STUDY PROTOCOL

Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treatment for patients with COVID-19	
EudraCT No.	2020-001172-15
IND	151312
Protocol No.	APN01-01-COVID19
Version/Date	Version 7.0, 10 AUG 2020
Sponsor	APEIRON Biologics AG Campus-Vienna-Biocenter 5 1030 Vienna, Austria
Coordinating Investigator	Prof. Dr. med. Henning Bundgaard The Capital Region's Unit of Inherited Cardiac Diseases Faculty of Health and Medical Sciences University of Copenhagen Rigshospitalet, University of Copenhagen Department of Cardiology The Heart Centre Blegdamsvej 9 2100 Copenhagen Ø, Denmark Telephone: +45 3545 0512

SIGNATURES

Sponsor Signature

This protocol has been approved by APEIRON Biologics AG.

Sponsor Signature	Date
Sponsor Name	

Coordinating Investigator Signature

I hereby confirm that I have acknowledged the protocol and agree to conduct the clinical trial in compliance with the protocol.

Coordinating Investigator Signature	Date
Coordinating Investigator Name	

Statistician Signature

I hereby confirm that I have acknowledged the protocol and agree to conduct the clinical trial in compliance with the protocol.

Statistician Signature	Date
Statistician Name	

SUMMARY OF CHANGES

Summary of changes since last version of the protocol (protocol version 1.0 to version 2.0)		
Amendment Number	**Date of Amend-ment**	**Section Affected by Change**
01	27 Mar 2020	Study schedule & Section 9.5.2.2.6
Brief description of change: Clinical laboratory parameter (HIV, HBV and HBC serology) entered for screening.		
01	27 Mar 2020	Section 9.4.6.
Brief description of change: Unblinding process was described in more detail.		
01	27 Mar 2020	Section 9.5.2.1.2
Brief description of change: Wording regarding re-screening was corrected.		
01	27 Mar 2020	Synopsis & Section 9.3.2
Brief description of change: Exclusion criterion 1 was specified.		
01	27 Mar 2020	Section 9.3.3.3
Brief description of change: Holding rules were amended for a discontinuation criterion regarding renal impairment.		
01	27 Mar 2020	Section 7.4
Brief description of change: Information about Figure 1 added.		
01	27 Mar 2020	Section 9.4.5
Brief description of change: Detailed information for the chosen dose and dose regimen was added.		
01	27 Mar 2020	Study schedule
Brief description of change: “Other exploratory indicators: specific exploratory indicators will be determined as needed” in the footnote deleted.		
01	27 Mar 2020	Section 13
Brief description of change: References were updated		
Summary of changes since last version of the protocol (protocol version 2.0 to version 3.0)		
02	05 APR 2020	Title page, Signature Page & Study structure
Brief description of change: Sponsor name changed		
02	05 APR 2020	Synopsis
Brief description of change: Study purpose: Administrative correction “respiratory tract specimen” deleted as only blood samples re drawn and sign > corrected to ≥		
02	05 APR 2020	Study schedule
Brief description of change: Detection of viral nucleic acid or viral gene sequencing corrected and deleted on Day 2,4,6 and 10 (same timepoints as biomarkers)		
02	05 APR 2020	Synopsis & Section 9.1, & 9.4.2.1. & 9.4.2.2
Brief description of change:		

Time for dose application corrected from 30 minutes to “3 to 30 minutes”		
02	05 APR 2020	9.4.3
Brief description of change: For clarification sentence added that randomization is via the eCRF.		
02	05 APR 2020	9.5.2.2.6
Brief description of change: “serum” deleted		
02	05 APR 2020	9.4.2.4&5
Brief description of change: “unblinded member of study team” added		
02	05 APR 2020	9.5.2.2.13.2.1
Brief description of change: “fax” deleted		
02	05 APR 2020	Study schedule, 8.2.1 & 9.5.2.2.6
Brief description of change: Parameters for Immune function and Biomarker adapted		
02	05 APR 2020	Synopsis, 9.1, 9.4.1.1 & 9.4.1.4
Brief description of change: Time window for dose application added.		
02	05 APR 2020	9.5.2.2.9
Brief description of change: Reference to Investigator Manual added		
02	05 APR 2020	Study schedule & 9.5.2.2.6
Brief description of change: eGFR added		
Summary of changes since last version of the protocol (protocol version 3.0 to version 4.0)		
03	22 APR 2020	Study synopsis & 8.3.1
Brief description of change: Inclusion criterion 4 was deleted		
03	22 APR 2020	Study schedule & 8.5.2.1
Brief description of change: Clarification regarding time period between screening and randomization added.		
03	22 APR 2020	8.5.2.2.7
Brief description of change: Collection tube for individual Biomarkers changed and harmonized with the Lab Manual.		
Summary of changes since last version of the protocol (protocol version 4.0 to version 5.0)		
04	04 MAY 2020	Synopsis
Brief description of change: Number of planned study sites increased to 16, US added as possible country		
04	04 MAY 2020	Synopsis & 8.3.1
Brief description of change: Inclusion criterion body weight increased		
04	04 MAY 2020	Synopsis & 8.3.2
Brief description of change: Exclusion criterion 1 redefined and exclusion criteria 2 modified.		
04	04 MAY 2020	Study schedule
Brief description of change:		

