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

Subtitle: The EME-TIPAC study

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Key Points

Question: What is the clinical efficacy of co-trimoxazole (trimethoprim-sulfamethoxazole) in idiopathic pulmonary fibrosis (IPF) in terms of time to death (all causes), lung transplant, or first non-elective hospital admission?

Findings: In this randomized clinical trial, which included 343 patients with moderate or severe IPF, the incidence of the composite outcome among those treated with oral co-trimoxazole 960 mg twice daily vs placebo was 0.45 vs 0.38 per person-year after median follow-up of 1.02 years; the hazard ratio was not statistically significant.

Meaning: Co-trimoxazole compared to placebo did not improve a composite clinical outcome among patients with moderate or severe IPF.

Keywords: Idiopathic pulmonary fibrosis, co-trimoxazole, mortality, hospitalisation, cough, randomized controlled trial

ABSTRACT

Importance: Idiopathic pulmonary fibrosis (IPF) has a poor prognosis, and limited treatment options. Patients with IPF have altered lung microbiota, with bacterial burden within the lungs associated with mortality; previous studies have suggested benefit with co-trimoxazole (trimethoprim-sulfamethoxazole).

Objective: To determine the efficacy of co-trimoxazole in patients with moderate and severe IPF.

Design, Setting and Participants: Double-blind, placebo-controlled, parallel, randomized trial of 342 patients with IPF, breathlessness (Medical Research Council (MRC) dyspnea score > 1) and impaired lung function (forced vital capacity (FVC) <75% predicted) conducted in 39 UK specialist interstitial lung disease centers between April 2015 (first patient visit) and April 2019 (last patient follow-up).

Intervention: Study participants were randomized to receive 960mg twice daily oral co-trimoxazole (n=170) or matched placebo (n=172) for between 12 and 42 months. All patients received 5mg folic acid orally once daily.

Main Outcome and Measures: The primary outcome was time to death (all causes), lung transplant, or first non-elective hospital admission. There were 15 secondary outcomes, including the individual components of the primary endpoint respiratory-related events, lung function (FVC and gas transfer) and patient reported outcomes (MRC dyspnea score, EuroQol 5-dimension 5-level, Cough Score, Leicester Cough Questionnaire and King's Brief Interstitial Lung Disease questionnaire).

Results: Among 342 individuals who were randomized (mean age 71.3 years; 46 [13%] female), 283 (83%) completed the trial. The median (interquartile range) duration of follow-up was 1.02 (0.35 to 1.73) years. Events/person year of follow up among participants randomized to the co-trimoxazole and placebo groups were 0.45 (84/186) and 0.38 (80/209) respectively, with a hazard ratio of 1.2 (0.9 to 1.6) (p=0.32). There were no statistically significant differences in other event outcomes, lung function, or patient reported outcomes. Patients in the co-trimoxazole group experienced 696 adverse events (nausea n=89, diarrhea n=52, vomiting n=28, rash n=31) whereas patients in the placebo group experienced 640 adverse events (nausea n= 67, diarrhea n=84, vomiting n=20, rash n=20).

Conclusion and relevance: Among patients with moderate or severe IPF, treatment with oral co-trimoxazole did not reduce a composite outcome of time to death, transplant, or non-elective hospitalization compared with placebo.

Trial Registration: ISRCTN 17464641

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease with a median survival of 5.7 years[1] (European IPF registry, 2018), increasing incidence[2] and limited treatment options. Respiratory tract infection is common in patients with IPF[3] and bronchial washings contain pathogenic bacteria, as identified by quantitative culture[4,5] or non-culture-dependent techniques[6]. Bronchoalveolar lavage studies, from two separate groups, have shown that a high bacterial load was associated with reduced lung function and death[7,8] and a lung microbiota enriched with *Streptococcus* spp. and *Staphylococcus* spp. was associated with reduced progression-free survival[9] in IPF. Moreover, innate immune responses may be abnormal in IPF, potentially increasing susceptibility to infection[10,11].

