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 exlcusion 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 expect 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 (±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.

Arm title	Placebo

Arm description:

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.

Number of subjects in period 1[1]	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 exlcusion 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[1]	90[2]		
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:
• H0: pAPN01 = placebo versus the alternative
• H1: pAPN01 ≠ placebo
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

Statistical analysis title	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 were 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[3]	90[4]		
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[5]	90[6]		
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

Statistical analysis title	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[7]
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).

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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 ≥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 ≥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 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. 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[8]	90[9]		
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 th 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[10]
P-value	= 0.4971 [11]
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.

Statistical analysis title	Day 10 - chi-squared test

Statistical analysis description:

Chi-squared test
Proportion of responder, i.e. those patients that have >= 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[12]
P-value	= 0.4631 [13]
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.

Statistical analysis title	Day 14 - chi-squared test

Statistical analysis description:

Chi-squared test
Proportion of responder, i.e. those patients that have >= 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[14]
P-value	= 0.3116 [15]
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.

Statistical analysis title	Day 28 - chi squared test

Statistical analysis description:

Chi-squared test
Proportion of responder, i.e. those patients that have >= 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[16]
P-value	= 0.3306 [17]
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[18]	90[19]		
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

	days or hospital discharge

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[20]	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 PaO2/FiO2 ratio over time

End point title	Absolute values and absolute change in PaO2/FiO2 ratio over time

End point description:

PaO2 = partial pressure of arterial oxygen; FiO2 = 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 PaO2/FiO2 ratio ware considered until date of study completion/discontinuation or date of death respectively. Baseline was defined as first observation of PaO2/FiO2 ratio (individual start value). Basic statistics for the PaO2/FiO2 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[21]	90[22]		
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 be 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[23]	88[24]		
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[25]	90[26]		
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 [27]
Method	Cox regression: Wald Tests

Notes:

[27] - P-value for paramenter "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[28]	90[29]		
Units: 10^9/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[30]	90[31]		
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[32]	90[33]		
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[34]	90[35]		
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[36]	90[37]		
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 ≥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[38]	90[39]		
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

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

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 groupsThe linear regression model of log-transformed. LDH data specified in the SAP was not uniquely estimable.
Assesed 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[40]	90[41]		
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

Statistical analyses

No statistical analyses for this end point

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

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.

End point values	APN01	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[42]	90[43]		
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 spatients 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 catergory "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 catergory "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 catergory "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, spesis" - 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 subjects affected / exposed occurrences (all)	6 / 90 (6.67%) 6	2 / 88 (2.27%) 2	
Hepatic enzyme increased subjects affected / exposed occurrences (all)	5 / 90 (5.56%) 5	0 / 88 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2020	After the first patient was enrolled under v3.0, the protocol was amended 4 times as follows: Version 4.0, dated 23-Apr-2020: o Inclusion criterion 4 was removed to include patients with a lower respiratory frequency (≥25 breaths/min) 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 o Collection tubes for individual Biomarkers were corrected according to the Lab Manual
04 May 2020	Version 5.0, dated 04-May-2020: o Number of planned study centers was increased to 16 and the USA was added as possible participating country o Allowed body weight for inclusion of patients was increased to up to 100 kg (inclusion criterion 7) 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) 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) Clarified that vital signs must be tested within 30 minutes before and after IMP administration during the treatment period o Clarified that if serology results are not available before randomization, previous results obtained within 4 weeks before randomization are acceptable 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 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) o Included that standard of care treatment (concomitant medication and ventilation techniques) has to be followed to national guidelines (https://www.ersnet.org/covid-19-guidelines-and-recommendations-directory), documented in the eCRF and considered for evaluation of study data o Clarified that the first dosing could be done either in the morning of Day 1 or in the evening of Day -1 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 o The study rationale had been updated regarding new findings

08 June 2020	V6.0 o # planned study centers was increased to 40 & Russia was added as participating country. The restriction that each site should target between 10 &20 patients was removed o Incl. criterion 1 was modified to include patients between 18 & 80 years of age 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 <65 years" o Body weight restriction for incl. (incl. criterion 7) was removed for the US sites o Removal excl. criterion 10 to include patients with history of sensitivity to heparin or heparin-induced thrombocytopenia o Specification excl. criterion 18 to exclude only patients who are in clin. trials with an IMP for COVID-19 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 & available test results could be used o Pulse oximetry was added as an alternative to blood gas analysis (oxygenation index, blood lactic acid) to assess the patient's respiratory status o Clarified that follow-up visit on D28 could be performed as phone visit/in-home visit (in Russia) o Clarified that pre-existing conditions that were present at screening were not to be reported as AEs. An AE reported between screening & IMP application was defined as pre-treatment AE. Changes in lab values that were clinically significant & 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 o Presence of at least 1 relevant co-morbid condition (hypertension, diabetes, coronary artery disease) was removed as a stratification factor for randomization o Remote/video monitoring strategy during COVID-19 pandemic was added o Issues arising from the change to the mSOFA score but not yet implemented in protocol v5.0 were adjusted
10 August 2020	Version 7.0, dated 10-Aug-2020: o Body weight restriction for inclusion (inclusion criterion 6) was removed for all participating sites o Change in viral RNA over time was added as secondary endpoint o If a patient was discharged from hospital before Day 7, treatment could be stopped at day of discharge o Remdesivir was added as potential standard of care treatment 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 o Clarified that follow-up visits could be performed as outpatients/phone visits o A placebo strength of 10 mL physiological saline was added 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) 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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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

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