Clarification regarding serology and vital signs		
04	04 MAY 2020	8.4.2.3, & 8.4.2.4
Brief description of change: Wording from reconstitution changed to preparation of study drug		
04	04 MAY 2020	8.4.6
Brief description of change: Unblinded team added for clarification and harmonization.		
04	04 MAY 2020	Study schedule & 8.5.2.2.4
Brief description of change: Clarification regarding physical examination		
04	04 MAY 2020	8.1
Brief description of change: Clarification regarding randomization and standard of care treatment		
04	04 MAY 2020	6.1
Brief description of change: Rational updated		
04	04 MAY 2020	Study schedule & 8.4.1.1
Brief description of change: Clarification regarding 1st dose administration		
04	04 MAY 2020	8.5.2.2.11
Brief description of change: SOFA score changed to mSOFA score		
Summary of changes since last version of the protocol (protocol version 5.0 to version 6.0)		
05	08 JUN 2020	Synopsis & 8.3.1 & 8.3.2
Brief description of change: Inclusion criterion 1 modified, Inclusion criterion 5 deleted, Inclusion criterion 7 deleted for US, Exclusion criterion 10 deleted, Exclusion criterion 18: clarified that it refers only to clinical trials		
05	08 JUN 2020	Study schedule & 8.5.2.1
Brief description of change: Detection of viral nucleic acid or viral gene sequencing (PCR) modified (quantitative and qualitative analyses allowed)		
05	08 JUN 2020	Study schedule & 8.5.2.9
Brief description of change: PCR test results up to 5 days before screening		
05	08 JUN 2020	Synopsis
Brief description of change: Timelines, number of sites and countries updated		
05	08 JUN 2020	Study schedule & 8.5.2.2.9
Brief description of change: Assessment of respiratory condition can also be performed by pulse oximetry		
05	08 JUN 2020	Study schedule & 8.5.2.2
Brief description of change: Follow-up Visits may be performed as phone visit or in-home visit (in Russia).		
05	08 JUN 2020	8.5.2.2.13
Brief description of change: Clarification regarding pre-treatment adverse events		
05	08 JUN 2020	8.5.2.2.13.1.4
Brief description of change: Clarification regarding clinically significant laboratory changes to be reported as an adverse event		

05	08 JUN 2020	Synopsis & 8.1
Brief description of change: Factor “presence of one co-morbid condition” is now excluded as stratification factor from randomization		
05	08 JUN 2020	Annex 2
Brief description of change: Remote/Video Monitoring strategy during COVID-19 pandemic added		
Summary of changes since last version of the protocol (protocol version 6.0 to version 7.0)		
06	10 AUG 2020	Synopsis & 8.3.1
Brief description of change: Inclusion criterion 6 deleted		
06	10 AUG 2020	Synopsis & 7.2.1 & 8.7.1.2.5
Brief description of change: Additional Endpoint (change of viral RNA) added		
06	10 AUG 2020	Synopsis & 8.1 & 8.3.3.2 & 8.4.1.1 & 8.4.1.4
Brief description of change: If a patient will be discharged before day 7 IMP treatment can be stopped earlier.		
06	10 AUG 2020	6.7 & 8.2
Brief description of change: “no available cure/treatment of COVID-19” deleted		
06	10 AUG 2020	8.1
Brief description of change: Remdesivir as potential standard of care treatment added		
06	10 AUG 2020	8.5.2.2.6
Brief description of change: Clarification of number of samples		
06	10 AUG 2020	8.2.1.1 & 8.5.2.1.2
Brief description of change: Clarification of wording regarding screening failures		
06	10 AUG 2020	Study schedule
Brief description of change: Correction of biomarkers regarding tubes		
06	10 AUG 2020	Synopsis & 8.7.1.2.5
Brief description of change: Adaption of secondary endpoint 28-day mortality		
06	10 AUG 2020	Study schedule & 8.4.1.3
Brief description of change: Follow-up visits may be performed as outpatients/phone visits		
06	10 AUG 2020	8.4.2.2
Brief description of change: 10 ml as strength for placebo added		
06	10 AUG 2020	8.4.6
Brief description of change: Wording adapted		
06	10 AUG 2020	4.1
Brief description of change: EMA & FDA COVID-19 Guidelines added		
06	10 AUG 2020	10
Brief description of change: DSMB review adapted for overall options for COVID-19 patients and consequential adaption of study design if necessary.		

SYNOPSIS

Title	Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treatment for patients with COVID-19
Short Title	APN01-COVID-19
Protocol Identifier	APN01-01-COVID19, EudraCT Number: 2020-001172-15, IND: 151312
Drug development phase	Phase II
Planned Study Period	FPI: Anticipated Q2 2020 LPO: Anticipated Q4 2020
Study Duration	Up to 29 days per patient. Total study duration (FPI until LPO) up to 5 months, with 2-4 months recruitment period per country
Targeted Accrual	200 patients, patient accrual planned as follows: Approximately 40 sites planned in Europe, Russia and US, hence for a 1:1 (APN01: Placebo) randomization scheme.
Study Rationale	• SARS-CoV-2 spike uses the ACE2 receptor for entry into various cells including alveolar epithelial cells and other cells in multiple organs • SARS-CoV-2 has been found in a number of ACE2 expressing tissues • Competitive binding by exogenous ACE2 may block viral entry and decrease viral replication in ACE2 expressing organs and protect the lung and distal organ from injury induced by SARS-CoV-2 • Preliminary studies in cell culture and multiple organoids have shown that ACE2 can decrease viral replication
Study Purpose	• To evaluate the clinical efficacy and safety of APN01 in patients with severe COVID-19, defined as those with hypoxemia and tachypnea • To monitor the biomarker changes (e.g. IL-6, Ang II) in respiratory tract specimen in patients with severe COVID-19 treated with APN01
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 efficacy of APN01using log transformed levels of Lactate dehydrogenase (LDH) as a surrogate marker for organ damage. • To evaluate the safety of APN01 in patients with severe COVID-19 • To monitor other biomarker changes (e.g. IL-6, Ang II) in patient with severe COVID-19 treated with APN01
Study design	Randomized, double blind, placebo-controlled trial The study is a parallel-group, randomized, double blind, placebo-controlled study on top of best standard of care. The study will comprise two treatment groups as follows:

