



## Clinical trial results:

### Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treat-ment for patients with COVID-19

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2020-001172-15   |
| Trial protocol           | DE DK AT GB      |
| Global end of trial date | 26 December 2020 |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 09 August 2022 |
| First version publication date | 09 August 2022 |

#### Trial information

##### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | APN01-01-COVID19 |
|-----------------------|------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04335136 |
| WHO universal trial number (UTN)   | -           |
| Other trial identifiers            | IND: 151312 |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | APEIRON Biologics AG                             |
| Sponsor organisation address | Campus-Vienna-Biocenter 5, Vienna, Austria, 1030 |
| Public contact               | Sponsor, APEIRON Biologics AG, dwi@invios.com    |
| Scientific contact           | Sponsor, APEIRON Biologics AG, dwi@invios.com    |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 26 December 2020 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 26 December 2020 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 26 December 2020 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

Primary objective: To assess clinical efficacy of APN01 using a composite outcome of all cause-death or need of invasive mechanical ventilation up to 28 days.

Secondary objectives:

- To assess the efficacy of APN01 using log-transformed levels of lactate dehydrogenase (LDH) as a surrogate marker for organ damage.

- To monitor other biomarker changes in patients with severe Corona-virusdisease 2019 (COVID-19) treated with APN01.

- To evaluate the safety of APN01 in patients with severe COVID-19.

Protection of trial subjects:

A Data and Safety Monitoring Board (DSMB) was established to protect the safety of study participants. Patients who experienced any kind of hypersensitivity reaction had to stop treatment with the IMP. Treatment could be discontinued if in the opinion of the investigator or of the medical monitor there was a risk to the patient's safety if they further received IMP.

Background therapy:

Both treatments (APN01 [0.4 mg/kg BID] or placebo [0.9% sodium chloride, BID]) were given on top of best standard of care. Details of the standard care provided (concomitant medication, remdesivir, if approved and available, and ventilation techniques) were documented in the patient's eCRF and submitted to statistical analysis.

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 14 April 2020 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Austria: 40             |
| Country: Number of subjects enrolled | Germany: 5              |
| Country: Number of subjects enrolled | Russian Federation: 139 |
| Country: Number of subjects enrolled | Denmark: 1              |
| Worldwide total number of subjects   | 185                     |
| EEA total number of subjects         | 46                      |

Notes:

### Subjects enrolled per age group

|          |   |
|----------|---|
| In utero | 0 |
|----------|---|

|   |     |
|---|-----|
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 121 |
| From 65 to 84 years                       | 64  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

17 centers in Austria, Denmark, Germany, and Russia recruited for the clinical trial. The recruitment period was 7 months (Apr-Nov 2020).

### Pre-assignment

Screening details:

185 patients were screened; Screening failures n=4 --> Inclusion criteria not met or exclusion criteria applied. 181 patients were randomized. N = 3 patients were excluded before treatment due to screening failure, randomization key pressed by mistake (2) or withdrew for private reasons (1). 178 patients received IMP.

### Pre-assignment period milestones

|  |                 |
|--|-----------------|
| Number of subjects started                 | 185             |
| Intermediate milestone: Number of subjects | Randomized: 181 |
| Number of subjects completed               | 178             |

### Pre-assignment subject non-completion reasons

|                            |                              |
|----------------------------|------------------------------|
| Reason: Number of subjects | screening failure: 4         |
| Reason: Number of subjects | Excluded before treatment: 3 |

### Period 1

|                              |                              |
|------------------------------|------------------------------|
| Period 1 title               | Treated set (overall period) |
| Is this the baseline period? | Yes                          |
| Allocation method            | Randomised - controlled      |
| Blinding used                | Double blind                 |
| Roles blinded                | Subject, Investigator, Carer |

Blinding implementation details:

The entire study team was blinded except for the pharmacist or another unblinded team member, e.g., unblinded clinical research assistant, who prepared the IMP, the statistician who compiled the necessary information for the DSMB, DSMB members, and data managers involved in the generation and upload of treatment listings and biomarker data to the eCRF.

### Arms

|                              |       |
|------------------------------|-------|
| Are arms mutually exclusive? | Yes   |
| Arm title                    | APN01 |

Arm description:

APN01 is the active treatment: it is a soluble recombinant human angiotensin-converting enzyme 2 (rhACE2) that is currently under development as a therapy for coronavirus-disease 2019 (COVID-19). N=90 subjects were randomized to APN01, but N=3 subjects were excluded from APN01 arm before receiving treatment due to screening failure, randomization key pressed by mistake (2) and 1 subject withdrew for private reasons. Thus, N=88 subjects were treated with APN01.

|  |                                 |
|--|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | APN01                           |
| Investigational medicinal product code |                                 |
| Other name                             | GSK2586881                      |
| Pharmaceutical forms                   | Infusion, Solution for infusion |
| Routes of administration               | Infusion , Intravenous use      |

Dosage and administration details:

APN01 was administered intravenously every 12 hours ( $\pm 1$  hour) for 7 days (14 doses in total). If the patient was discharged from hospital before Day 7, treatment could be stopped on the day of discharge.

|  |  |
|--|--|
| <b>Arm title</b>   | Placebo                                      |
| Arm description:<br>The placebo is physiological saline. |  |
| Arm type   | Placebo                                      |
| Investigational medicinal product name                   | Placebo                                      |
| Investigational medicinal product code                   |  |
| Other name   |  |
| Pharmaceutical forms                                     | Infusion, Solution for solution for infusion |
| Routes of administration                                 | Infusion , Intravenous use                   |

**Dosage and administration details:**

Placebo (physiological saline; 0,9 % NaCl) was administered intravenously BID for 7 days (14 doses in total). If the patient was discharged from hospital before Day 7, treatment could be stopped on the day of discharge.

Administration: slow intravenous infusion (3 to 30 minutes) using a polypropylene syringe with a 0.22 micron filter.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | APN01 | Placebo |
|---|-------|---------|
| Started   | 88    | 90      |
| Completed   | 77    | 83      |
| Not completed                                       | 11    | 7       |
| Adverse event, serious fatal                        | 8     | 4       |
| Consent withdrawn by subject                        | -     | 1       |
| Day 28 assessment by phone; no protocol option yet  | 1     | -       |
| Suspected SAE                                       | -     | 1       |
| Health-threatening condition                        | -     | 1       |
| Lost to follow-up                                   | 2     | -       |

**Notes:**

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Justification: N=185 patients were screened; there were N=4 Screening failures (Inclusion criteria not met or exclusion criteria applied). N=181 patients were randomized to APN01 (N=91) and Placebo (N=90). N=3 patients in the APN01-arm were excluded before treatment due to screening failure, randomization key pressed by mistake (2) or withdrew for private reasons (1). Thus, N=88 patients of the active arm received APN01. The FAS included these N=178 patients receiving APN01 or Placebo.