Co-trimoxazole (trimethoprim-sulfamethoxazole), a broad-spectrum antibiotic, was reported to improve clinical outcomes in IPF in two small randomized clinical trials[12,13] and to be cost-effective[14]. Exploratory analysis suggested an improvement in health-related quality-of-life and oxygen requirements and, in those adhering to the study protocol, a reduction in mortality over a 12-month period; however, evidence of a survival benefit was not conclusive[13].

The aim of this study was to determine the clinical efficacy of co-trimoxazole in patients with moderate-severe IPF (defined as FVC≤75% predicted), in terms of the time to death (all-cause), lung transplant, or first non-elective hospital admission. Secondary aims were to assess the effects on respiratory-related outcomes, patient-reported outcomes (in terms of health-related quality of life, cough and breathlessness) and lung function.

METHODS

This was a phase III double blind, placebo-controlled, parallel, randomized multi-center study of oral co-trimoxazole added to standard care. The protocol has been published[15] and the final protocol, amendments and statistical analysis plan are available in supplement 1. The study was conducted according to Good Clinical Practice, and the study protocol received ethical approval (14/LO/1800).

Patients were treated from randomization until withdrawal, death, first non-elective admission (for any reason), lung transplant or the end of the study follow-up, with a minimum duration of 12 months and maximum of 42 months. The study was conducted in 43 specialist interstitial lung disease (ILD) centers, or in sites affiliated with them, from all regions in the UK.

All participants provided written informed consent. Participants were randomized between April 2015 and April 2018 and follow-up was completed in April 2019. In May 2016, modifications removed an exclusion of participants diagnosed more than 2 years before randomization and increased the permitted FVC% predicted value from 70% to 75% to improve recruitment. An optional bronchoscopy sub-study was discontinued in June 2017.

Patients were recruited into the study if they had IPF diagnosed according to contemporaneous international guidelines[16] and had a modified Medical Research Council (MRC) dyspnea score >1. They could receive licensed medication for IPF at a stable regimen. Patients were excluded if they had FVC >75% predicted, a

significant co-existing respiratory or other comorbidity, or a respiratory tract infection during the preceding 4 weeks or were receiving immunosuppression.

Patients were randomized on a 1:1 basis to receive either oral co-trimoxazole 960 mg twice daily (as 2 tablets of 480 mg each) or 2 matched placebo tablets. The treatment allocated was generated via a computer code using minimisation for site, current use of antifibrotic therapy and involvement in bronchoscopy sub-study, under the supervision of the study statistician. All patients received 5mg folic acid orally once daily to prevent impaired hematopoiesis. Treatments were given in addition to standard care as defined by National Institute for Health and Clinical Excellence (NICE) guidelines (www.nice.org.uk/CG163).

A reduction of treatment dose to 2 tablets (i.e. 960 mg co-trimoxazole or 2 placebo tablets daily) plus 5 mg folic acid three times weekly was permitted if a participant developed gastrointestinal adverse effects rash, grade 1 hyperkalemia, or any other adverse event requiring dose reduction in the view of the Principal Investigator.

Outcomes

The primary outcome was the time to death (all causes), lung transplant, or first non-elective hospital admission for any reason. These data were obtained at each site, until the date of withdrawal or the end of the study, by screening hospital records and capturing details of out-of-hospital death from Primary Care records, if required. The primary outcome was censored at the date of withdrawal if patients withdrew consent to be followed up. Secondary outcomes included the individual components of the primary outcome. Respiratory-related events, determined by an independent

committee, were analyzed separately. Spirometry[17] and gas transfer (an assessment of carbon monoxide uptake by the lung which reflects the ability of the lungs to exchange gas into the bloodstream)[18] were captured at baseline, 6 and 12 months. The MRC dyspnea scale[19], Euroqol 5-dimension 5-level (EQ-5D-5L) questionnaire[20], cough score (captured on visual analogue scale, ranging from 0mm “I have not been bothered by my cough at all” to 100mm “My cough has been the worst it can be”), Leicester Cough Questionnaire (LCQ)[21] and King’s Brief Interstitial Lung Disease (K-BILD) questionnaire[22] were undertaken at baseline, at 3 and 6 months, then 6-monthly throughout the study, including a final assessment at the end of the study. Sputum was obtained, where clinically relevant, and sent for local microbiological culture and antibiotic susceptibility testing. Blood was taken for full blood count, urea and electrolytes and liver function at baseline, 6 weeks, 3, 6, 9 and 12 months then 6-monthly for the duration of the study. Adverse events were captured at each visit and assessed for severity. Blood biomarker analysis is not reported here.