	• Group A (active): APN01 (5 mg/ml, 4 ml/vial) • Group B (placebo control): sterile, 0.9% sodium chloride Eligible patients will be centrally allocated using a dynamic randomization (1:1) to Group A or B to receive the treatment or placebo. Dynamic randomization factors will be age in years (continuous) and center. Investigators and patients will be blinded to the treatment administered. After screening at day -1 and randomization at day -1 or 1, patients will be treated with APN01 or Placebo intravenously twice daily (BID) every 12 hours ±1 hour over 3 to 30 minutes (morning and the evening) for 14 doses (until day 7). If a patient will be discharged from hospital before day 7 treatment can be stopped at day of discharge. Follow up visits will be done at a daily basis for the first seven days and then on day 10, 14 and 28 to asses efficacy and safety. The study assessments will be performed according to the study schedule (Table 1).
Inclusion Criteria	A patient will be eligible for inclusion in this study only if all the following criteria apply: Inclusion: 1. Hospitalized male or female, ≥ 18 to ≤ 80 years of age 2. Diagnosed to be COVID-19 POSITIVE（SARS-CoV-2 nucleic acid – qPCR） 3. Oxygenation criterion: • Oxygen saturation ≤93% (either on Room Air or while the patient is on supplement oxygen) 4. ALT < 5xULN; bilirubin ≤ 1.5xULN 5. Signed Inform Consent Form
Exclusion Criteria	A patient will not be eligible for inclusion in this study if any of the following criteria apply: 1. Any patient for whom the investigator does not consider there is a reasonable expectation that they will be able to complete the study. 2. Known history of positive Hepatitis B surface antigen, Hepatitis C antibody or HIV antibody. 3. Current or chronic history of liver disease (Child Pugh score ≥ 10), or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 4. The patient has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). 5. Patients requiring high doses of loop diuretics (i.e. > 240 mg furosemide daily) with significant intravascular volume depletion, as assessed clinically. 6. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation. 7. Pregnant females as determined by positive serum or urine hCG test prior to dosing.

	8. Lactating females. 9. Unwillingness or inability to follow the procedures outlined in the protocol. 10. Unstable Hemoglobin (Hb < 7) at time of drug infusion (i.e. Hb must be > 7 mg/dL at the time of drug infusion. Transfusion is permitted to increase Hb levels to allow entry into the study. 11. Malignancy or other irreversible condition for which 6-month mortality is estimated to be >50%. 12. Arterial blood pH less than 7.2 or serum HCO3- <15 (if ABG not available) before infusion is started. 13. Known severe chronic pulmonary disease: • known FEV1/FVC less than 45% predicted, or • known chronic hypercapnia (PaCO2 > 45 mmHg) or chronic hypoxemia [(PaO2<55 mmHg) on FiO2 =0.21, or supplemental oxygen therapy prior to this admission], or • known FEV1 <15 ml/kg (e.g. 1L for 70 kg person), or • known radiographic evidence of chronic interstitial infiltration, or • known hospitalization within the past six months for respiratory failure (PaCO2 > 50 mmHg or PaO2 < 55 mmHg, or oxygen saturation <88% on FiO2 = 0.21), • known chronic restrictive, obstructive, neuromuscular, chest wall, or pulmonary vascular disease resulting in severe exercise restriction (i.e. unable to climb stairs or perform household duties), known secondary polycythemia, severe pulmonary hypertension, or ventilator dependency 14. Known vasculitis with diffuse alveolar hemorrhage 15. Lung transplantation 16. Pre-existing renal failure, i.e. requiring renal replacement therapy with hemodialysis or peritoneal dialysis 17. There are other uncontrolled co-morbidities that increase the risks associated with the study drug administration, that are assessed by the medical expert team as unsuitable 18. Patient in clinical trials with an IMP for COVID-19 within 30 days before ICF 19. Unstable hemodynamics in the preceding 4 hours (MAP ≤ 65 mmHg, or SAP < 90 mmHg, DAP < 60 mmHg, and vasoactive agents required) 20. Immunocompromised patients (chemotherapy, HIV, organ transplants, stem cell transplants), 21. Receive any Angiotensin-Converting-Enzyme inhibitor (ACEi) or renin inhibitor treatment within 7 days before ICF
Primary endpoint	The primary endpoint is a composite endpoint of all cause-death or invasive mechanical ventilation up to 28 days or hospital discharge.
Secondary endpoints	1. Log transformed levels of Lactate dehydrogenase (LDH) at day 5 as a surrogate marker for organ damage (powered secondary endpoint) 2. 28-day mortality (all cause-death) 3. Ventilator-free days (VFD) up to 28 days or hospital discharge 4. Proportion of responders, defined as ≥2 improvement in WHO's 11-Point Score system at day 7, 10, 14 and 28 5. Time to death (all cause)