## Baseline characteristics

### Reporting groups

|  |         |
|--|---------|
| Reporting group title  | APN01   |
| Reporting group description:   |         |
| APN01 is the active treatment: it is a soluble recombinant human angiotensin-converting enzyme 2 (rhACE2) that is currently under development as a therapy for coronavirus-disease 2019 (COVID-19). N=90 subjects were randomized to APN01, but N=3 subjects were excluded from APN01 arm before receiving treatment due to screening failure, randomization key pressed by mistake (2) and 1 subject withdrew for private reasons. Thus, N=88 subjects were treated with APN01. |         |
| Reporting group title  | Placebo |
| Reporting group description:   |         |
| The placebo is physiological saline.   |         |

| Reporting group values                             | APN01 | Placebo | Total |
|--|-------|---------|-------|
| Number of subjects                                 | 88    | 90      | 178   |
| Age categorical                                    |       |         |       |
| Units: Subjects                                    |       |         |       |
| In utero   | 0     | 0       | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0     | 0       | 0     |
| Newborns (0-27 days)                               | 0     | 0       | 0     |
| Infants and toddlers (28 days-23 months)           | 0     | 0       | 0     |
| Children (2-11 years)                              | 0     | 0       | 0     |
| Adolescents (12-17 years)                          | 0     | 0       | 0     |
| Adults (18-64 years)                               | 58    | 60      | 118   |
| From 65-84 years                                   | 30    | 30      | 60    |
| 85 years and over                                  | 0     | 0       | 0     |
| Gender categorical                                 |       |         |       |
| Units: Subjects                                    |       |         |       |
| Female   | 33    | 31      | 64    |
| Male   | 55    | 59      | 114   |
| Race   |       |         |       |
| Units: Subjects                                    |       |         |       |
| Missing  | 0     | 1       | 1     |
| Asian  | 1     | 1       | 2     |
| Black or African American                          | 1     | 0       | 1     |
| Caucasian or White                                 | 86    | 88      | 174   |
| Ethnicity  |       |         |       |
| Units: Subjects                                    |       |         |       |
| Not Hispanic or Latino                             | 88    | 90      | 178   |

## End points

### End points reporting groups

|  |         |
|--|---------|
| Reporting group title  | APN01   |
| Reporting group description:   |         |
| APN01 is the active treatment: it is a soluble recombinant human angiotensin-converting enzyme 2 (rhACE2) that is currently under development as a therapy for coronavirus-disease 2019 (COVID-19). N=90 subjects were randomized to APN01, but N=3 subjects were excluded from APN01 arm before receiving treatment due to screening failure, randomization key pressed by mistake (2) and 1 subject withdrew for private reasons. Thus, N=88 subjects were treated with APN01. |         |
| Reporting group title  | Placebo |
| Reporting group description:   |         |
| The placebo is physiological saline.   |         |

### Primary: All-cause death or invasive mechanical ventilation (up to 28 days or hospital discharge)

|   |  |
|---|--|
| End point title   | All-cause death or invasive mechanical ventilation (up to 28 days or hospital discharge) |
| End point description:  |  |
| Primary efficacy endpoint = composite endpoint of all-cause death or invasive mechanical ventilation (up to 28 days or hospital discharge). |  |
| Primary endpoint was based on FAS; FAS=178 patients.  |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| Up to 28 days or hospital discharge.  |  |

| End point values            | APN01             | Placebo           |  |  |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type          | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed | 88 <sup>[1]</sup> | 90 <sup>[2]</sup> |  |  |
| Units: Patients             | 9                 | 12                |  |  |

Notes:

[1] - FAS

[2] - FAS

### Statistical analyses

|  |                                    |
|--|------------------------------------|
| Statistical analysis title   | Primary endpoint: Chi-squared test |
| Statistical analysis description:  |                                    |
| Primary endpoint: composite endpoint.  |                                    |
| The following null hypothesis was tested:  |                                    |
| <ul style="list-style-type: none"><li>• H0: pAPN01 = placebo versus the alternative</li><li>• H1: pAPN01 ≠ placebo</li></ul> |                                    |
| H0 was tested using a Chi-squared test. The level of significance is 5% (two-sided).   |                                    |
| Comparison groups  | APN01 v Placebo                    |

|   |               |
|---|---------------|
| Number of subjects included in analysis | 178           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | other         |
| P-value                                 | = 0.5207      |
| Method                                  | Chi-squared   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Primary endpoint: Logistic regression analysis |
|-----------------------------------|--|

Statistical analysis description:

A logistic regression with the responder (yes/no) as independent variable was applied. The following co-factors were included in the logistic regression: Arterial hypertension, Diabetes, Coronary artery disease, Age (<65 years vs. ≥65 years), Center. The odds ratio along with its associated 95% confidence intervals will be reported.

Shown: The odds ratio of treatment group (APN01/placebo) was calculated as APN01/PBO (FAS, N = 178).

|   |                      |
|---|----------------------|
| Comparison groups                       | APN01 v Placebo      |
| Number of subjects included in analysis | 178                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | other                |
| P-value                                 | = 0.3588             |
| Method                                  | Regression, Logistic |
| Parameter estimate                      | Odds ratio (OR)      |
| Point estimate                          | 0.63                 |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 0.23                 |
| upper limit                             | 1.7                  |

## Secondary: 28-day mortality (all-cause death)

|                 |                                    |
|-----------------|------------------------------------|
| End point title | 28-day mortality (all-cause death) |
|-----------------|------------------------------------|

End point description:

28-day mortality (all-cause death) was analyzed using both the chi-squared test and Fisher's exact test. Depending on the expected frequency for each cell, either the results of the chisquared test (all expected frequencies ≥5) or the results of Fischer's test were used for the evaluation and interpretation of the data. In addition, logistic regression analysis including the 5 cofactors specified for the primary analysis was carried out.

Endpoint was based on FAS; FAS=178 patients.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Day 28.



| End point values              | APN01             | Placebo           |  |  |
|-------------------------------|-------------------|-------------------|--|--|
| Subject group type            | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed   | 88 <sup>[3]</sup> | 90 <sup>[4]</sup> |  |  |
| Units: Percentage of patients | 10                | 8                 |  |  |

Notes:

[3] - FAS

[4] - FAS

## Statistical analyses

| Statistical analysis title  | 28-day mortality - 2°endpoint: Chi-squared test |
|---|---|
| Statistical analysis description:   |   |
| Chi-squared test: Proportion of responder, i.e. those patients that died, as well as the p-value (two-sided) were reported. |   |
| Comparison groups   | APN01 v Placebo                                 |
| Number of subjects included in analysis   | 178   |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| P-value   | = 0.5678  |
| Method  | Chi-squared                                     |

| Statistical analysis title   | 28-day mortality - logistic regression |
|--|--|
| Statistical analysis description:  |  |
| The following co-factors will be included in the logistic regression: Arterial hypertension, Diabetes, Coronary artery disease, Age (<65 years vs. ≥65 years), Center. |  |
| The odds ratio along with its associated 95% confidence intervals were reported.   |  |
| Shown: Treatment group (as randomized): APN01 vs Placebo.  |  |
| Comparison groups  | APN01 v Placebo                        |
| Number of subjects included in analysis  | 178                                    |
| Analysis specification   | Pre-specified                          |
| Analysis type  | other                                  |
| P-value  | = 0.7914                               |
| Method   | Regression, Logistic                   |
| Parameter estimate   | Odds ratio (OR)                        |
| Point estimate   | 1.16                                   |
| Confidence interval  |  |
| level  | 95 %                                   |
| sides  | 2-sided                                |
| lower limit  | 0.38                                   |
| upper limit  | 3.57                                   |

## Secondary: Ventilator-free days (VFD) up to 28 days or hospital discharge

| End point title | Ventilator-free days (VFD) up to 28 days or hospital discharge |
|-----------------|--|
|-----------------|--|

End point description:

Ventilator-free days (VFD) were compared between treatments using the Wilcoxon rank sum test and bootstrap methods.

VFD and mechanical-VFD (mVFD) were calculated as time in the study minus duration of ventilation and were set to zero if the duration of ventilation exceeded the time in the study.

