

Online Data Supplement

Table E1. Change-from-baseline results of primary and secondary outcomes, per-protocol analysis with no imputation.

Table E2. Cause of Death in the Per Protocol Analysis

Table E3. Sensitivity analysis of FVC (change from baseline) between the original sample and the subsamples in the PP analysis

Table E1. **Change-from-baseline results of primary and secondary outcomes, per-protocol analysis with no imputation.**

| Outcome | Placebo | | Co-trimoxazole | | Unadjusted | | Adjusted for baseline | |
|------------------------|---------|----------------------|----------------|---------------------|------------|---------------------------|-----------------------|---------------------------|
| | N | Mean (SD/%) | N | Mean (SD/%) | p-value | 95% CI | p-value | 95% CI |
| FVC (millilitres) | 51 | -183.73 (279.90) | 48 | -175.21 (359.30) | 0.864 | 11.09 (-115.47,137.64) | 0.985 | 1.23 (-125.92,128.37) |
| FVC % pred (%) | 51 | -4.35 (8.88) | 48 | -4.80 (10.88) | 0.851 | -0.37 (-4.23,3.49) | 0.819 | -0.45 (-4.33,3.42) |
| TLC (millilitres) | 42 | -427.14 (1371.93) | 34 | -167.35 (635.41) | 0.104 | 381.28 (-78.36,840.92) | 0.811 | 44.10 (-317.16,405.37) |
| TLC % pred (%) | 42 | -5.92 (20.19) | 34 | -3.11 (10.49) | 0.169 | 4.77 (-2.03,11.57) | 0.881 | 0.41 (-4.98,5.80) |
| DLCO (mmol/min/PKa) | 43 | -0.21 (0.84) | 33 | -0.39 (0.70) | 0.222 | -0.22 (-0.56,0.13) | 0.247 | -0.20 (-0.55,0.14) |
| DLCO % pred (%) | 43 | -4.03 (11.11) | 33 | -4.66 (7.91) | 0.456 | -1.63 (-5.91,2.65) | 0.368 | -1.94 (-6.18,2.29) |
| SGRQ symptoms | 47 | 0.36 (16.44) | 49 | -4.63 | 0.121 | -5.30 | 0.046 | -5.73 |

| | | | | | | | | |
|---|----|-------------------|----|-------------------|-------|----------------|-------|------------------|
| (units) | | | | (16.75) | | (-11.99,1.40) | | (-11.38,-0.10) |
| SGRQ activity | | | | 1.56 | 0.879 | -0.52 | 0.660 | -1.23 |
| (units) | 49 | 2.99 (13.97) | 48 | (14.91) | | (-7.25,6.21) | | (-6.73,4.27) |
| SGRQ impact | | | | 1.26 | 0.811 | -0.92 | 0.839 | 0.66 |
| (units) | 48 | 0.49 (14.05) | 47 | (17.97) | | (-8.48,6.64) | | (-5.68,6.99) |
| SGRQ total (units) | | | | 0.36 | 0.694 | -1.08 | 0.602 | -1.38 |
| | 46 | 1.40 (11.93) | 46 | (14.07) | | (-6.49,4.32) | | (-6.59,3.82) |
| Six minute walk (6MW) distance (metres) | | | | | 0.768 | -7.21 | 0.546 | -15.31 |
| | 29 | -13.34 (85.10) | 19 | -20.74 (76.89) | | (-55.15,40.72) | | (-64.97,34.36) |
| EQ5D-based utility | | | | -0.05 | 0.025 | 0.12 | 0.024 | 0.11 (0.01,0.21) |
| | 64 | -0.16 (0.30) | 53 | (0.28) | | (0.01,0.22) | | |
| MRC score (units) | | | | 0.08 | 0.643 | -0.07 | 0.841 | -0.03 |
| | 51 | 0.16 (0.83) | 50 | (0.72) | | (-0.38,0.23) | | (-0.33,0.27) |
| Hospital days | | 0.89 (1.99) | | 3.28 | 0.181 | 0.53* | 0.182 | 0.53 |
| | 54 | | 50 | (12.95) | | (0.21,1.34) | | (0.21,1.35) |
| Death | | 14/65 | | 3/53 | 0.020 | 0.21* | | |

| | | | | | | | | |
|-----------------------------------|--|-------------------|--|-------------------|-------|---------------------|-------|---------------------|
| | | (21.5%) | | (5.7%) | | (0.06,0.78) | | |
| Medicine increase | | 18/58 (31.0) | | 9 /51 (17.7) | 0.08 | 0.39 (0.14,1.12) | | |
| Medicine decrease | | 4 / 51 (7.8) | | 6 /50 (12.0) | 0.610 | 1.42 (0.37,5.56) | | |
| Oxygen increase | | 10 / 55 (18.2) | | 1 / 50 (2.0) | 0.019 | 0.05 (0.00,0.61) | | |
| Oxygen decrease | | 0 /51 | | 0 /50 | - | - | - | |
| 6MW desaturation of 4% or more | | 27 / 31 (87.1) | | 15 / 19 (79.0) | 0.446 | 0.55 (0.12,2.54) | 0.644 | 0.64 (0.10,4.15) |