	6. Proportion of patients with any use of invasive mechanical ventilation up to 28 days or hospital discharge 7. Time to first use of invasive mechanical ventilation up to 28 days or hospital discharge 8. Absolute values and absolute change in P/F ratio over time 9. Absolute values and absolute change in the modified Sequential Organ Failure Assessment score (mSOFA score) over time 10. Time to a 2-point decrease in WHO scoring scheme 11. Absolute values and absolute change in lymphocyte counts over time 12. Absolute values and absolute change in C-reactive protein levels over time 13. Absolute values and absolute change in D-dimer over time 14. Absolute values and absolute change in log transformed levels of LDH over time 15. Time to hospital discharge 16. Change in viral RNA over time **Biomarker endpoints:** Absolute values and absolute changes in relevant biomarkers over time: 1. Angiotensin II (Ang II), Angiotensin 1-7 (Ang 1-7), Angiotensin 1-5 (Ang 1-5), renin and aldosterone, Angiotensin-converting enzyme (ACE), Angiotensin-converting enzyme 2 (ACE2), Angiotensin I (Ang I), Angiotensin 1-9 (Ang 1-9) 2. Cytokines: Interleukin 6 (IL-6), Interleukin 8 (IL-8), soluble Tumor Necrosis Factor receptor type II (sTNFrII), Plasminogen Activator Inhibitor type-1 (PAI-1), von Willebrand Factor (vWF), Tumor necrosis factor-α (TNF-α) 3. Alveolar epithelial markers: soluble Receptor for Advanced Glycation End products (sRAGE), Surfactant protein-D(SP-D) 4. Endothelial markers: Angiopoietin-2 5. Change in clinical laboratory markers associated with poor outcome over time (e.g., lymphocyte counts, hsTnI (high sensitivity troponin)) 6. NT-proBNP, Ferritin **Safety endpoints:** Frequency of adverse events (AEs) and serious adverse events (SAEs) in vital signs, clinical laboratory assessments and in ECG parameters
Study drug	• Recombinant human angiotensin-converting enzyme 2 (rhACE2) – APN01* • Control Group: Placebo (physiological saline solution) *In other study documents (e.g. IB) APN01 is also referred to as GSK2586881
Study drug dosage	• 0.4 mg/kg IV BID (for seven days) Intravenous administration of undiluted IMP using a polypropylene syringe with a 0.22 micron filter
Statistical analysis plan	Continuous variables will be summarized with means, standard deviations, medians, lower and upper quartiles, minimums and maximums. Frequencies and percentages will be used to summarize categorical

variables.

For time-to-event analyses censoring information will be used.

It is assumed that no patients will discontinue the study early prior to day 28 or hospital discharge in this Covid-19 setting. It is also assumed, that only very few missing values will arise due to not done evaluations. No imputation of missing values (e.g., no last observation carried forward (LOCF)) is planned, unless stated otherwise.

Analysis sets:

Safety Analysis Set (SAF):

All randomized patients who received study medication (independent of whether it is APN01 or placebo) will be valid for the SAF. The SAF will be used for the evaluation of the safety assessments (as treated).

Full Analysis Set (FAS):

The FAS includes all randomized subjects. The FAS serves as the primary efficacy analysis set (as randomized).

Per-protocol Analysis Set (PP):

The PP includes all subjects included in the SAF who had no significant protocol deviations and completed through Day 28 or until discharge from the hospital (end of study follow-up). The PP will only be analyzed for main efficacy outcome measures (as treated).

Analysis of primary efficacy endpoint

The primary endpoint of this trial is a composite of all cause-death or any use of invasive mechanical ventilation up to 28 days or hospital discharge. Invasive mechanical ventilation is defined as patients who are intubated or have a tracheostomy tube and are receiving positive pressure ventilation. Patients discharged from hospital before day 28 will be considered as non-event after confirmation by telephone interview that they are alive at day 28. Patients who will be discharged from hospital or early terminated before Day 28 will be considered having an event on the day of discharge or early termination, if a telephone interview was not possible and/or no information about alive/death status is known.

Hypothesis to be tested:

H0: pAPN01 = pPlacebo

H1: pAPN01 ≠ pPlacebo

H0 will be tested using a Chi-squared test. The level of significance is 5% (two-sided). In addition, logistic regression analyses will be conducted considering additional co-factors (will be detailed in the statistical analysis plan).

Analysis of secondary efficacy endpoints

Secondary efficacy variables will be tested descriptively and in an exploratory manner.

1. Log transformed levels of Lactate dehydrogenase (LDH) at day 5 as a surrogate marker for organ damage.

   Log transformed levels of LDH will be analyzed using linear regression adjusted for baseline log levels of LDH, centre and minimization factors.

95% confidence intervals will be calculated.
Statistical procedures to check on a normal distribution of data, to be applied in case of non-normally distributed data, and to verify and handle minimization factors will be described in the statistical analysis plan, which will be finalized prior to unblinding.

2. 28-day mortality (all cause death)
The percentage of patients who have died at day 28 will be presented by treatment group. Patients who will be discharged from hospital or early terminated before Day 28 will be considered having an event on the day of discharge or early termination, if a telephone interview was not possible and/or no information about alive/death status is known. The Chi-squared or Fisher's exact test will be used to compare proportions. 95% CIs will be additionally calculated. Logistic regression analyses will be conducted considering additional co-factors (will be detailed in the statistical analysis plan).

