

## Supplementary files

Supplementary table 1: Baseline characteristics of the AdrenOSS-1 cohort

|                                   |                  | sTREM-1 Q1       | sTREM-1 Q2       | sTREM-1 Q3       | sTREM-1 Q4       |         |
|-----------------------------------|------------------|------------------|------------------|------------------|------------------|---------|
|                                   | all              | (42,299]         | (299,497]        | (497,809]        | (809,5.54e+03]   | p-value |
| <b>Characteristics</b>            | <b>n=293</b>     | <b>n=74</b>      | <b>n=73</b>      | <b>n=73</b>      | <b>n=73</b>      |         |
| sTREM-1 at admission (pg/ml)      | 497 [299-809]    |                  |                  |                  |                  |         |
| Age (year)                        | 67.2 [57.8-77.1] | 63.2 [52.5-70.0] | 69.8 [60.0-76.4] | 69.9 [58.7-81.1] | 66.7 [60.4-77.1] | 0.0055  |
| Females (No. %)                   | 106 (36.2)       | 22 (29.7)        | 27 (37)          | 28 (38.4)        | 29 (39.7)        | 0.5931  |
| Body Mass Index (kg/m2)           | 25.9 [23.0-30.4] | 25.9 [22.9-29.6] | 25.4 [22.5-29.0] | 26.7 [23.3-30.0] | 28.4 [23.9-33.3] | 0.1056  |
| <b>Type of ICU admission:</b>     |                  |                  |                  |                  |                  | 0.1452  |
| Medical                           | 215 (73.4)       | 55 (74.3)        | 53 (72.6)        | 54 (74)          | 53 (72.6)        |         |
| Surgical - emergency procedure    | 67 (22.9)        | 19 (25.7)        | 14 (19.2)        | 15 (20.5)        | 19 (26)          |         |
| Surgical - elective procedure     | 11 (3.8)         | 0 (0)            | 6 (8.2)          | 4 (5.5)          | 1 (1.4)          |         |
| <b>Origin of sepsis:</b>          |                  |                  |                  |                  |                  | 0.4141  |
| Lung                              | 81 (27.6)        | 26 (35.1)        | 24 (32.9)        | 16 (21.9)        | 15 (20.5)        |         |
| Blood stream                      | 40 (13.7)        | 5 (6.8)          | 8 (11)           | 14 (19.2)        | 13 (17.8)        |         |
| Urinary tract                     | 50 (17.1)        | 9 (12.2)         | 13 (17.8)        | 14 (19.2)        | 14 (19.2)        |         |
| Catheter                          | 19 (6.5)         | 4 (5.4)          | 4 (5.5)          | 8 (11)           | 3 (4.1)          |         |
| Peritonitis                       | 17 (5.8)         | 4 (5.4)          | 3 (4.1)          | 6 (8.2)          | 4 (5.5)          |         |
| Endocarditis                      | 18 (6.1)         | 6 (8.1)          | 4 (5.5)          | 3 (4.1)          | 5 (6.8)          |         |
| Bile duct infection               | 4 (1.4)          | 1 (1.4)          | 1 (1.4)          | 2 (2.7)          | 0 (0)            |         |
| CNS                               | 3 (1)            | 2 (2.7)          | 0 (0)            | 0 (0)            | 1 (1.4)          |         |
| Other                             | 61 (20.8)        | 17 (23)          | 16 (21.9)        | 10 (13.7)        | 18 (24.7)        |         |
| <b>Organ support at admission</b> |                  |                  |                  |                  |                  |         |
| <b>Mechanical ventilation:</b>    |                  |                  |                  |                  |                  | 0.1110  |
| invasive                          | 149 (50.9)       | 34 (45.9)        | 34 (46.6)        | 36 (49.3)        | 45 (61.6)        |         |
| non-invasive                      | 47 (16)          | 8 (10.8)         | 12 (16.4)        | 14 (19.2)        | 13 (17.8)        |         |
| none                              | 97 (33.1)        | 32 (43.2)        | 27 (37)          | 23 (31.5)        | 15 (20.5)        |         |
| Renal replacement therapy (yes)   | 38 (13)          | 1 (1.4)          | 5 (6.8)          | 9 (12.3)         | 23 (31.5)        | <0.0001 |
| <b>Organ dysfunction scores</b>   |                  |                  |                  |                  |                  |         |
| SOFA (points)                     | 9 [7-11]         | 7 [6-10]         | 9 [7-11]         | 10 [8.5-12]      | 11 [9-13]        | <0.0001 |
| SAPS2 (points)                    | 58 [46-71]       | 52 [42.25-60]    | 55 [44-69]       | 59 [48-71]       | 65 [57-77]       | <0.0001 |
| APACHE 2 (points)                 | 18 [13-22]       | 15 [11-18.75]    | 15 [12-20]       | 18 [15-23]       | 21 [17-24]       | <0.0001 |

