**Supplementary File 1 - Supplementary Tables**

Supplementary File 1A: Duration of dexamethasone treatment prior to recruitment and initiation of dornase alfa treatment

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| --- | --- | --- | --- | --- | --- |
|  | **R-BAC+DA (N=30)** | **R-BAC (N=9)** |  **CC-BAC** **(N=60)** | **T-BAC (N=69)** | **Total (N=99)** |
| **Length of Dexamethasone at baseline (days)** |  |  |  |  |  |
|  N | 30 | 8 | 60 | 68 | 98 |
|  Mean | 0.67 | 1 | 1.38 | 1.34 | 1.13 |
|  SD | 0.76 | 1.20 | 0.64 | 0.73 | 0.79 |
|  Median | 1 | 0.5 | 1 | 1 | 1 |
|  Min | 0 | 0 | 0 | 0 | 0 |
|  Max | 3 | 3 | 3 | 3 | 3 |

Supplementary File 1B. Secondary endpoints in randomised participants only

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **R-BAC+DA**  | **R-BAC** | **Difference**  | **p-value\*** |
| **Time to discharge (days)** |  |  |  |  |
| Number discharged | 27 | 8 | 19 |  |
| Median time to discharge\*\* (95% CI) | 6 (4 to 7) | 4 (2 to-n.a.) | 2 |  |
| Hazard ratio\*\*\* (95% CI) |  |  | 1.18 (0.53 to 2.69) | 0.62 |
| **D-dimer (ug/L) FEU** |   |   |   |   |
| N | 28 | 6 |  |  |
| Least-squares mean (log)\* (95% CI) | 6.37 (6.01 to 6.74) | 7.55 (6.71 to 8.39) | -1.18 (-2.02 to -0.33) | 0.008 |
| Least-square mean\*\* (95% CI) | 586.87(407.44 to 845.31) | 1903.82 (821.57 to 4411.69) | 0.31 (0.13 to 0.72) |  |
| **Lymphocyte count (×109/L)** |   |   |   |   |
| N | 30 | 9 |  |  |
| Least-squares mean (log)\* (95% CI) | -0.06 (-0.25 to 0.12) | -0.46 (-0.82 to -0.1) | 0.4 (0.03 to 0.76) | 0.033 |
| Least-square mean\*\* (95% CI) | 0.94 (0.78 to 1.13) | 0.63 (0.44 to 0.9) | 1.49 (1.03 to 2.13) |  |
| **Procalcitonin count (ng/ml)** |   |   |   |   |
| N | 26 | 7 |  |  |
| Least-square mean\* (95% CI) | 0.18 (-0.2 to 0.56) | 1.31 (0.56 to 2.05) | -1.13 (-1.88 to -0.37) | 0.005 |

\*From log-rank test with treatment as a stratification variable.

\*\*Estimated from Kaplan-Meier curve.

\*\*\*From Cox proportional hazard model, adjusting for age, baseline CRP and treatment.

Supplementary File 1C. Secondary clinical endpoints

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| **Admission to ICU over 7 days of follow up**  |

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| --- | --- | --- | --- | --- | --- |
| N | R-BAC+DA n=30 |  T-BAC n=69 |  |  |  |
|  | 23.3% | 21.74% |  |  | p=0.866 |
| **Length of ICU stay** |
| LSM | 21.25 h | 19.85h |  |  | p=0.883 |
| 95% CI | 4.65-37.84 | 8-31.7 |  |  |  |
| **Admission to ICU over 35 d follow up**  |
| N | 23% | 23.19 |  |  | p=0.983 |
| LSM | 55.21 h | 60.6 h |  |  | P=0.905 |
| 95% CI | -23.59-134.00 h | 4.34-116.86 h |  |  |  |
|  |  |  |  |  |  |