3. Ventilator-free days (VFD) up to 28 days or hospital discharge
VFD will be analyzed for both all patients as well as for the subgroup of patients who were alive at day 28 or hospital discharge. For the analysis of all patients separate analyses will be conducted for patients who died: a) VFD will be set to 0, b) the observed VFD until death will be considered. Summary tables will be generated the VFD will be compared using Wilcoxon rank sum test. In addition, bootstrap methods will be applied to calculate 95% confidence intervals and two-sided p-values for the difference in means.

4. Proportion of responders, defined as ≥2 improvement in WHO's 11-Point Score system at day 7, 10, 14 and 28
Similar analyses as for 28-day mortality will be conducted.

5. Time to death (all cause) will be analyzed using Kaplan-Meier estimates and plots, log-rank test, and Cox proportional hazards model (adjusted for minimization factors to derive hazard ratios and corresponding 95% confidence intervals). Patients who will be alive at day 28, or who will be discharged from hospital before day 28 will be censored at discharge if they cannot be reached at or after day 28 by means of a telephone interview. Further details will be described in the statistical analysis plan.

6. Proportion of patients with any use of invasive mechanical ventilation up to 28 days or hospital discharge.
Similar analyses as for 28-day mortality will be conducted.

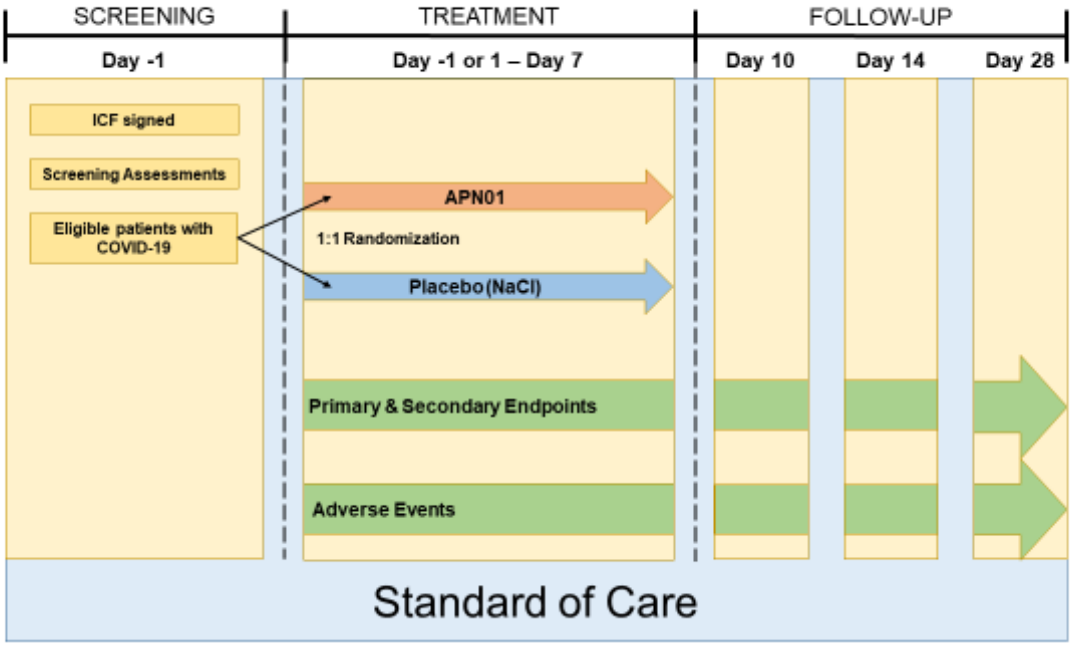
7. Time to first use of invasive mechanical ventilation up to 28 days or hospital discharge.
Similar analyses as for time to death will be conducted.

8. Absolute values and absolute change in P/F ratio over time
The PF ratio is defined as PaO2 [mmHg] divided by FiO2 in [%] and will be evaluated on each visit. Summary statistics for the PF ratio for both the absolute values and the absolute change from Baseline (day 1) will be tabulated.

9. Absolute values and absolute change in the modified Sequential organ failure assessment score (mSOFA score) over time
Similar analyses as for the PF ratio will be conducted.

	10. Time to a 2-point decrease in the WHO scale. Similar analyses as for time to death will be conducted. 11. Absolute values and absolute change in lymphocyte counts over time Summary statistics for both the absolute values and the absolute change from Baseline (day 1) will be tabulated. 12. Absolute values and absolute change in C-reactive protein levels over time Summary statistics for both the absolute values and the absolute change from Baseline (day 1) will be tabulated. 13. Absolute values and absolute change in D-dimer over time Summary statistics for both the absolute values and the absolute change from Baseline (day 1) will be tabulated (prognostic information: Zhou et al. Lancet 2020). 14. Absolute values and absolute change in log transformed levels of LDH over time Summary statistics for both the absolute values and the absolute change from Baseline (day 1) will be tabulated. 15. Time to hospital discharge Similar analyses as for time to death will be conducted. 16. Change in viral RNA over time Summary statistics for both the absolute values and the absolute change from Base-line (day 1) will be tabulated. <u>Other biomarker endpoints</u> Other biomarker endpoints will be analyzed using descriptive statistics.
Sample size	186 patients (93 per group) will yield 80% power to detect a 20% absolute risk reduction in the primary composite endpoint, from 50% in the placebo group to 30% in the APN01 group at a two-sided alpha of 0.05. To consider patients who will be randomized but not treated a total of 200 patients (100 per group) will be enrolled.
Data Safety Monitoring Board (DSMB)	The study will be monitored by a DSMB.