Supplementary table 2: Baseline characteristics of the MOT-C-201 Study

|                                        | Placebo<br>N=12 | Nangibotide<br>0.3 mg/kg/h<br>N=13 | Nangibotide<br>1.0 mg/kg/h<br>N=12 | Nangibotide<br>3.0 mg/kg/h<br>N=12 | Total<br>N=49 |
|----------------------------------------|-----------------|------------------------------------|------------------------------------|------------------------------------|---------------|
| Age (years), mean (SD)                 | 66 (10)         | 63 (13)                            | 65 (14)                            | 62 (17)                            | 64 (13)       |
| Male, n (%)                            | 8 (66.7)        | 7 (53.8)                           | 7 (58.3)                           | 8 (66.7)                           | 30 (61.2)     |
| Weight (kg), mean (SD)                 | 72.7 (18.9)     | 74.6 (16.6)                        | 76.7 (20.1)                        | 68.8 (9.3)                         | 73.2 (16.5)   |
| BMI (kg/m <sup>2</sup> ), mean (SD)    | 26.1 (6.6)      | 25.5 (4.9)                         | 26.1 (5.2)                         | 25.1 (5.2)                         | 25.7 (5.3)    |
| Patient type                           |                 |                                    |                                    |                                    |               |
| Medical                                | 8 (66.7)        | 6 (46.2)                           | 9 (75.0)                           | 9 (75.0)                           | 32 (65.3)     |
| Surgical                               | 4 (33.3)        | 7 (53.8)                           | 3 (25.0)                           | 3 (25.0)                           | 17 (34.7)     |
| Infection at screening                 |                 |                                    |                                    |                                    |               |
| Proven                                 | 7 (58.3)        | 10 (76.9)                          | 12 (100.0)                         | 12 (100.0)                         | 41 (83.7)     |
| Suspected                              | 5 (41.7)        | 3 (23.1)                           | -                                  | -                                  | 8 (16.3)      |
| Primary type of infection at screening |                 |                                    |                                    |                                    |               |
| Bacterial Gram Positive                | 2 (16.7)        | 5 (38.5)                           | 5 (41.7)                           | 6 (50.0)                           | 18 (36.7)     |
| Bacterial Gram Negative                | 4 (33.3)        | 5 (38.5)                           | 6 (50.0)                           | 1 (8.3)                            | 16 (32.7)     |
| Viral                                  | -               | -                                  | -                                  | 1 (8.3)                            | 1 (2.0)       |
| Unknown                                | 5 (41.7)        | 3 (23.1)                           | -                                  | 2 (16.7)                           | 10 (20.4)     |
| Other                                  | 1 (8.3)         | -                                  | 1 (8.3)                            | 2 (16.7)                           | 4 (8.2)       |
| Site of infection, n (%)               |                 |                                    |                                    |                                    |               |
| Abdominal cavity                       | 5 (41.7)        | 8 (61.5)                           | 4 (33.3)                           | 4 (33.3)                           | 21 (42.9)     |
| Lung                                   | 6 (50.0)        | 5 (38.5)                           | 6 (50.0)                           | 8 (66.7)                           | 25 (51.0)     |
| Urinary tract                          | 1 (8.3)         | -                                  | 2 (16.7)                           | -                                  | 3 (6.1)       |
| Vasopressor duration (h), mean (SD)    | 16.4 (6.3)      | 16.9 (6.5)                         | 14.2 (4.8)                         | 13.4 (5.9)                         | 15.3 (5.9)    |
| IMV, n (%)                             | 9 (75.0)        | 10 (76.9)                          | 11 (91.7)                          | 9 (75.0)                           | 39 (79.6)     |
| CRRT, n (%)                            | 0 (0.0)         | 2 (15.4)                           | 2 (16.7)                           | 1 (8.3)                            | 5 (10.2)      |
| APACHE II, mean (SD)                   | 22.3 (7.75)     | 22.5 (4.93)                        | 25.1 (9.21)                        | 24.4 (5.55)                        | 23.6 (6.91)   |
| SOFA, mean (SD)                        | 10.3 (3.4)      | 9.6 (2.8)                          | 10.8 (3.5)                         | 10.3 (2.4)                         | 10.2 (3.0)    |
| Lactate, mmol/l, mean (SD)             | 3.9 (2.5)       | 4.0 (2.4)                          | 4.3 (1.8)                          | 3.6 (1.4)                          | 4.0 (2.0)     |
| sTREM-1 (pg/mL), mean (SD)             | 676 (622)       | 474 (221)                          | 519 (306)                          | 616 (365)                          | 569 (399)     |