Statistical analysis

The trial was designed to have 80% power (two-sided test, significance level of 5%) to show a change in hospitalization-free survival from a median value of 28.8 months in the placebo group to 51.1 months in the co-trimoxazole group (hazard ratio (HR) of 0.56) over this study period, assuming 330 patients were randomized and 20% withdrew from the study. This was based on a sensitivity analysis of patients from the previous study[13] with reduced lung function (FVC<70% predicted) using an intention-to-treat analysis.

The primary outcome, and secondary event measurements, were analysed using a

Cox proportional hazards model adjusted for the baseline variables, licensed IPF medication use and site as a random effect. If the model did not converge then site was included as a strata in the analysis and a sandwich-based robust cluster variance was used. The proportionality assumption was assessed using the global test with Schoenfeld residual. This had a test statistic of 1.58 and a p-value of 0.45, thus providing no evidence that the assumption was violated. The results are presented as the Kaplan-Meier estimate with median time to outcome. The EQ-5D-5L was converted to utilities by mapping to standard health state valuations[23] and the K-BILD was calculated using the logit-scoring method[24]. The MRC dyspnea score was analyzed using a Mann-Whitney test at 12 months; other questionnaires and lung function measurements were analyzed for the using linear mixed models to compare the mean values at 12 months between the treatment and placebo groups adjusted for the baseline variables, licensed IPF medication use and site as a random effect. A repeated measures model was fitted for each outcome at all time-points with a fixed term for licensed IPF medication, randomization group and time and random effects were included for site and the person identification number. For this analysis, the significance of the between group contrast at each time-point was adjusted using a Bonferroni correction.

All analyses were two sided at the 5% level of significance and were undertaken as pre-specified, including all participants analyzed in the group to which they were randomized. Additionally, pre-specified per-protocol ($\geq$80% adherence to study medication) and modified-per-protocol (those who adhered to the high-dose regimen) analyses were undertaken.

The missing endpoints at 12 months were imputed using the iterative chained equations approach[25]. The outcomes at 12 months and baseline were included in the equations, along with randomization group, body mass index and gender. As the rate of missing data was high, a total of 45 imputations were created and the results model estimates combined using Rubin's equations. The analysis was conducted using Stata/MP 16. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. The model assumptions were assessed visually by plotting the residuals, which were all approximately normally distributed.

The adverse event analysis was based on all patients who received at least one dose of drug or placebo. Data were analysed for event rates and percentage of patients with at least one adverse event and coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Safety blood measures were compared at 12 months.

RESULTS

A total of 1305 participants were screened at 43 sites; 349 met the inclusion criteria and 342 were randomized from 39 sites (Figure 1). One participant, randomized to the intervention (co-trimoxazole) group, was randomized in error and their data were not analysed. Fifty-eight individuals (17%) withdrew from the study partway through follow-up, 32 (19%) from the co-trimoxazole group (21 (12%) within the first 12 months) and 26 (15%) from the placebo group (16 (9%) within the first twelve months), without meeting an endpoint; their data are included until the point of withdraw. A total follow-up of 395-person years was assessed with 164 events. The mean (standard deviation (SD)) patient age was 71.3 (7.5) years, with a mean FVC of 2.25 (0.56) liters (L) or 55.7 (9.4) % predicted. Baseline characteristics and other factors were balanced between the two treatment groups, other than for gender and the presence of diabetes (Table 1).

The mean (SD) compliance in the co-trimoxazole group was 81.4 (22.8) %, compared with 85.5 (21.7) % in the control (placebo) group. The number of participants who met the 80% treatment threshold was 120 (71.9%) in the co-trimoxazole group compared with 125 (72.1%) in the placebo group. Dose reduction occurred in 47 (18%) individuals: 16 (9%) in the placebo group and 32 (19%) in the co-trimoxazole group (eTable 1 in supplement 2).