1 STUDY SCHEME



2 STUDY SCHEDULES

Table 1:

	Screening period	Treatment period [20]							Follow up period		
Procedures and assessments	Day -1*	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 10 (±1 day)[16]	Day 14 (± 1 day)[16]	Day 28 End of Study Visit (or early termination visit) (± 1 day)[15]
Informed consent	X										
Inclusion and exclusion criteria	X	X ※**									
Demographics [1]	X										
Medical history [2]	X										
Randomization*		X ※*									
Treatment		X[14]	X	X	X	X	X	X			
Score Assessment of WHO`s 11-point scale	X	X ※**	X	X	X	X	X	X	X	X	X[19]
PCR (quantitative or qualitative) [3]	X	X ※**		X		X		X		X	X[17]
Vital signs [4]	X	X ※	X	X	X	X	X	X	X	X	X[17, 18, 19]
Physical examination[5]	X	X ※**	X	X	X	X	X	X	X	X	X[17, 19]
Serum or urine pregnancy test [6]	X										X[17, 19]
Clinical laboratory assessments [7]	X	X ※**	X	X		X		X	X	X	X[17, 19]

	Screening period	Treatment period [20]							Follow up period		
Procedures and assessments	Day -1*	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 10 (±1 day)[16]	Day 14 (± 1 day)[16]	Day 28 End of Study Visit (or early termination visit) (± 1 day)[15]
HIV/HBV/HCV Serology[8]	X										
ECG [9]	X	X ※**	X	X		X		X	X	X	X[17, 19]
Assessment of Respiratory condition [10]	X	X ※**	X	X	X	X	X	X	X	X	X[17]
mSOFA score	X	X ※**	X	X	X	X	X	X	X	X	X[17]
Assessment of Immune function [11]		X ※**	X	X		X		X	X	X	X[17, 19]
Biomarker [12]		X ※		X		X		X		X	X[17, 19]
Patient status assessment [13]			X	X	X	X	X	X	X	X	X[17]
Adverse Events		X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X	X	X	X	X

* In case the required screening procedures take less time, randomization and start of treatment could be performed also on the same day then screening. The time period between start of screening procedures and start of treatment must not exceed 24 hours.
** Events do not need to be done if randomization is on the same day as Screening
※: prior dosing
mSOFA score: modified Sequential Organ Failure Estimated Score

[1] Demographic data: gender, age, ethnicity, height, history of allergies, history of smoking and alcohol use, weight, body mass index.
[2] Medical history: Medical history for the least 4 weeks.

[3] If PCR was performed within 5 days before the screening visit, the test does not need to be repeated at screening and the available test results can be used.

[4] Vital signs include temperature, heart rate, respiration, blood pressure, and oxygen saturation. Vital signs need to be tested before and after each dose (within 30 min before/after IMP administration).
[5] physical examination could also be documented in the context of the general visit/health status assessment e.g. during a general clinical review
[6] Pregnancy Test: for FOCP only
[7] Laboratory tests include the following: in case a local lab cannot perform any of these parameters it should be reported as missing value

- Inflammatory indicators: C- reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin.
- Blood routines include: red blood cell (RBC) count, hematocrit (HCT) or hematocrit total, and classification of white blood cells (WBC), hemoglobin (Hb), platelet (PLT) count.
- Urine routine includes: glucose (GLU), pH (PH), urinary protein (PRO), red blood cells (BLD), and white blood cells (LEU).
- Stool routine + occult blood: red blood cells (BLD), white blood cells (LEU), occult blood.
- Blood biochemistry includes: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AKP), total bilirubin (TBI), total protein (ALB), albumin (ALB), urea nitrogen (BUN), Creatinine (Cr), uric acid (UA), potassium (K), sodium (Na), eGFR (assessment is calculated according to the formula used in local laboratory).
- Myocardial enzymes: creatine kinase (CK) and isoenzyme (CKMB), lactate dehydrogenase (of LDH), [alpha] - hydroxybutyrate dehydrogenase ([alpha] - HBD), troponin (of cTnI).
- Coagulation functions include: prothrombin time (PT), activated partial thromboplastin time (APTT), D- dimer, FIB

[8] results do not need to be available before randomization, results up to 4 weeks old are acceptable
[9] 12- lead ECG: within 30 min after IMP administration
[10] Respiration: blood gas analysis (oxygenation index, blood lactic acid) or pulse oximetry.
[11] Immune function: immunoglobulin (Ig A, Ig M, Ig G)
[12] Biomarkers comprising (per collection of whole blood 10-12 ml)

1 Li-Heparin blood collection tube (5-6 ml):

1. Plasma equilibrium angiotensin levels: Angiotensin II (Ang II), Angiotensin 1-7 (Ang. 1 -7), Angiotensin 1-5 (Ang 1-5), Angiotensin I (Ang I), Angiotensin 1-9 (Ang 1-9)
2. Aldosterone
3. ACE2 Activity and ACE2 concentration
4. Other exploratory RAAS Biomarkers indicators: specific exploratory indicators will be determined as needed

1 EDTA blood collection tube (5-6 ml):

1. Plasma-Renin-Concentration (PRC)
2. Cytokines: interleukin- 6 (IL-6), interleukin- 8 (IL-8), soluble tumor necrosis factor receptor II (sTNFrII), PAI-1, vWF, tumor necrosis factor - α
3. Alveolar epithelial markers: soluble advanced glycation product receptor (sRAGE), surface-active protein- D (SP-D)
4. endothelial markers: angiopoietin -2 (Angiopoietin-2)
5.
6. COVID-19 antibodies, viral load

[13] Patient status assessments includes: no change, discharge from hospital, transition to critical illness, and death.
[14] 1st dosing could also be on the evening of Day -1 in case randomization is on the same day as screening.
[15] Follow-up Visits (Day 28) may be performed as phone visit or in-home visit where applicable. .