Supplementary Table 3 and 4: Logistic regression model, univariate and multivariate results for LogsTREM-1 and other potential predictive variables (Age, sex, cardiac morbidity, non-cardiac morbidity, lactate at baseline).

| Variable               | d.f. | Chi Sqr | OR (95% CI)      | p-value  | n   |
|------------------------|------|---------|------------------|----------|-----|
| log10(sTREM.d1)        | 1    | 26.3    | 2.89 (1.93-4.33) | <0.00001 | 293 |
| age                    | 1    | 4.8     | 1.48 (1.04-2.09) | 0.02862  | 293 |
| D1.SEX.LIB             | 1    | 0.3     | 0.87 (0.52-1.46) | 0.6013   | 293 |
| D1.CARDCOMORB.YN       | 1    | 5.8     | 2.1 (1.15-3.84)  | 0.01622  | 293 |
| D1.NCARDCOMORB.YN      | 1    | 3.7     | 1.86 (0.99-3.52) | 0.05525  | 293 |
| log10(D1.LACT.MAX.NUM) | 1    | 39.1    | 3.32 (2.28-4.84) | <0.00001 | 286 |
| Total                  | 6    |         |                  |          |     |

Model Summary, multivariable results (OR in next table).

| Variable               | d.f. | Chi Sqr | p-value | n   |
|------------------------|------|---------|---------|-----|
| log10(sTREM.d1)        | 1    | 8.4     | 0.0038  | 286 |
| age                    | 1    | 1.2     | 0.271   | 286 |
| D1.SEX.LIB             | 1    | 2       | 0.1545  | 286 |
| D1.CARDCOMORB.YN       | 1    | 1.9     | 0.1694  | 286 |
| D1.NCARDCOMORB.YN      | 1    | 5       | 0.0253  | 286 |
| log10(D1.LACT.MAX.NUM) | 1    | 26.5    | <0.0001 | 286 |
| Total                  | 6    | 49.4    | <0.0001 | 286 |

Supplementary Table 5: ANCOVA Model – Missing data replaced by the LOCF method. ANCOVA model adjusting for treatment and baseline SOFA.