3 analysis types were used: 1. Deaths not censored: VFD/mVFD were set to zero for patients who died; 2. Deaths censored: Patients who died before or on Day 28 were censored at the day before death; 3. Alive patients: Only patients who were alive at Day 28, hospital discharge, or early termination were included.

Endpoint was based on FAS; FAS=178 patients.

|                                      |           |
|--------------------------------------|-----------|
| End point type                       | Secondary |
| End point timeframe:                 |           |
| Up to 28 days or hospital discharge. |           |

| End point values                     | APN01             | Placebo           |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 88 <sup>[5]</sup> | 90 <sup>[6]</sup> |  |  |
| Units: days                          |                   |                   |  |  |
| arithmetic mean (standard deviation) |                   |                   |  |  |
| VFD (deaths not censored)            | 17.2 (± 8.8)      | 16.7 (± 8.4)      |  |  |
| VFD (deaths censored)                | 17.4 (± 8.6)      | 16.7 (± 8.4)      |  |  |
| VFD (alive patients)                 | 18.9 (± 7.3)      | 17.9 (± 7.4)      |  |  |
| mVFD (deaths not censored)           | 25.7 (± 8.4)      | 25.1 (± 8.7)      |  |  |
| mVFD (deaths censored)               | 26.3 (± 6.6)      | 25.6 (± 7.6)      |  |  |
| mVFD (alive patients)                | 28.2 (± 1.9)      | 26.9 (± 5.8)      |  |  |

Notes:

[5] - FAS; with exception VFD (alive patients) : N=80 and mVFD (alive patients): N=79

[6] - FAS; with exception VFD (alive patients): N=84 and mVFD (alive patients): N=83

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | VFD (alive patients) - Wilcoxon rank sum test |
|-----------------------------------|---|

Statistical analysis description:

VFD was compared using Wilcoxon rank sum test at a significance level of 5% (two-sided) and p-value (two-sided) was reported.

|   |                         |
|---|-------------------------|
| Comparison groups                       | Placebo v APN01         |
| Number of subjects included in analysis | 178                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other <sup>[7]</sup>    |
| P-value                                 | = 0.0273                |
| Method                                  | Wilcoxon (Mann-Whitney) |

Notes:

[7] - The Wilcoxon rank sum test showed a statistically significant difference in mechanical-VFDs for the population of patients who were alive at Day 28, hospital discharge, or early termination (P <0.05).

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | VFD (deaths not censored) - bootstrap methods |
|-----------------------------------|---|

Statistical analysis description:

Bootstrap methods will be applied to calculate 95% confidence intervals and two-sided p-values for the difference in means between treatment groups.

VFD (deaths not censored): VFD was set to zero for patients who died.

|                   |                 |
|-------------------|-----------------|
| Comparison groups | APN01 v Placebo |
|-------------------|-----------------|

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 178               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | other             |
| P-value                                 | = 0.7215          |
| Method                                  | t-test, 2-sided   |
| Parameter estimate                      | bootstrap methods |
| Point estimate                          | 0.47              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | -1.99             |
| upper limit                             | 2.96              |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | VFD (deaths censored) - bootstrap methods |
|-----------------------------------|---|

Statistical analysis description:

Bootstrap methods will be applied to calculate 95% confidence intervals and two-sided p-values for the difference in means between treatment groups.

Patients who died before Day 28 were censored at the day before death.

|   |                  |
|---|------------------|
| Comparison groups                       | APN01 v Placebo  |
| Number of subjects included in analysis | 178              |
| Analysis specification                  | Pre-specified    |
| Analysis type                           | other            |
| P-value                                 | = 0.6381         |
| Method                                  | t-test, 2-sided  |
| Parameter estimate                      | bootstrap method |
| Point estimate                          | 0.66             |
| Confidence interval                     |                  |
| level                                   | 95 %             |
| sides                                   | 2-sided          |
| lower limit                             | -1.77            |
| upper limit                             | 3.14             |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | VFD (alive patients) - bootstrap method |
|-----------------------------------|---|

Statistical analysis description:

Bootstrap methods will be applied to calculate 95% confidence intervals and two-sided p-values for the difference in means between treatment groups.

Only patients who were alive until Day 28 or hospital discharge/early termination were included in the analysis.

|   |                  |
|---|------------------|
| Comparison groups                       | APN01 v Placebo  |
| Number of subjects included in analysis | 178              |
| Analysis specification                  | Pre-specified    |
| Analysis type                           | other            |
| P-value                                 | = 0.5296         |
| Method                                  | t-test, 2-sided  |
| Parameter estimate                      | bootstrap method |
| Point estimate                          | 1.02             |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -1.2    |
| upper limit         | 3.25    |

## Secondary: Proportion of responders, defined as $\geq 2$ point improvement in WHO's 11-point score system at Days 7, 10, 14 and 28

|                 |   |
|-----------------|---|
| End point title | Proportion of responders, defined as $\geq 2$ point improvement in WHO's 11-point score system at Days 7, 10, 14 and 28 |
|-----------------|---|

### End point description:

The WHO 11-point scale assessment was not done at in-home visits at Day 28. Missing values were included in the calculation of percentages but not used for statistical testing. It was analyzed using both the chi-squared test and Fisher's exact test. Depending on the expected frequency for each cell, either the results of the chi-squared test (all expected frequencies  $\geq 5$ ) or the results of Fisher's test were used for the evaluation and interpretation of the data. In addition, logistic regression analysis including the 5 cofactors specified for the primary analysis was carried out. The odds ratio along with its associated 95% confidence intervals was reported.

Endpoint was based on FAS; FAS=178 patients.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

### End point timeframe:

Measurements at Days 7, 10, 14 and 28.

| End point values            | APN01             | Placebo           |  |  |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type          | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed | 88 <sup>[8]</sup> | 90 <sup>[9]</sup> |  |  |
| Units: Patients             |                   |                   |  |  |
| Day 7                       | 2                 | 0                 |  |  |
| Day 10                      | 17                | 13                |  |  |
| Day 14                      | 38                | 32                |  |  |
| Day 28                      | 72                | 74                |  |  |

### Notes:

[8] - FAS, with exceptions:

Day 10: N=86

Day 14: N=83

Day 28: N=79

[9] - FAS, with exceptions:

D10: N=85

D14: N=85

D28: N=83

## Statistical analyses

|                            |                             |
|----------------------------|-----------------------------|
| Statistical analysis title | Day 7 - Fisher's exact test |
|----------------------------|-----------------------------|

### Statistical analysis description:

Fisher's exact test

Proportion of responder, as well as the p-value (two-sided) was reported for Day 7.

|                   |                 |
|-------------------|-----------------|
| Comparison groups | APN01 v Placebo |
|-------------------|-----------------|

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 178                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[10]</sup>    |
| P-value                                 | = 0.4971 <sup>[11]</sup> |
| Method                                  | Fisher exact             |

Notes:

[10] - Exception from FAS: Patient numbers Day 7: APN01 and Placebo both N=88.

[11] - Exception from FAS: Patient numbers Day 7: APN01 and Placebo both N=88.

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | Day 10 - chi-squared test |
|-----------------------------------|---------------------------|

Statistical analysis description:

Chi-squared test

Proportion of responder, i.e. those patients that have  $\geq 2$  improvement in WHO's 11-Point Score system, as well as the p-value (two-sided) was reported for Day 10, 14 and 28.

|   |                          |
|---|--------------------------|
| Comparison groups                       | APN01 v Placebo          |
| Number of subjects included in analysis | 178                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[12]</sup>    |
| P-value                                 | = 0.4631 <sup>[13]</sup> |
| Method                                  | Chi-squared              |

Notes:

[12] - Exception from FAS: Patient numbers Day 10: APN01 N=86 and Placebo N=85.