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| --- |
| **Time on Oxygen over 7 days follow-up (hours)** |
| N | 30 | 69 |  |  |
| Least-square mean\*(95% CI) | 94.32(72.86 to 115.79) | 88.96(73.64 to 104.29) | 5.36(-18.92 to 29.65) | 0.662 |
| **Time on Oxygen over 35 days follow-up (hours)** |
| N | 30 | 69 |  |  |
| Least-square mean\*(95% CI) | 133.22(52.01 to 214.43) | 156.35(98.36 to 214.33) | -23.12(-115.02 to 67.77) | 0.618 |
| **Proportion of individuals on mechanical ventilation over 7 days follow-up** |
| N (%) | 5 (16.67) | 9 (13.04) | -4 (3.62) |  |
| Odds ratio\* (95%CI) |  |  | 1.36 (0.39 to 4.66) | 0.628 |
| **Proportion of individuals on mechanical ventilation over 35 days follow-up** |
| N (%) | 5 (16.67) | 9 (13.04) | -4 (3.62) |  |
| Odds ratio\* (95% CI) |  |  | 1.36 (0.39 to 4.66) | 0.628 |
| \*From Logistic regression model, adjusted for age, sex, BMI, baseline CRP, serious condition and treatment. |
| **Proportion of individuals with Superadded Bacterial Pneumonia over 7 days follow-up** |
| N (%) | 1 (3.33) | 3 (4.35) |  |  |
| Odds ratio\* (95% CI) | 0.9 (0.08 to 10.21) |  |  | 0.934 |
| **Proportion of individuals with Superadded Bacterial Pneumonia over 35 days follow-up** |
| N (%) | 2 (6.67) | 3 (4.35) |  |  |
| Odds ratio\* (95% CI) | 1.81 (0.26 to 12.61) |  |  | 0.548 |
| \*From Logistic regression model, adjusted for age, sex, BMI, baseline CRP, serious condition, and treatment. |

Supplementary File 1D. Safety

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| --- | --- | --- | --- | --- |
| **Subject**  | **R-BAC+DA or R-BAC only** | **Adverse event**  | **Serious?**  | **Relationship to study drug**  |
| COV002  | Dornase-alfa + BAC  | Cough & SOB  | No  | Not related  |
| COV003  | Dornase-alfa + BAC  | Mild depression  | No  | Not related  |
| COV003  | Dornase-alfa + BAC  | Mild cognitive impairment  | No  | Not related  |
| COV005  | Dornase-alfa + BAC  | Struggle to sleep  | No  | Not related  |
| COV005  | Dornase-alfa + BAC  | Transaminitis (ALT 91 - NR 10-35 iu/L)  | No  | Not related  |
| COV005  | Dornase-alfa + BAC  | Constipation  | No  | Not related  |
| COV007  | Dornase-alfa + BAC  | Blood stain in sputum  | No  | Not related  |
| COV012  | Dornase-alfa + BAC  | Small Pericardial Effusion  | No  | Not related  |
| COV012  | Dornase-alfa + BAC  | Dysphonia  | No  | Not related  |
| COV012  | Dornase-alfa + BAC  | Hypercapnia  | No  | Not related  |
| COV013  | Dornase-alfa + BAC  | Ulcerative Colitis flare  | No  | Not related  |
| COV013  | Dornase-alfa + BAC  | Bradycardia  | No  | Not related  |
| COV015  | Dornase-alfa + BAC  | Mechanical Fall  | No  | Not related  |
| COV015  | Dornase-alfa + BAC  | Dizziness  | No  | Not related  |
| COV018  | Dornase-alfa + BAC  | Dehydration  | No  | Not related  |
| COV018  | Dornase-alfa + BAC  | Lower Respiratory Tract Infection  | No  | Not related  |
| COV018  | Dornase-alfa + BAC  | Haemoptysis  | No  | Not related  |
| COV020  | Dornase-alfa + BAC  | Chest pain  | No  | Not related  |
| COV022  | Dornase-alfa + BAC  | Microcytic anaemia  | No  | Not related  |
| COV022  | Dornase-alfa + BAC  | Elevated Blood glucose  | No  | Not related  |
| COV023  | Dornase-alfa + BAC  | Tachypnoea (PR 32BPM)  | No  | Not related  |
| COV023  | Dornase-alfa + BAC  | Hyperglycaemia (BM 14.9)  | No  | Not related  |
| COV031  | Dornase-alfa + BAC  | Chest Pain  | No  | Not related  |
| COV035  | Dornase-alfa + BAC  | Left leg spasm  | No  | Not related  |
| COV035  | Dornase-alfa + BAC  | Rectal bleed due to haemorrhoids  | No  | Not related  |
| COV037  | Dornase-alfa + BAC  | Chest Pain  | No  | Not related  |
| COV002  | Dornase-alfa + BAC  | Tingling of the mouth  | No  | Definitely  |
| COV035  | Dornase-alfa + BAC  | Headache  | No  | Unlikely |

Supplementary File 1E: Cumulative Summary Tabulations of Serious Adverse Events (SAEs)

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| --- | --- |
| **System Organ Class (SOC)**Preferred Term | **Total**  |
| **Dornase alfa (IMP) arm** | **Best Available Care (control) arm** |
| **Infections and infestations**Pyelonephritis | 11 |  |
| **Respiratory, thoracic and mediastinal disorders**Aspiration pneumoniaHospital acquired pneumoniaOrganising pneumoniaPulmonary embolism | 3111 | 11 |
| **Vascular disorders**Acute subdural haematoma |  | 11 |
| **Total**  | 4 | 2 |