*Hazard ratio. FVC: forced expiratory volume, TLC: total lung capacity, DLCO: total lung diffusing capacity of carbon monoxide, % pred: percent predicted, SGRQ: St George's Respiratory Questionnaire, 6MW: six minute walk, EQ5D: EuroQol, MRC score: Medical Research Council Dyspnoea Score. Units are number of patients unless indicated.

Table E2. **Cause of death in per the protocol analysis.**

| | Placebo (n=14) | Co-trimoxazole (n=3) |
|--|-------------------|-------------------------|
| Mean age, years | 72.8 | 74 |
| Respiratory related* | 14 (100%) | 3 (100%) |
| IPF related | 5 (36%) | 2 (67%) |
| Non-IPF related | 9 (64%) | 1 (33%) |
| Pneumonia | 5 (36%) | 0 |
| LRTI | 1 (7%) | 0 |
| Aspiration pneumonia | 1 (7%) | 0 |
| Cardiorespiratory failure [†] | 1 (7%) | 0 |
| Multiorgan failure [‡] | 1 (7%) | 0 |
| Metastatic lung cancer | 0 | 1 (33%) |

* Death was defined as respiratory related if resulted from respiratory failure, acute exacerbation or progression of IPF, pneumonia or respiratory tract infection, pulmonary embolism, lung cancer, or pneumothorax.

[†]Due to IPF and ischaemic heart disease. [‡] Due to IPF, LRTI and perforated Meckel's diverticulum

All 17 deaths were due to a respiratory cause with 7 (40%) resulting from gradual progression of IPF itself and 5 following pneumonia (all in placebo arm), with 80% of non-IPF related deaths exhibiting signs in keeping with a gradual rather than acute progression of the underlying IPF.

Table E3. Sensitivity analysis of FVC (change from baseline) and deaths between the original sample and the subsamples in the PP analysis

| Outcome | Placebo | | Co-trimoxazole | | Unadjusted | | Adjusted for baseline | |
|---|---------|------------------|----------------|------------------|------------|---------------------------|-----------------------|----------------------------|
| | N | Mean (SD) | N | Mean (SD) | p-value | 95 CI% | p-value | 95% CI |
| FVC (millilitres) [primary analysis] | 51 | -183.73 (279.90) | 48 | -175.21 (359.30) | 0.864 | 11.09 (-115.47,137.64) | 0.985 | 1.23 (-125.92,128.37) |
| FVC (millilitres) [Fell criteria] | 50 | -184.80 (282.64) | 42 | -185.24 (365.68) | 0.992 | -0.65 (-132.18,130.87) | 0.865 | -11.47 (-144.15,121.21) |
| FVC (millilitres) [radiology review] | 47 | -173.19 (279.65) | 38 | -218.16 (351.31) | 0.552 | -39.69 (-170.48,91.09) | 0.329 | -65.72 (-197.62,66.17) |
| | | Number (%) | | Number (%) | p-value | 95 CI% | | |
| Deaths [primary analysis] | | 14/65 (21.54) | | 3/53 (5.66) | 0.02 | 0.21 (0.06,0.78) | | |
| Deaths [Fell criteria] | | 12/62 (19.35) | | 2/46 (4.35) | 0.024 | 0.17 (0.04,0.79) | | |
| Deaths [radiology] | | 11/58 (18.97) | | 2/42 (4.76) | 0.032 | 0.18 | | |

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|---------|--|--|--|--|--|-------------|--|--|
| review] | | | | | | (0·04,0·86) | | |
|---------|--|--|--|--|--|-------------|--|--|

FVC: Forced vital capacity. Fell Criteria based on Fell CD, Martinez FJ, Liu LX, Murray S, Han MK, Kazerooni EA, et al. Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2010;181:832-7. Radiology review based on Silva CI, Muller NL, Hansell DM, Lee KS, Nicholson AG, Wells AU. Nonspecific interstitial pneumonia and idiopathic pulmonary fibrosis: changes in pattern and distribution of disease over time. *Radiology.* 2008;247:251-9.