[13] - Exception from FAS: Patient numbers Day 10: APN01 N=86 and Placebo N=85.

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | Day 14 - chi-squared test |
|-----------------------------------|---------------------------|

Statistical analysis description:

Chi-squared test

Proportion of responder, i.e. those patients that have  $\geq 2$  improvement in WHO's 11-Point Score system, as well as the p-value (two-sided) was reported for Day 10, 14 and 28.

|   |                          |
|---|--------------------------|
| Comparison groups                       | APN01 v Placebo          |
| Number of subjects included in analysis | 178                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[14]</sup>    |
| P-value                                 | = 0.3116 <sup>[15]</sup> |
| Method                                  | Chi-squared              |

Notes:

[14] - Exception from FAS: Patient numbers Day 14: APN01 N=83 and Placebo N=85.

[15] - Exception from FAS: Patient numbers Day 14: APN01 N=83 and Placebo N=85.

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | Day 28 - chi squared test |
|-----------------------------------|---------------------------|

Statistical analysis description:

Chi-squared test

Proportion of responder, i.e. those patients that have  $\geq 2$  improvement in WHO's 11-Point Score system, as well as the p-value (two-sided) was reported for Day 10, 14 and 28.

|   |                          |
|---|--------------------------|
| Comparison groups                       | APN01 v Placebo          |
| Number of subjects included in analysis | 178                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[16]</sup>    |
| P-value                                 | = 0.3306 <sup>[17]</sup> |
| Method                                  | Chi-squared              |

Notes:

[16] - Exception from FAS:

Day 28: Patients in APN01 N=79 and Placebo N=84.

[17] - Exception from FAS:  
Day 28: Patients in APN01 N=79 and Placebo N=84.

## Secondary: Time to death (all causes)

|                 |                            |
|-----------------|----------------------------|
| End point title | Time to death (all causes) |
|-----------------|----------------------------|

End point description:

Patients who were alive at Day 28, or were discharged from hospital/early terminated before Day 28 were censored at discharge/early termination if they could not be reached at or after Day 28 by means of a telephone interview. Patients who were reached at or after Day 28 by means of a telephone interview were censored at the date of telephone contact if they were alive.

Analyzed using Kaplan-Meier estimates and plots (not shown), log-rank tests, and Cox proportional hazards models (adjusted for center and age adjusted for center and age to derive hazard ratios and corresponding 95% confidence intervals).

Endpoint was based on FAS; FAS=178 patients.

Median or quartile times to death could not be estimated.

The Cox proportional hazards model of time to death specified in the SAP was not uniquely estimable -> thus, no results reported for this analysis.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 28 days.

Time to death [days] = Date of death - Date of randomization

| End point values                     | APN01                | Placebo              |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 88 <sup>[18]</sup>   | 90 <sup>[19]</sup>   |  |  |
| Units: days                          |                      |                      |  |  |
| median (confidence interval 95%)     |                      |                      |  |  |
| Probability of being alive at Day 28 | 0.898 (0.81 to 0.95) | 0.899 (0.78 to 0.96) |  |  |

Notes:

[18] - FAS

[19] - FAS

## Statistical analyses

|                            |               |
|----------------------------|---------------|
| Statistical analysis title | log-rank test |
|----------------------------|---------------|

Statistical analysis description:

Treatments groups were compared with Log-rank test.

|                   |                 |
|-------------------|-----------------|
| Comparison groups | APN01 v Placebo |
|-------------------|-----------------|

|   |     |
|---|-----|
| Number of subjects included in analysis | 178 |
|---|-----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |       |
|---------------|-------|
| Analysis type | other |
|---------------|-------|

|         |         |
|---------|---------|
| P-value | = 0.608 |
|---------|---------|

|        |         |
|--------|---------|
| Method | Logrank |
|--------|---------|

## Secondary: Time to first use of invasive mechanical ventilation up to 28 days or hospital discharge

|                 |   |
|-----------------|---|
| End point title | Time to first use of invasive mechanical ventilation up to 28 |
|-----------------|---|

## End point description:

Analyzed using Kaplan-Meier estimates and plots (not shown), log-rank tests, and Cox proportional hazards models adjusted for center and age.

Median or quartile times to first invasive mechanical ventilation could not be estimated.

The Cox proportional hazards model of time to first use of invasive mechanical ventilation specified in the SAP was not uniquely estimable.

Endpoint was based on FAS; FAS=178 patients.

Patients without documented invasive mechanical ventilation were censored at the date of study completion or discontinuation/discharge from hospital, respectively. N=81 patients from the APN01 group and N=83 patients from placebo group were censored.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

Up to 28 days or hospital discharge.

| End point values                 | APN01                | Placebo              |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed      | 88 <sup>[20]</sup>   | 90                   |  |  |
| Units: Days                      |                      |                      |  |  |
| median (confidence interval 95%) | 0.920 (0.84 to 0.96) | 0.921 (0.84 to 0.96) |  |  |

Notes:

[20] - FAS; N= 81 patients from the APN01 group were censored.

## Statistical analyses

|                            |               |
|----------------------------|---------------|
| Statistical analysis title | log-rank test |
|----------------------------|---------------|

## Statistical analysis description:

Treatments groups were compared with Log-rank test.

|   |                 |
|---|-----------------|
| Comparison groups                       | APN01 v Placebo |
| Number of subjects included in analysis | 178             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other           |
| P-value                                 | = 0.9944        |
| Method                                  | Logrank         |

Secondary: Absolute values and absolute change in PaO<sub>2</sub>/FiO<sub>2</sub> ratio over time

|                 |   |
|-----------------|---|
| End point title | Absolute values and absolute change in PaO <sub>2</sub> /FiO <sub>2</sub> ratio over time |
|-----------------|---|

## End point description:

PaO<sub>2</sub> = partial pressure of arterial oxygen; FiO<sub>2</sub> = fraction of inspired oxygen.

Was evaluated on each visit for ventilated patients only. If entries were not changed compared to previous entries, no entry was done within the eCRF. If ventilation was ongoing and/or no stop date was available, the PaO<sub>2</sub>/FiO<sub>2</sub> ratio were considered until date of study completion/discontinuation or date of death respectively. Baseline was defined as first observation of PaO<sub>2</sub>/FiO<sub>2</sub> ratio (individual start value). Basic statistics for the PaO<sub>2</sub>/FiO<sub>2</sub> ratio for both the absolute values and the absolute change from baseline were tabulated by day of ventilation. Daily = used when more than one assessment was available per day.

Endpoint was based on FAS; FAS=178 patients. In the analyses the high number of missing values must

be taken into consideration.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to Day 28.        |           |

| End point values                     | APN01              | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 88 <sup>[21]</sup> | 90 <sup>[22]</sup> |  |  |
| Units: Patients                      |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Day 1                                | 223.07 (± 99.70)   | 185.14 (± 79.79)   |  |  |
| Day 7                                | 218.74 (± 91.66)   | 192.21 (± 92.71)   |  |  |
| Day 10                               | 290.00 (± 204.70)  | 186.62 (± 87.83)   |  |  |
| Day 14                               | 197.00 (± 99.42)   | 185.00 (± 67.20)   |  |  |
| Day 28                               | 261.00 (± 0)       | 185.00 (± 116.73)  |  |  |

Notes:

[21] - FAS:

D1: N=30

D7: N=19

D10: N=14

D14: N=9

D28: N=1, standard deviation not available

[22] - FAS:

D1: N=28

D7: N=24

D10: N=13

D14: N=11

D28: N=3

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute values and absolute change in modified sequential organ failure assessment (mSOFA) score over time

|                 |   |
|-----------------|---|
| End point title | Absolute values and absolute change in modified sequential organ failure assessment (mSOFA) score over time |
|-----------------|---|

End point description:

The modified sequential organ failure assessment score (mSOFA) score was introduced with protocol version 5.0 and was available for patients who were included with protocol version 5.0 and higher. For patients who were included with previous protocol versions (protocol version 4.0 and lower), mSOFA score was available from the time when protocol was in effect at the centers.