Primary Outcome

A total of 164 primary outcome events occurred (Figure 2). The incidence of events was 0.45 (84/186) per person-year in the co-trimoxazole group and 0.38 (80/209) in the placebo group. The HR was 1.2 (0.9,1.6) for both the unadjusted analysis and

adjusted analysis. The median (inter quartile range (IQR)) survival was 1.45 (1.28, 1.78) years in the co-trimoxazole group and 1.94 (1.48,2.84) in the placebo group. The site could not be included in this model due to model instability; a robust variance method gave HR 1.2 (0.8,1.6), p=0.37 and with stratification gave HR 1.2 (0.9,1.7), p=0.24. There were no statistically significant differences between the two groups for the per-protocol or modified per protocol analyses (eTable 2 in supplement 2) for event outcomes.

Secondary Outcomes

The individual components of the primary outcome are shown in Figure 2 and eTable 2 in supplement 2. There was no statistically significant difference in all-cause mortality (HR = 1.5 (0.8, 2.8), p=0.17), respiratory related deaths (HR = 1.4 [0.7, 2.6], p=0.34), all cause (HR = 1.1 [0.7, 1.5], p=0.75) or respiratory related (HR = 1.0 [0.7, 1.6] p=0.83) hospitalizations between the two groups. There were no statistically significant differences between the two groups for the per-protocol or modified per protocol analyses (eTable 2 in supplement 2) for event outcomes.

There was no statistically significant differences for the lung function or patient-related outcomes (Table 2). In the per-protocol analysis there were no statistically significant differences between co-trimoxazole or placebo groups for the lung function measurements or the patient reported outcomes other than for the chest domain of the K-BILD (adjusted and unadjusted analysis) and physiological and social domains of the LCQ (unadjusted analysis) which favoured co-trimoxazole (eTable 3 in supplement 2). The modified per protocol analysis is shown in eTable 4 in supplement 2.

When reviewing the data at all time-points, there was a statistically significant (p=0.02) difference in cough score (15.0 [1.2, 28.8] mm) at 18 months in favor of the co-trimoxazole group, and, overall, the differential between the groups was statistically significant (p=0.04), with a mean difference of 5.7 (0.1, 11.2) (eTable 5 in supplement 2). There were no statistically significant differences for the LCQ and K-BILD total scores or sub-domains, MRC score, or lung function measurements between the groups and no overall treatment effect.

Adverse events

There were 696 adverse events (20 serious adverse events) in the co-trimoxazole group and 640 (17 serious adverse events) in the placebo group (Table 3).There were more reports of nausea in the co-trimoxazole group (89/157) compared to placebo (67/163), whereas diarrhea was reported more frequently in the placebo group (52/157 vs 84/163). There were more episodes of hyperkalemia (24/157 vs 14/163), vomiting (28/157 vs 20/163) and rash (31/157 vs 20/163) with co-trimoxazole (Table 3, eTable 6 in supplement 2). There was no difference in the 12 months safety blood analysis between the two groups (eTable 7 in supplement 2) except for creatinine which was statistically significantly higher in the co-trimoxazole group.

Seventeen sputum samples and one nasal swab were obtained in total for all patient visits. Three of these grew possible relevant microbiological agents on culture: *Staphylococcus aureus* (n=1), *Haemophilus influenzae* (n=1) and “yeasts” (n=1).

DISCUSSION

In this double-blinded, randomized, placebo-controlled trial, there was no significant reduction in the incidence of the composite outcome of death, lung transplant, or non-elective hospitalization with co-trimoxazole in patients with moderate-severe IPF.

In contrast to the previous smaller study[13], there was no reduction in mortality with co-trimoxazole. In this previous study, nearly 60% of patients were taking prednisolone (mostly at high dose) and 30% were taking azathioprine whereas in the current trial, those receiving immunosuppression other than low-dose corticosteroids (6% of individuals) were excluded. It is therefore plausible that, in the previous study[13], co-trimoxazole prevented infection-related adverse outcomes that were contingent on immunosuppression, which is known to result in poor outcomes in IPF[26]. Furthermore, antifibrotic therapy (pirfenidone and nintedanib) was not available at the time of the previous study[13], whereas 75% of patients in the current study were receiving this treatment. Pirfenidone, for example, has been estimated to improve IPF life expectancy by 2.47 years[27]. Overall, the changes between the two studies resulted in a doubling of the hospital-free survival (mean 23.3 months versus 12.8 months). In addition, inclusion in the current study was restricted to people with moderate to severe IPF, as defined by a FVC <75% predicted, whereas no such restriction pertained in the previous study. However, it is unlikely that co-trimoxazole would have been more effective in a less severe population, as there was no subgroup effect of baseline disease severity in the previous study[13], and neither bacterial burden[28] nor response to antifibrotic therapy[29,30] is known to be related to FVC in IPF.