[16] If a patient is already discharged from the hospital, the follow-up visits could be performed on an out-patient basis or at patient's home provided the patient agrees to that.

[17] Assessments do not have to be performed in case of a phone visit
[18] Targeted Physical examination by phone interview
[19] The following assessments will be performed during in home-visits (Clinical Laboratory assessment, ECG, Assessment of immune function and Biomarker, if possible)
[20] If a patient will be discharged from hospital before day 7 treatment can be stopped at day of discharge.

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3 LIST OF ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
ABG	Arterial blood gas
ACE	Angiotensin-converting enzyme
ACEi	Angiotensin-Converting-Enzyme inhibitor
AE	Adverse event
AKP	Alkaline phosphatase
ALB	Albumin
ALT	Alanine aminotransferase
Ang	Angiotensin
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	taken two times a day
BLD	Red blood cells
BMI	Body mass index
BUN	Urea nitrogen
CA	Competent authority
CI	Confidence interval
CoV	Coronavirus
COVID-19	Corona-virus-disease 2019
Cr	Creatinine
CRO	Contract research organization
CRP	C-reactive protein
CS	Clinically significant
CSR	Clinical study report
cTnI	Troponin
DAP	Diastolic arterial pressure
DMP	Data Management Plan
DRM	Data review meeting
DSMB	Data Safety Monitoring Board
DVP	Data Validation Plan
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	Ethylene Diamine Tetra-acetic Acid
ELISA	Enzyme-linked immunosorbent assay
eGFR	Estimated Glomerular filtration rate
ESR	Erythrocyte Sedimentation Rate
EU	European Union
FAS	Full Analysis Set
FEV1	Forced Expiratory Pressure in 1 Second
FIH	First in Human
FOCP	Female of Child-bearing Potential
FU	Follow-up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice

GCS	Glasgow coma score
GEO	Geometric
GLU	Glucose
HCT	Hematocrit
HLA-DR	Human Leukocyte Antigen- DR isotype
hsTnI	high sensitivity troponin
i.v.	intravenous
IB	Investigators brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL	Interleukin
IMP	Investigational Medicinal Product
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
K	Potassium
LDH	Lactate Dehydrogenase
LEU	White blood cells
LOCF	last observation carried forward
LPLV	Last patient last visit
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minute
mSOFA	Modified Sequential Organ Failure Assessment
N	Number
Na	Sodium
NCS	Not clinically significant
NOAEL	No Observed Adverse Effect Level
NSVT	Non-sustained ventricular tachycardia
PAH	Pulmonary Arterial Hypertension
PAI-1	Plasminogen activator inhibitor type-1
PI	Principal Investigator
PK	Pharmacokinetic
PLT	Platelet
PP	Per-protocol Analysis Set
PRO	Urinary protein
PT	Prothrombin time
QAU	Quality Assurance Unit
QC	Quality Control
QP	Qualified Person
qPCR	quantitative polymerase chain reaction
RBC	Red blood cell count
rhACE2	Recombinant human angiotensin-converting enzyme 2
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Systolic arterial pressure
SAR	Severe adverse reaction

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDV	Source Data Verification
SHR	Spontaneously hypertensive rats
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SOP	Standard Operating Procedure
SP-D	Surfactant protein-D
sRAGE	soluble Receptor for Advanced Glycation End products
sTNFrII	Soluble tumor necrosis factor receptor type II
SUSAR	Suspected unexpected Serious Adverse Reaction
TBI	Total bilirubin
TMF	Trial Master File
TP	Total protein
UA	Uric acid
ULN	Upper limits of normal
VFD	Ventilator-free days
VPC	Ventricular Premature Complexes
vWF	von Willebrand Factor
WBC	White blood cell
WHO	World Health Organization
WHO-CPS	WHO Clinical Progression Scale

4 ETHICS AND LEGAL ASPECTS

4.1 Independent Ethics Committee (IEC) or Institutional Review Board

This clinical trial will be planned and performed in accordance with

- The Declaration of Helsinki in its version of Fortaleza, 2013;
- The EU Clinical Trial Directive 2001/20/EC;
- The EU Clinical Trial Directive 2001/83/EC;
- ICH Guideline for Good Clinical Practice E6(R2), of 9 November 2016;
- Code of Federal Regulations Title 21 – Part 312 EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic in its most current version
- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency in its most current versionApplicable national laws

4.2 Ethical Conduct of the Clinical Trial

The sponsor or a designee will submit, among other documents, the study protocol, the patient information and the informed consent form to all involved ethics committees (EC) and request approval (favorable opinion). The sponsor or a designee will provide the clinical trial application to all involved national competent authorities (CA). The approval of both, the Ethics Committee and the Competent Authority must be obtained prior to the start of any study related intervention in a country.

4.3 Patient Information and Consent

Before any study specific procedures can take place, an investigator will explain to the patients the nature, significance and implications of the clinical trial. He/she will explain all methods, rules of conduct, and any restrictions which may apply. Possible effects and side effects will be discussed. Patients will be informed that they are free to withdraw from the clinical trial at any time, without giving any reason for doing so. They must be able to understand the full implications of their decision.