Basic statistics for the mSOFA score for both the absolute values and the absolute change from baseline were tabulated by visit.

Endpoint based on FAS; FAS N=178.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 28 days.       |           |



| End point values                     | APN01              | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 88 <sup>[23]</sup> | 88 <sup>[24]</sup> |  |  |
| Units: Patients                      |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Day -1                               | 2.6 (± 1.2)        | 2.2 (± 1.4)        |  |  |
| Day 7                                | 1.8 (± 2.5)        | 1.6 (± 2.1)        |  |  |
| FU Day 10                            | 1.0 (± 1.7)        | 1.0 (± 1.6)        |  |  |
| FU Day 14                            | 1.0 (± 2.4)        | 0.9 (± 1.7)        |  |  |
| FU Day 28/EOS                        | 0.2 (± 0.6)        | 0.8 (± 1.8)        |  |  |

Notes:

[23] - FAS:

D-1: N=80

D7: N=83

D10: N=80

D14: N=79

D28: N=39

[24] - FAS:

D-1: N=80

D7: N=77

D10: N=77

D14: N=75

D28: N=38

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to a 2-point decrease in WHO's 11-point score system (WHO clinical progression scale [CPS])

|                 |  |
|-----------------|--|
| End point title | Time to a 2-point decrease in WHO's 11-point score system (WHO clinical progression scale [CPS]) |
|-----------------|--|

End point description:

Patients without documented 2-point decrease who completed the study or were early terminated or discharged from hospital before Day 28 were censored at the date of last WHO assessment available. Analyzed using Kaplan-Meier estimates and plots (not shown), log-rank tests, and Cox proportional hazards models adjusted for center and age.

Endpoint based on FAS; FAS: N=178. N=14 patients from the APN01 group and N=15 patients from placebo group were censored.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 28 days.

| End point values                 | APN01               | Placebo             |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 88 <sup>[25]</sup>  | 90 <sup>[26]</sup>  |  |  |
| Units: Days                      |                     |                     |  |  |
| median (confidence interval 95%) |                     |                     |  |  |
| Median time to improvement       | 27 (14.00 to 27.00) | 27 (17.00 to 27.00) |  |  |

Notes:

[25] - FAS

[26] - FAS

## Statistical analyses

| Statistical analysis title                          | log-rank test   |
|---|-----------------|
| Statistical analysis description:                   |                 |
| Treatments groups were compared with Log-rank test. |                 |
| Comparison groups                                   | APN01 v Placebo |
| Number of subjects included in analysis             | 178             |
| Analysis specification                              | Pre-specified   |
| Analysis type                                       | other           |
| P-value   | = 0.2173        |
| Method  | Logrank         |

| Statistical analysis title  | Cox proportional hazards regression analyses |
|---|--|
| Statistical analysis description:   |  |
| Cox proportional hazards model  |  |
| The hazards ratio along with its associated 95% confidence intervals as well as parameter estimate and p-value (two-sided) were reported. |  |
| Comparison groups   | APN01 v Placebo                              |
| Number of subjects included in analysis   | 178  |
| Analysis specification  | Pre-specified                                |
| Analysis type   | other  |
| P-value   | = 0.3725 <sup>[27]</sup>                     |
| Method  | Cox regression: Wald Tests                   |

Notes:

[27] - P-value for parameter "Treatment group (as randomized)".

## Secondary: Absolute values and absolute change in lymphocyte count over time

| End point title   | Absolute values and absolute change in lymphocyte count over time |
|---|---|
| End point description:  |   |
| Lymphocytes assessed in blood samples of patients.  |   |
| Endpoint based on FAS; FAS: N=178. Note: Analysis with a high number of missing values; number of evaluable patients varied between visits. |   |
| Summarized with descriptive statistics.   |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Up to 28 days.  |   |

| End point values                     | APN01              | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 88 <sup>[28]</sup> | 90 <sup>[29]</sup> |  |  |
| Units: 10 <sup>9</sup> /L            |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Screening (Day -1)                   | 1.13 (± 0.694)     | 1.06 (± 0.629)     |  |  |
| Day 1                                | 0.96 (± 0.376)     | 0.92 (± 0.372)     |  |  |
| Day 2                                | 1.14 (± 0.628)     | 1.14 (± 0.629)     |  |  |
| Day 3                                | 1.25 (± 0.843)     | 1.16 (± 0.662)     |  |  |
| Day 5                                | 1.35 (± 1.026)     | 1.40 (± 0.757)     |  |  |
| Day 7                                | 1.45 (± 0.948)     | 1.62 (± 0.940)     |  |  |
| Day 8                                | 1.09 (± 0.773)     | 1.35 (± 0.349)     |  |  |
| FU Day 10                            | 1.74 (± 1.444)     | 1.79 (± 0.782)     |  |  |
| FU Day 14                            | 1.70 (± 0.773)     | 1.71 (± 0.730)     |  |  |
| FU Day 28/EOS                        | 2.28 (± 3.420)     | 1.72 (± 0.559)     |  |  |

Notes:

[28] - FAS:

D-1: 82

D1: 14

D2: 83

D3: 85

D5: 81

D7: 82

D8: 7

D10: 81

D14: 77

D28: 37

[29] - FAS:

D-1: 82

D1: 14

D2: 78

D3: 83

D5: 79

D7: 80

D8: 4

D10: 75

D14: 73

D28 EOS: 37

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute values and absolute change in C-reactive protein (CRP) levels over time

|                 |  |
|-----------------|--|
| End point title | Absolute values and absolute change in C-reactive protein (CRP) levels over time |
|-----------------|--|

End point description:

CRP assessed in blood samples of patients.

Endpoint based on FAS; FAS: N=178. Note: Analysis with a high number of missing values; number of evaluable patients varied between visits.

Summarized with descriptive statistics.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 28 days.

| End point values                     | APN01              | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 88 <sup>[30]</sup> | 90 <sup>[31]</sup> |  |  |
| Units: mg/L                          |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Screening (Day -1)                   | 56.0 (± 64.53)     | 62.8 (± 51.75)     |  |  |
| Day 1                                | 85.8 (± 100.54)    | 94.5 (± 73.02)     |  |  |
| Day 2                                | 48.1 (± 66.45)     | 51.8 (± 43.35)     |  |  |
| Day 3                                | 36.1 (± 53.75)     | 43.7 (± 45.13)     |  |  |
| Day 5                                | 28.7 (± 57.06)     | 37.1 (± 42.04)     |  |  |
| Day 7                                | 21.7 (± 41.58)     | 26.1 (± 38.71)     |  |  |
| Day 8                                | 39.3 (± 54.11)     | 8.4 (± 7.60)       |  |  |
| FU Day 10                            | 13.9 (± 24.24)     | 26.3 (± 48.75)     |  |  |
| FU Day 14                            | 15.8 (± 29.66)     | 38.3 (± 133.24)    |  |  |
| FU Day 28/EOS                        | 4.9 (± 5.69)       | 8.5 (± 11.54)      |  |  |

Notes:

[30] - Pt

D-1: 77

D1: 12

D2: 78

D3: 80

D5: 76

D7: 78

D8: 7

FU D10: 74

FU D14: 69

FU D28/EOS: 36

[31] - Pt

D-1: 79

D1: 13

D2: 74

D3: 74

D5: 73

D7: 76

D8: 3

FU D10: 71

FU D14: 73

FU D28/EOS: 37

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute values and absolute change in D-dimer levels over time

|                 |   |
|-----------------|---|
| End point title | Absolute values and absolute change in D-dimer levels over time |
|-----------------|---|

End point description:

D-Dimer assessed in blood samples of patients.