The benefit of co-trimoxazole in terms of the cough score, LCQ and the chest symptom domain of the K-BILD questionnaire (which captures chest tightness, air hunger and wheeze) only met clinical relevant thresholds at 18 months but support the previously-identified clinical benefit of co-trimoxazole[13] in respect of the 'symptom' domain of the SGRQ[31] (which captures cough, sputum, breathlessness and wheeze). However, given the null primary outcome and large number of secondary outcomes, the findings for cough should be consider only hypothesis-generating.

The results of this study do not disprove the hypothesis that the "lung microbiome" influences disease progression and outcomes in IPF[7,9,28]. A potential antibacterial benefit of co-trimoxazole may have been lost owing to widespread bacterial resistance, despite in-therapy selection of resistance being rare for co-trimoxazole[32] and acquired resistance, whilst not uncommon, unlikely to have been so universal as to overwhelm a positive effect. Furthermore, the possibility of an unrecognised IPF-associated co-trimoxazole-resistant pathogen cannot be entirely dismissed, though there is no evidence to support such a hypothesis; an ongoing randomised open-label trial of co-trimoxazole or doxycycline vs standard care may provide further insight[33]. However, a study of explanted lungs yielded very few bacterial 16S rRNA gene reads in the IPF interstitium compared with the airways of IPF patients and healthy controls. It is, therefore, possible that airway and lung tissue compartments are separate in IPF, with different microbiota[34].

This was an adequately-powered, multi-centered academic clinical trial using a clinically-relevant outcome with high follow-up rates and long timescales. It recruited and evaluated 342 individuals from 39 geographically diverse sites, of varying sizes,

for up to 3 years. The primary endpoint included (i) unplanned hospital admission, which is financially and socially costly, with a high frequency of death, and (ii) all-cause mortality, which is the most clinical meaningful primary endpoint[35]. The study was aligned to clinical care, minimizing the research burden for patients. The event rate (164 events) was higher than anticipated (99 events), so the study likely had adequate power to detect a meaningful difference in the primary endpoint.

Limitations

This study has several limitations. First, there was a lack of evaluation of the lung microbiome, or quantitation of the influence that co-trimoxazole had on its composition and ecology, including antimicrobial resistance. However, given the lack of efficacy, it is questionable whether any such analysis would have been clinically meaningful. Second, it is not possible to determine whether co-trimoxazole reduced infection-related events, as the numbers of respiratory tract infections were not captured; rather "respiratory related" events were assessed, encompassing all events related to the respiratory system. Assessing whether respiratory infection is present or not during acute exacerbations or other clinical settings is challenging[36]. Third, a protocol exclusion was allergy to co-trimoxazole and although few people were reported to have this allergy this, and the FVC criteria, may have limited the generalizability of the study. Fourth, the entry criteria were modified, by removing the exclusion of participants diagnosed more than 2 years before randomization as well as increasing the permitted FVC% predicted value from 70% to 75%. Fifth, the statistical analysis plan did not include adjustment for gastroesophageal reflux disease or proton pump inhibitor usage, however the occurrences of these were similar in both groups, and an

exploratory post hoc analysis, adjusting for these variables, did not change the conclusion of the study.

Conclusions

Among patients with moderate or severe IPF, treatment with oral co-trimoxazole did not reduce a composite outcome of time to death, lung transplant, or non-elective hospitalization compared with placebo.

Conflicts of Interest and Financial Disclosures

The following authors have nothing to disclose: Allan Clark, Tony Cahn, Edwin Chilvers, William Fraser, Matthew Hammond, Helen Parfrey, Ann Marie Swart, Susan Stirling, David Thickett, Moira Whyte.