| Baseline s-TREM1 | Group              | N | Adjusted Mean Change | Difference vs placebo | p-value |
|------------------|--------------------|---|----------------------|-----------------------|---------|
| cutoff >= 350    | Placebo            | 6 | -0.87                |                       |         |
|                  | Nangibotide 0.3 mg | 9 | -2.85                | -1.98 ± 1.25          | 0.13    |
|                  | Nangibotide 1 mg   | 8 | -1.76                | -0.89 ± 1.26          | 0.49    |
| cutoff >= 360    | Placebo            | 5 | -0.13                |                       |         |
|                  | Nangibotide 0.3 mg | 9 | -2.84                | -2.71 ± 1.25          | 0.04    |
|                  | Nangibotide 1 mg   | 7 | -1.97                | -1.84 ± 1.27          | 0.17    |
| cutoff >= 370    | Placebo            | 5 | -0.14                |                       |         |
|                  | Nangibotide 0.3 mg | 8 | -2.94                | -2.80 ± 1.31          | 0.05    |
|                  | Nangibotide 1 mg   | 7 | -1.97                | -1.84 ± 1.30          | 0.18    |
| cutoff >= 380    | Placebo            | 5 | -0.14                |                       |         |
|                  | Nangibotide 0.3 mg | 8 | -2.94                | -2.80 ± 1.31          | 0.05    |
|                  | Nangibotide 1 mg   | 7 | -1.97                | -1.84 ± 1.30          | 0.18    |
| cutoff >= 390    | Placebo            | 5 | -0.12                |                       |         |
|                  | Nangibotide 0.3 mg | 7 | -2.92                | -2.80 ± 1.44          | 0.07    |
|                  | Nangibotide 1 mg   | 6 | -2                   | -1.88 ± 1.45          | 0.22    |
| cutoff >= 400    | Placebo            | 5 | -0.12                |                       |         |
|                  | Nangibotide 0.3 mg | 7 | -2.92                | -2.80 ± 1.44          | 0.07    |
|                  | Nangibotide 1 mg   | 6 | -2                   | -1.88 ± 1.45          | 0.22    |
| cutoff >= 410    | Placebo            | 5 | -0.12                |                       |         |
|                  | Nangibotide 0.3 mg | 6 | -2.73                | -2.61 ± 1.51          | 0.11    |
|                  | Nangibotide 1 mg   | 6 | -2.01                | -1.89 ± 1.49          | 0.23    |
| cutoff >= 420    | Placebo            | 5 | -0.12                |                       |         |
|                  | Nangibotide 0.3 mg | 6 | -2.73                | -2.61 ± 1.51          | 0.11    |
|                  | Nangibotide 1 mg   | 6 | -2.01                | -1.89 ± 1.49          | 0.23    |
| cutoff >= 430    | Placebo            | 5 | -0.12                |                       |         |
|                  | Nangibotide 0.3 mg | 6 | -2.73                | -2.61 ± 1.51          | 0.11    |
|                  | Nangibotide 1 mg   | 6 | -2.01                | -1.89 ± 1.49          | 0.23    |
| cutoff >= 440    | Placebo            | 5 | -0.04                |                       |         |
|                  | Nangibotide 0.3 mg | 6 | -2.89                | -2.85 ± 1.41          | 0.07    |
|                  | Nangibotide 1 mg   | 5 | -1.29                | -1.24 ± 1.43          | 0.4     |
| cutoff >= 450    | Placebo            | 5 | -0.04                |                       |         |
|                  | Nangibotide 0.3 mg | 6 | -2.89                | -2.85 ± 1.41          | 0.07    |
|                  | Nangibotide 1 mg   | 5 | -1.29                | -1.24 ± 1.43          | 0.4     |
| cutoff >= 460    | Placebo            | 4 | -0.22                |                       |         |
|                  | Nangibotide 0.3 mg | 6 | -2.91                | -2.69 ± 1.62          | 0.12    |
|                  | Nangibotide 1 mg   | 5 | -1.33                | -1.11 ± 1.59          | 0.5     |
| cutoff >= 470    | Placebo            | 4 | -0.16                |                       |         |
|                  | Nangibotide 0.3 mg | 5 | -3.56                | -3.40 ± 1.62          | 0.06    |
|                  | Nangibotide 1 mg   | 5 | -1.32                | -1.16 ± 1.52          | 0.46    |