Endpoint based on FAS; FAS: N=178. Note: Analysis with a high number of missing values; number of evaluable patients varied between visits.

Summarized with descriptive statistics.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 28 days.

| End point values                     | APN01              | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 88 <sup>[32]</sup> | 90 <sup>[33]</sup> |  |  |
| Units: µg/L                          |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Screening (Day -1)                   | 1341 (± 2757)      | 1187 (± 3994)      |  |  |
| Day 1                                | 965 (± 796)        | 3787 (± 9918)      |  |  |
| Day 2                                | 1133 (± 1538)      | 909 (± 1013)       |  |  |
| Day 3                                | 1109 (± 1316)      | 881 (± 959)        |  |  |
| Day 5                                | 1286 (± 1588)      | 1023 (± 1132)      |  |  |
| Day 7                                | 1208 (± 1485)      | 1139 (± 1590)      |  |  |
| Day 8                                | 1473 (± 1609)      | 1303 (± 970)       |  |  |
| FU Day 10                            | 988 (± 1135)       | 1219 (± 2228)      |  |  |
| FU Day 14                            | 1015 (± 1520)      | 1013 (± 2243)      |  |  |
| FU Day 28/EOS                        | 573 (± 629)        | 685 (± 939)        |  |  |

Notes:

[32] - Pt #

D-1: 71

D1: 11

D2: 73

D3: 69

D5: 72

D7: 73

D8: 7

FU D10: 70

FU D14: 70

FU D28/EOS: 32

[33] - Pt #

D-1: 73

D1: 12

D2: 69

D3: 74

D5: 69

D7: 68

D8: 3

FU D10: 66

FU D14: 66

FU D28/EOS: 31

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute values and absolute change in log-transformed levels of LDH over time

|                 |  |
|-----------------|--|
| End point title | Absolute values and absolute change in log-transformed levels of LDH over time |
|-----------------|--|

End point description:

Lactate dehydrogenase (LDH) was assessed in blood samples of patients.

Endpoint based on FAS; FAS: N=178. Note: Analysis with a high number of missing values; number of evaluable patients varied between visits.

Summarized with descriptive statistics.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 28 days.

| End point values                     | APN01              | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 88 <sup>[34]</sup> | 90 <sup>[35]</sup> |  |  |
| Units: U/L                           |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Screening (Day -1)                   | 5.91 (± 0.442)     | 5.87 (± 5.87)      |  |  |
| Day 1                                | 5.74 (± 0.402)     | 5.85 (± 5.85)      |  |  |
| Day 2                                | 5.89 (± 0.468)     | 5.92 (± 0.366)     |  |  |
| Day 3                                | 5.86 (± 0.440)     | 5.88 (± 0.422)     |  |  |
| Day 5                                | 5.82 (± 0.470)     | 5.80 (± 0.433)     |  |  |
| Day 7                                | 5.77 (± 0.459)     | 5.75 (± 0.387)     |  |  |
| Day 8                                | 6.11 (± 0.528)     | 6.23 (± 0.292)     |  |  |
| FU Day 10                            | 5.66 (± 0.464)     | 5.67 (± 0.401)     |  |  |
| FU Day 14                            | 5.55 (± 0.467)     | 5.52 (± 0.406)     |  |  |
| FU Day 28/EOS                        | 5.43 (± 0.305)     | 5.50 (± 0.383)     |  |  |

Notes:

[34] - Pt #

D-1: 78

D1: 14

D2: 74

D3: 76

D5: 74

D7: 78

D8: 7

FU D10: 72

FU D14: 69

FU D28/EOS: 38

[35] - Pt #

D-1: 77

D1: 14

D2: 73

D3: 76

D5: 74

D7: 74

D8: 3

FU D10: 74

FU D14: 71

FU D28/EOS: 38

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to hospital discharge

|                 |                            |
|-----------------|----------------------------|
| End point title | Time to hospital discharge |
|-----------------|----------------------------|

End point description:

Dased on FAS; FAS=178.

Analyzed using Kaplan-Meier estimates and plots, log-rank tests, and Cox proportional hazards models adjusted for center and age.

Time to hospital discharge [days] = date of first discharge from hospital - date of randomization.

Patients without documented hospital discharge were censored at the date of study completion or discontinuation.

Patients who died before Day 28 were censored at the date of death even if early terminated before.

N = 14 patients from each group were censored.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 28 days.       |           |

| End point values              | APN01               | Placebo             |  |  |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type            | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed   | 88 <sup>[36]</sup>  | 90 <sup>[37]</sup>  |  |  |
| Units: Days                   |                     |                     |  |  |
| median (full range (min-max)) | 14 (12.00 to 15.00) | 14 (13.00 to 15.00) |  |  |

Notes:

[36] - FAS

[37] - FAS

## Statistical analyses

| Statistical analysis title | Log-rank test |
|----------------------------|---------------|
|----------------------------|---------------|

Statistical analysis description:

The log-rank test did not reveal any statistically significant difference between the no-discharge probabilities over time.

|   |                 |
|---|-----------------|
| Comparison groups                       | APN01 v Placebo |
| Number of subjects included in analysis | 178             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other           |
| P-value                                 | = 0.829         |
| Method                                  | Logrank         |

| Statistical analysis title | Cox proportional hazards regression analysis |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Cox proportional hazards regression analysis revealed that patients  $\geq 65$  years were less likely to be discharged from hospital within 28 days (hazard ratio 0.594, 95% CI, 0.40–0.88; P = 0.0101).

The analysis indicated that the time to hospital discharge differed between centers (Wald test, P < 0.01).

|   |                         |
|---|-------------------------|
| Comparison groups                       | APN01 v Placebo         |
| Number of subjects included in analysis | 178                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.0101                |
| Method                                  | Regression, Cox         |
| Parameter estimate                      | Cox proportional hazard |
| Point estimate                          | 0.594                   |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.4                     |
| upper limit                             | 0.88                    |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.2027                     |

## Secondary: Change in viral ribonucleic acid (RNA) over time

|  |  |
|--|--|
| End point title  | Change in viral ribonucleic acid (RNA) over time |
| End point description:   |  |
| Viral RNA was assessed in blood samples of patients.   |  |
| Endpoint based on FAS; FAS: N=178. Note: The number of missing values was relatively high and varied between visits.     |  |
| Assessments could be omitted for Day 28/EOS phone visits.  |  |
| Only results that could be converted to standard units were submitted to analysis. "No SARS-CoV2 detected" was set to 0. |  |
| Summarized with descriptive statistics.  |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Up to 28 days.   |  |

| End point values                     | APN01              | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 88 <sup>[38]</sup> | 90 <sup>[39]</sup> |  |  |
| Units: copies/mL                     |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Day 1                                | 27996 (± 78877)    | 3900 (± 5848)      |  |  |
| Day 3                                | 20931 (± 53182)    | 13681 (± 45287)    |  |  |
| Day 5                                | 9825 (± 32979)     | 11912 (± 75457)    |  |  |
| Day 7                                | 5229 (± 24514)     | 2094 (± 8742)      |  |  |
| FU Day 14                            | 9274 (± 78304)     | 53 (± 455)         |  |  |
| FU Day 28/EOS                        | 36 (± 217)         | 0 (± 0)            |  |  |