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Access to data

Andrew Wilson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of Funder/Sponsor

The funding and sponsoring organisations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript and decision to submit the manuscript for publication. In addition they had no right to veto publication or to control the decision regarding to which journal the paper was submitted

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Data sharing statement: See supplement 3

Acknowledgements

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Andrew M Wilson: (Professor of Respiratory Medicine) was the Chief Investigator and oversaw the delivery of the study. He contributed to the conception and design of the

trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report

Allan B Clark (Senior Trial Statistician) oversaw the statistical analysis and contributed to the design of the trial. He was responsible for statistical analysis, and contributed to the interpretation of results and writing/editing the report

Dr Tony Cahn (Consultant physician) provided expertise in clinical trial design and delivery. He contributed to the conception and design of the trial, the interpretation of results and writing/editing the report.

Edwin R Chilvers (Professor of Medicine) provided expertise in ILD and lung inflammation. He contributed to the conception and design of the trial, the interpretation of results and writing/editing the report.

William Fraser (Professor of Medicine) oversaw the biochemical analyses. He contributed to the conception and design of the trial, the interpretation of results and writing/editing the report, with particular emphasis on the biochemical analysis.

Matthew Hammond (CTU Deputy Director) was responsible for the day-to-day management of the trial, and contributed to the interpretation of results and writing/editing the report.

David M Livermore (Professor of Medical Microbiology) provided expertise in the microbiological aspects of the study. He contributed to the conception and design of the trial, the interpretation of results and writing/editing the report, with particular emphasis on the microbiological aspects.

Toby M Maher (Professor of Respiratory Medicine) provided expertise in ILD and clinical trial methodology. He contributed to the conception and design of the trial,

conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

Helen Parfrey (Consultant Physician) provided expertise in ILD. She contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

Ann Marie Swart (CTU Director) was responsible for the day-to-day management of the trial. She contributed to the interpretation of results and writing/editing the report.

Susan Stirling (Trial Statistician) undertook the statistical analysis. She contributed to the interpretation of results and writing/editing the report

David R Thickett (Professor of Respiratory Medicine) provided expertise in ILD. He contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

Moira Whyte (Professor of Respiratory Medicine) provided expertise in ILD. She contributed to the conception and design of the trial, the interpretation of results and writing/editing the report.

The EME-TIPAC team contributed to the data collection of the study and the editing of the manuscript.

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Figure Legends

Figure 1 Enrolment, randomization and follow-up of participants

Abbreviation: FVC = Forced vital capacity

[a] A reduction of the dose to 2 tablets (i.e. 960 mg co-trimoxazole or 2 placebo tablets daily) plus 5 mg folic acid three times weekly was permitted if a participant developed gastrointestinal side effects or rash, grade 1 hyperkalemia (potassium >5.0 mmol/L), or any other adverse event requiring dose reduction in the view of the Principal Investigator, [b] 32 and [c] 26 individuals withdrew during the study and their data is included until the point of withdrawal. The secondary outcome data illustrates that of lung function.

Figure 2 Kaplan-Meier estimate for the primary endpoint

Kaplan-Meier estimates for time to event for primary endpoint (death (all causes), lung transplant or first non-elective hospital admission) analysed according to the group to which participants were randomised. There was no significant difference between the co-trimoxazole and placebo groups. The graph is truncated at 24 months.

Table 1 Baseline characteristics of the randomized participants

	Co-trimoxazole	Placebo
Baseline characteristics		
Number in group [a]	169	172
Male participants: n (%)	138 (81.7)	157 (91.3)
Female participants: n (%)	31 (18.3)	15 (8.7)
Age in years: mean (SD)	71.9 (7.8)	70.7 (7.1)
Smoking status: never smoked: n (%)	59 (34.9)	56 (32.6)
ex-smoker: n (%)	109 (64.5)	114 (66.3)
current smoker: n (%)	1 (0.6)	2 (1.2)
Comorbidities[b]		
Gastroesophageal reflux disease: n (%)	69 (40.8)	62 (36.1)
Ischaemic heart or angina: n (%)	38 (22.5)	44 (25.6)
Diabetes mellitus: n (%)	40 (23.7)	25 (14.5)
Anxiety or Depression: n (%)	17 (10)	23 (13.4)
Pulmonary hypertension: n (%)	13 (7.7)	10 (5.8)
Osteoporosis: n (%)	11 (6.5)	11 (6.4)
COPD: n (%)	6 (3.6)	6 (3.5)
Bronchiectasis: n (%)	2 (1.2)	7 (4.1)[1]
Maintenance treatments		
PPI	87 (51.5%)	78 (45.3%)
Pirfenidone	71 (42.0%)	66 (38.4%)

