 (86%)		142 (83%)
Number with at least two adverse events		119 (70%)		121 (70%)

Adverse events were captured at each study visit and coded using Medical Dictionary for Regulatory Activities (MedDRA) terms. Data are presented where an event occurred on at least 10 occasions in either treatment group. Hyperkalaemia was defined as a potassium > 5.0 mmol/l. Investigations include abnormal laboratory results and weight change.

eTable 7 Summary of safety blood measures at 12 months

	Co-trimoxazole		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