Notes:

[38] - Pt numbers

D1: 59

D3: 47

D5: 56

D7: 65

FU D14: 73

FU D28 EOS: 37

[39] - Pt numbers

D1: 49

D3: 58

D5: 64

D7: 61

FU D14: 73

FU D28 EOS: 36

## Statistical analyses

No statistical analyses for this end point



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**Secondary: Log-transformed levels of LDH at Day 5 as a surrogate marker for organ damage (powered secondary endpoint)**

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|                 |  |
|-----------------|--|
| End point title | Log-transformed levels of LDH at Day 5 as a surrogate marker for organ damage (powered secondary endpoint) |
|-----------------|--|

End point description:

Powered secondary endpoint: Log transformed levels of LDH were analyzed using linear regression adjusted for baseline log levels of LDH, center and age. 95% confidence intervals were additionally calculated.

Both the mean and the median log-transformed LDH concentrations at Day 5 were similar in both treatment groups. The linear regression model of log-transformed LDH data specified in the SAP was not uniquely estimable.

Assessed in patients blood as a surrogate marker for organ damage.

The endpoint was based on FAS; FAS=178 patients.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measurement at Day 5.

---

| End point values                     | APN01              | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 88 <sup>[40]</sup> | 90 <sup>[41]</sup> |  |  |
| Units: Concentration (U/L)           |                    |                    |  |  |
| arithmetic mean (standard deviation) | 5.82 (± 0.470)     | 5.80 (± 0.433)     |  |  |

Notes:

[40] - Based on FAS; analysed patients N=74

[41] - Based on FAS; analysed patients N=74

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Proportion of patients with any use of invasive mechanical ventilation up to 28 days or hospital discharge**

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|                 |  |
|-----------------|--|
| End point title | Proportion of patients with any use of invasive mechanical ventilation up to 28 days or hospital discharge |
|-----------------|--|

End point description:

Based on FAS; FAS=175 patients.

The number of patients receiving mechanical ventilation and supplemental oxygen was evaluated. A patient may have received ventilations/supplemental oxygen multiple times and of different types during the study.

Analyzed using both the chi-squared test and Fisher's exact test. In addition, logistic regression analysis including the 5 cofactors specified for the primary analysis was carried out.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 28 days or hospital discharge.

---

| <b>End point values</b>                         | APN01              | Placebo            |  |  |
|---|--------------------|--------------------|--|--|
| Subject group type                              | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed                     | 88 <sup>[42]</sup> | 90 <sup>[43]</sup> |  |  |
| Units: Percentage of patients                   |                    |                    |  |  |
| Invasive mechanical ventilation                 | 8                  | 8                  |  |  |
| Total receiving ventilation/supplemental oxygen | 98                 | 98                 |  |  |
| No supplemental oxygen/ventilation              | 2                  | 2                  |  |  |
| Missing data                                    | 2                  | 2                  |  |  |

Notes:

[42] - FAS

[43] - FAS

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

30-Apr-2020 until 26-Dec-2020

Adverse event reporting additional description:

The investigator was responsible for ensuring that all adverse events observed by the investigator or reported by patient are properly captured in the patients' medical records.

Adverse events were recorded in the AE page of the eCRF using a recognized medical term or diagnosis that accurately reflects the event.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Study participants receiving placebo.

Reports of fatal AEs are available for 6 of the 7 patients from the placebo group.

|                       |             |
|-----------------------|-------------|
| Reporting group title | APN01 (IMP) |
|-----------------------|-------------|

Reporting group description:

All patients receiving IMP (APN01). All AEs were treatment-emergent. 9 patients had died by Day 28, a 10th patients had died by Day 78.

Reports of fatal AEs are available for 9 of the 10 patients from the APN01 group.

| Serious adverse events                            | Placebo   | APN01 (IMP)      |  |
|---|---|------------------|--|
| Total subjects affected by serious adverse events |   |                  |  |
| subjects affected / exposed                       | 12 / 90 (13.33%)  | 10 / 88 (11.36%) |  |
| number of deaths (all causes)                     | 7   | 10               |  |
| number of deaths resulting from adverse events    | 6   | 9                |  |
| Injury, poisoning and procedural complications    |   |                  |  |
| Muscle rupture                                    |   |                  |  |
| subjects affected / exposed                       | 1 / 90 (1.11%)  | 0 / 88 (0.00%)   |  |
| occurrences causally related to treatment / all   | 0 / 1   | 0 / 0            |  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0            |  |
| Vascular disorders                                |   |                  |  |
| Infarction  | Additional description: MedDRA v23.0 preferred terms listed for both patients was "Infarction (myocardial)".  |                  |  |
| subjects affected / exposed                       | 1 / 90 (1.11%)  | 1 / 88 (1.14%)   |  |
| occurrences causally related to treatment / all   | 0 / 1   | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 1   | 0 / 1            |  |
| Thrombosis  | Additional description: MedDRA v23.0 preferred terms listed for the respective patient was "Pulmonary oedema, thrombosis" - fatality was entered in AE category "Pulmonary oedema". |                  |  |

|  |  |                |  |
|--|--|----------------|--|
| subjects affected / exposed                          | 0 / 90 (0.00%)   | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all      | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0  | 0 / 0          |  |
| Nervous system disorders                             |  |                |  |
| Cerebral infarction                                  | Additional description: MedDRA v23.0 preferred terms listed for the respective patient was "Respiratory failure, cerebral infarction" - fatality was entered in AE category "respiratory infarction".            |                |  |
| subjects affected / exposed                          | 1 / 90 (1.11%)   | 0 / 88 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0  | 0 / 0          |  |
| Haemorrhagic stroke                                  |  |                |  |
| subjects affected / exposed                          | 1 / 90 (1.11%)   | 0 / 88 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 1  | 0 / 0          |  |
| Syncope  |  |                |  |
| subjects affected / exposed                          | 1 / 90 (1.11%)   | 0 / 88 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0  | 0 / 0          |  |
| General disorders and administration site conditions |  |                |  |
| General physical health deterioration                |  |                |  |
| subjects affected / exposed                          | 1 / 90 (1.11%)   | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all      | 0 / 1  | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0  | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders      |  |                |  |
| Acute respiratory failure                            | Additional description: MedDRA v23.0 preferred terms listed for the respective patient was "Acute respiratory failure, pulmonary embolism" - fatality was entered in in AE category "Acute respiratory failure". |                |  |
| subjects affected / exposed                          | 0 / 90 (0.00%)   | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all      | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0  | 0 / 1          |  |
| Pulmonary embolism                                   | Additional description: MedDRA v23.0 preferred terms listed for the respective patient was "Acute respiratory failure, pulmonary embolism" - fatality was entered in "Acute respiratory failure".                |                |  |
| subjects affected / exposed                          | 0 / 90 (0.00%)   | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all      | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0  | 0 / 0          |  |
| Pulmonary oedema                                     | Additional description: MedDRA v23.0 preferred terms listed for the respective patient was "Pulmonary oedema, thrombosis" - fatality was entered here.   |                |  |