Nintedanib	56 (33.1%)	61 (35.5%)
Prednisolone	12 (7.1%)	10 (5.8%)
N-Acetyl cysteine	8 (4.7%)	7 (4.1%)
Other antioxidant	3 (1.8%)	5 (2.9%)
Lung Function[c]		
Absolute value		
FVC, L, mean, (SD)	2.2 (0.6)	2.3 (0.5)
FEV1, L, mean (SD) [N]	1.9 (0.5)	1.9 (0.4) [171]
FEV1/FVC ratio, mean (SD) [N]	0.8 (0.1)	0.8 (0.1) [171]
DLCO, mmol/min/kPa, mean (SD) [N]	3.6 (1.8) [123]	3.7 (1.5) [127]
Percent predicted		
FVC, mean (SD)	56.2 (8.9)	55.2 (10.0)
FEV1, mean (SD) [N]	61.5 (9.3)	60.0 (10.6) [171]
DLCO, mean (SD) [N]	43.3 (20.2) [123]	44.5 (18.0) [127]
Outcome measures		
Medical Research Council dyspnea score[d], median (IQR) [N]	3.0 (2.0, 3.0) [167]	2.00 (2.00, 3.00) [171]
EQ-5D-5L utility[e]: mean (SD) [N]	0.67 (0.20) [168]	0.69 (0.22) [171]
Cough score[f], mean (SD) [N]	39.5 (27.5) [167]	40.9 (26.6) [168]
Leicester Cough Questionnaire[g]		
total, mean (SD) [N]	16.1 (3.6) [161]	15.8 (3.7) [164]
physical, mean (SD) [N]	5.2 (1.1) [161]	5.1 (1.0) [165]]
psychological, mean (SD) [N]	5.4 (1.4) [167]	5.3 (1.5) [166]

social, mean (SD) [N]	5.4 (1.4) [167]	5.4 (1.4) [168]
King's Brief Interstitial Lung Disease questionnaire[h]		
total, mean (SD) [N]	53.7 (9.7) [168]	53.6 (10.6) [171]
breathlessness, mean (SD) [N]	37.7 (15.3) [168]	38.9 (14.3) [171]
chest, mean (SD) [N]	62.9 (20.8) [168]	62.6 (20.7) [171]
psychological, mean (SD) [N]	55.2 (14.9) [168]	54.9 (17.1) [171]

Abbreviations: SD = standard deviation, COPD = chronic obstructive pulmonary disease, PPI = proton pump inhibitor, FVC = forced vital capacity, FEV1 = forced expiry volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide, IQR = inter-quartile range, EQ-5D-%L = Euroqol 5-dimension 5-level questionnaire, N = number.

[a]These data exclude the individual excluded post randomisation. [b]Comorbidities were as detailed in the medical records. [c]The lung function test values were obtained at screening. [d]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. [e]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. [f]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. [g]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. [h]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.

Table 2 Between-group differences for secondary outcomes at 12 months analysed for all patients according to the group that they were randomised.

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)	63	2.26 (0.53)	77	2.23 (0.51)	-0.02 (-0.19, 0.15	0.81	-0.01 (-0.09, 0.07)	0.80
FEV1 (L)	63	1.86 (0.43)	77	1.86 (0.42)	0 (-0.14, 0.14)	>0.99	-0.02 (-0.08, 0.05)	0.62
DLCO (mmol/min/Ka)	50	3.49 (1.75)	60	3.71 (1.50)	0.19 (-0.39, 0.77	0.51	0.3 (-0.26, 0.85)	0.30
Percent predicted								
FVC (%)	63	54.0 (8.9)	77	53.6 (9.1)	-0.5 (-3.56, 2.47)	0.72	-0.6 (-2.6, 1.5)	0.59

