**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

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| --- | --- | --- | --- | --- |
|  | **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 | 1  1 |  |
| **Respiratory, thoracic and mediastinal disorders**  Aspiration pneumonia  Hospital acquired pneumonia  Organising pneumonia  Pulmonary embolism | 3  1  1  1 | 1  1 |
| **Vascular disorders**  Acute subdural haematoma |  | 1  1 |
| **Total** | 4 | 2 |