|   |   |                |  |
|---|---|----------------|--|
| subjects affected / exposed                     | 0 / 90 (0.00%)  | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1          |  |
| Respiratory distress                            |   |                |  |
| subjects affected / exposed                     | 1 / 90 (1.11%)  | 0 / 88 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Respiratory failure                             | Additional description: MedDRA v23.0 preferred terms listed for one patient in the Placebo arm was "Respiratory failure, cerebral infarction" and for one patient in the APN01 arm was "Respiratory failure, sepsis" - fatality was entered here. |                |  |
| subjects affected / exposed                     | 7 / 90 (7.78%)  | 6 / 88 (6.82%) |  |
| occurrences causally related to treatment / all | 0 / 7   | 0 / 6          |  |
| deaths causally related to treatment / all      | 0 / 4   | 0 / 6          |  |
| Renal and urinary disorders                     |   |                |  |
| Renal failure                                   |   |                |  |
| subjects affected / exposed                     | 0 / 90 (0.00%)  | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Infections and infestations                     |   |                |  |
| Sepsis  |   |                |  |
| subjects affected / exposed                     | 0 / 90 (0.00%)  | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events                            | Placebo          | APN01 (IMP)      |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 24 / 90 (26.67%) | 14 / 88 (15.91%) |  |
| Investigations  |                  |                  |  |
| Alanine aminotransferase increased                    |                  |                  |  |
| subjects affected / exposed                           | 11 / 90 (12.22%) | 10 / 88 (11.36%) |  |
| occurrences (all)                                     | 11               | 10               |  |
| Blood potassium increased                             |                  |                  |  |
| subjects affected / exposed                           | 4 / 90 (4.44%)   | 5 / 88 (5.68%)   |  |
| occurrences (all)                                     | 4                | 5                |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| Electrocardiogram QT prolonged<br>subjects affected / exposed<br>occurrences (all) | 6 / 90 (6.67%)<br>6 | 2 / 88 (2.27%)<br>2 |  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)       | 5 / 90 (5.56%)<br>5 | 0 / 88 (0.00%)<br>0 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 23 April 2020 | <p>After the first patient was enrolled under v3.0, the protocol was amended 4 times as follows:</p> <p>Version 4.0, dated 23-Apr-2020:</p> <ul style="list-style-type: none"><li>o Inclusion criterion 4 was removed to include patients with a lower respiratory frequency (<math>\geq 25</math> breaths/min)</li><li>o Included that the time interval between start of screening procedures and start of treatment must not exceed 24 hours. Randomization and treatment initiation may be performed on the day of screening, if possible</li><li>o Collection tubes for individual Biomarkers were corrected according to the Lab Manual</li></ul>   |
| 04 May 2020   | <p>Version 5.0, dated 04-May-2020:</p> <ul style="list-style-type: none"><li>o Number of planned study centers was increased to 16 and the USA was added as possible participating country</li><li>o Allowed body weight for inclusion of patients was increased to up to 100 kg (inclusion criterion 7)</li><li>o The specification, that any patient whose clinical condition deteriorates rapidly, i.e., in whom the clinician anticipates that the patient will need invasive mechanical ventilation within 12 hours, was removed as an exclusion criterion (exclusion criterion 1)</li><li>o Clarified that patients with a history of positive hepatitis B surface antigen, hepatitis C antibody, or HIV antibody were not eligible (exclusion criterion 2)</li><li>o Clarified that vital signs must be tested within 30 minutes before and after IMP administration during the treatment period</li><li>o Clarified that if serology results are not available before randomization, previous results obtained within 4 weeks before randomization are acceptable</li><li>o Clarified that as an alternative to the pharmacist, an unblinded member of the study team may also provide the principal investigator with the blinded treatment</li><li>o Clarified that physical examination could also be documented as a part of a general visit/health status (e.g., during a general clinical review assessment)</li><li>o Included that standard of care treatment (concomitant medication and ventilation techniques) has to be followed to national guidelines (<a href="https://www.ersnet.org/covid-19-guidelines-and-recommendations-directory">https://www.ersnet.org/covid-19-guidelines-and-recommendations-directory</a>), documented in the eCRF and considered for evaluation of study data</li><li>o Clarified that the first dosing could be done either in the morning of Day 1 or in the evening of Day -1</li><li>o The mSOFA score was introduced instead of the sequential organ failure assessment (SOFA) score to assess the degree of organ dysfunction to determine mortality risk</li><li>o The study rationale had been updated regarding new findings</li></ul> |

|                |   |
|----------------|---|
| 08 June 2020   | <p>V6.0</p> <ul style="list-style-type: none"> <li>o # planned study centers was increased to 40 &amp; Russia was added as participating country. The restriction that each site should target between 10 &amp; 20 patients was removed</li> <li>o Incl. criterion 1 was modified to include patients between 18 &amp; 80 years of age</li> <li>o Deletion incl. criterion 5 "Presence of at least 1 relevant co-morbid condition (defined as arterial hypertension, diabetes, or coronary artery disease) if age &lt;65 years"</li> <li>o Body weight restriction for incl. (incl. criterion 7) was removed for the US sites</li> <li>o Removal excl. criterion 10 to include patients with history of sensitivity to heparin or heparin-induced thrombocytopenia</li> <li>o Specification excl. criterion 18 to exclude only patients who are in clin. trials with an IMP for COVID-19</li> <li>o PCR for quantitative and qualitative detection of SARS-CoV-2 nucleic acid has been allowed. If the test was performed within 5 days before the screening visit, it did not need to be repeated at screening &amp; available test results could be used</li> <li>o Pulse oximetry was added as an alternative to blood gas analysis (oxygenation index, blood lactic acid) to assess the patient's respiratory status</li> <li>o Clarified that follow-up visit on D28 could be performed as phone visit/in-home visit (in Russia)</li> <li>o Clarified that pre-existing conditions that were present at screening were not to be reported as AEs. An AE reported between screening &amp; IMP application was defined as pre-treatment AE. Changes in lab values that were clinically significant &amp; specific for COVID-19 did not need to be documented as AE. Clin. significant changes in lab values that were not due to COVID-19 needed to be documented as AEs</li> <li>o Presence of at least 1 relevant co-morbid condition (hypertension, diabetes, coronary artery disease) was removed as a stratification factor for randomization</li> <li>o Remote/video monitoring strategy during COVID-19 pandemic was added</li> <li>o Issues arising from the change to the mSOFA score but not yet implemented in protocol v5.0 were adjusted</li> </ul> |
| 10 August 2020 | <p>Version 7.0, dated 10-Aug-2020:</p> <ul style="list-style-type: none"> <li>o Body weight restriction for inclusion (inclusion criterion 6) was removed for all participating sites</li> <li>o Change in viral RNA over time was added as secondary endpoint</li> <li>o If a patient was discharged from hospital before Day 7, treatment could be stopped at day of discharge</li> <li>o Remdesivir was added as potential standard of care treatment</li> <li>o For endpoint calculation (28-day mortality), patients discharged from the hospital or terminating the study early before Day 28 will be considered as not-event-free (i.e., death) on the day of discharge or early termination, if the alive/death status is unknown</li> <li>o Clarified that follow-up visits could be performed as outpatients/phone visits</li> <li>o A placebo strength of 10 mL physiological saline was added</li> <li>o It was clarified that the entire study team will be blinded except for an unblinded pharmacist or an unblinded team member (including team members involved in the IMP preparation, unblinded statisticians and DSMB members involved in DSMB, unblinded data managers involved in generation and the upload of treatment listings to eCRF)</li> <li>o Clarified that the DSMB had to review the overall options for COVID-19 patients to make a recommendation to adjust the study design, if necessary</li> </ul>  |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported



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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/3313160>

<http://www.ncbi.nlm.nih.gov/pubmed/3233383>