FEV1 (%)	63	57.8 (9.7)	77	58.2 (10.4)	0.2 (-3.2, 3.6	0.93	-0.7 (-2.8, 1.5)	0.55
DLCO (%)	50	40.2 (17.7)	60	43.2 (16.3)	2.5 (-3.7, 8.7)	0.43	3.9 (-2.4, 10.3)	0.22
Medical Research Council dyspnea score[a], Median (IQR)	72	3.0 (2.0, 4.0)	86	3.0 (2.0, 4.0)		0.94		0.29
EQ-5D-5L utility[b]	103	0.41 (0.36)	118	0.45 (0.35)	0.04 (-0.05, 0.13)	0.37	0.03 (-0.06,0.11)	0.55
Cough score[c] (mm)	72	44.7 (27.0)	84	49.7 (26.7)	5.1 (-3.4, 13.6)	0.24	2.2 (-5.4,9.9)	0.57
Leicester Cough Questionnaire, mean (SD)[d]								
total	69	15.4 (4.09)	71	14.6 (4.0)	-0.8 (-2.1, 0.6)	0.27	-0.6 (-1.6, 0.4)	0.22
physical	69	4.9 (1.2)	72	4.7 (1.2)	-0.2 (-0.6, 0.2)	0.36	-0.1 (-0.4, 0.2)	0.43
psychological	69	5.2 (1.4)	75	4.9 (1.5)	-0.3 (-0.8, 0.2)	0.25	-0.3 (-0.6, 0.1)	0.17
social	69	5.3 (1.5)	75	5.0 (1.5)	-0.3 (-0.8, 0.2)	0.28	-0.2 (-0.6, 0.1)	0.20

King's Brief Interstitial Lung Disease questionnaire[e]								
Total	71	50.3 (12.3)	85	50.7 (11.20)	0.4 (-3.3, 4.1)	0.83	0.1 (-2.8, 3.0)	0.93
Breathless-ness	72	34.4 (17.4)	86	35.0 (14.55)	0.9 (-4.1, 5.9)	0.73	-0.5 (-4.4, 3.3)	0.79
chest	72	59.9 (20.3)	86	56.8 (22.82)	-3.4 (-10.2, 3.4)	0.33	-2.0 (-7.8, 3.8)	0.50
psychological	71	49.7 (17.9)	85	51.9 (16.9)	2.0 (-3.5, 7.5)	0.48	1.5 (-3.0, 5.9)	0.53

Abbreviations: n = number, SD = standard deviation, CI = confidence interval, IQR = inter-quartile range, 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]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, [b]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. [c]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. [d]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. [e]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. Data was incomplete for some patients as they did not complete the questionnaires or attend for lung function assessments.

Table 3 Adverse events

Adverse event	Co-trimoxazole: total events	Placebo: total events
Blood and lymphatic system disorders	3	3
Cardiac disorders	6	4
Ear and labyrinth disorders	3	0
Eye disorders	5	6
Gastrointestinal disorders	216	224
- Nausea	89	67
- Diarrhoea	52	84
- Vomiting	28	20
- Constipation	11	5
General disorders and administration site conditions	36	20
- Fatigue	15	11
- Chest pain	8	6
- Edema peripheral	5	0
Immune system disorders	1	1
Infections and infestations	110	127
- Lower Respiratory Tract Infection	63	66
Injury, poisoning and procedural complications	7	10

Investigations	44	22
- Weight decrease	24	16
Metabolism and nutrition disorders	57	27
- Decreased appetite	26	9
- Hyperkalemia	24	14
Musculoskeletal and connective tissue disorders	21	20
Neoplasm/s benign, malignant and unspecified (incl cysts and polyps)	3	1
Nervous system disorders	41	32
- Headache	22	14
Psychiatric disorders	5	2
Renal and urinary disorders	14	7
Reproductive system and breast disorders	0	2
Respiratory, thoracic and mediastinal disorders	77	95
- Cough	27	33
- Dyspnoea	31	34
Skin and subcutaneous tissue disorders	46	30
- Rash	31	20

Surgical and medical procedures	1	2
Vascular disorders	0	5
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.