All participants will date and sign an informed consent form as evidence of consent. The investigator will also date and sign the informed consent form. The patient information sheet and the informed consent form of each participant will be filed in the investigator site file (ISF). A copy of the dated and signed consent form and the information sheet will be handed to patients after signature and before enrollment.

4.4 Confidentiality

The Principal Investigator (PI) at each study site must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code (i.e., consisting of an identification number, sex and year of birth) should be recorded on any form or biological sample submitted to the laboratory, Sponsor or EC. The PI must keep a patient identification log showing codes and names for all patients screened and for all patients enrolled in the trial.

4.5 Insurance

The Sponsor is responsible for the appropriate insurance coverage for the patients in accordance with all applicable national laws and provisions.

4.6 Publication Policy

The Sponsor has to publish the results of this study considering applicable legal requirements. Besides, it is in the sole discretion of the Sponsor whether to publish the results of this clinical trial.

4.7 Qualification of the Investigator

The PI and the deputy (only for Germany) fulfill the requirements of applicable national law. Curriculum vitae of both will be filed in the trial maser file (TMF).

For conducting the clinical trial, the PI may delegate tasks to investigators (or other qualified staff). This is to be documented properly. The PI is responsible for the adequate training and supervision of all delegates. No clinical trial related procedure must be performed by personnel which is not properly trained and delegated.

In the present document the mere term “Investigator” refers to the PI or the deputy (only for Germany).

5 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor:
APEIRON Biologics AG
Campus-Vienna-Biocenter 5
1030 Vienna, Austria

Coordinating Investigator:
Prof. Henning Bundgaard, MD
Faculty of Health and Medical Sciences
University of Copenhagen
Rigshospitalet, University of Copenhagen
Department of Cardiology, B 2141
The Heart Centre, Blegdamsvej 9
2100 Copenhagen Ø, Denmark
Phone: +45 3545 0512
Email: Henning.Bundgaard@Regionh.DK

National Coordinating Investigator:
For each country a national Coordinating Investigator is appointed. Names and contact details are filed in the TMF.

Medical Monitor:
Dr. Edgar Fenzl, MD
FGK Clinical Research GmbH
Heimeranstrasse 35, 80339 Munich, Germany
Phone: +49 89 893 119 22
Email: edgar.fenzl@fgk-cro.com

Lead Clinical CRO:
CTC North GmbH & Co. KG
at the University Medical Center Hamburg-Eppendorf
Martinistr. 64, 20251 Hamburg, Germany

Responsibilities:
Overall Project Management, Regulatory (Denmark, Austria, Germany, UK), Safety Management,
Overall Monitoring, Data Management, Medical Writing

Overall Project Lead
CTC North GmbH & Co. KG
Dr. Saskia Borregaard
Phone: +49 40 524719 200
Email: s.borregaard@ctc-north.com

Dr. Katharina Bartsch
Phone: +49 40 524719 218
Email: k.bartsch@ctc-north.com

Clinical CRO Russia
IPHARMA LLC (ChemRar group)
7, Nobel street
Skolkovo Innovative Centre
Moscow, 143026, Russia

Clinical CRO US	PRC Clinical 1350 Old Bayshore Highway, Ste. 125 Burlingame, CA 94010, US
Statistics:	FGK Clinical Research GmbH Heimeranstrasse 35, 80339 Munich, Germany Olaf Böhm Phone: +49 89 893 119 29 Email: olaf.boehm@fgk-cro.com

6 INTRODUCTION

6.1 Rationale

The contagious coronavirus, named SARS-CoV-2 (formerly 2019-nCoV), which broke out at the end of 2019, has led to a medical emergency across the world, with the World Health Organization (WHO) officially declaring the novel coronavirus a pandemic on 11 March 2020 [1].

Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as MERS-CoV and SARS-CoV.

To determine the urgent need for new drugs and vaccines data obtained for Italy as a seriously and in comparison to other European country's precocious effected country can be used.

The percentage of patients in intensive care reported daily in Italy between March 1 and March 11, 2020, was consistently between 9% and 11% of patients who are actively infected. The number of patients infected since February 21, 2020 in Italy closely follows an exponential trend. Italy has had 12.462 confirmed cases according to the Istituto Superiore di Sanità as of March 11, and 827 deaths [2].

Assuming the exponential progression of infected patients along with 9 % and 11 % of patients with the need of admission to intensive care units developing acute respiratory distress syndrome (ARDS) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia, the number of people infected in Italy will probably impose a major strain on critical care facilities [3].

A prospective observational cohort study with rapid data gathering and near real-time analysis, using a pre-approved questionnaire adopted by the WHO, performed in 166 UK hospitals between 6th February and 18th April 2020 included 16,749 people with COVID-19. The median age was 72 years [IQR 57, 82; range 0, 104], the commonest comorbidities were chronic cardiac disease (29%), uncomplicated diabetes (19%), non-asthmatic chronic pulmonary disease (19%) and asthma (14%); 47% had no documented reported comorbidity. Increased age and comorbidities including obesity were associated with a higher probability of mortality. Distinct clusters of symptoms were found: 1. respiratory (cough, sputum, sore throat, runny nose, ear pain, wheeze, and chest pain); 2. systemic (myalgia, joint pain and fatigue); 3. enteric (abdominal pain, vomiting and diarrhoea). Overall, 49% of patients were discharged alive, 33% have died and 17% continued to receive care at date of reporting. 17% required admission to High Dependency or Intensive Care Units; of these, 31% were discharged alive, 45% died and 24% continued to receive care at the reporting date. Of those receiving mechanical ventilation, 20% were discharged alive, 53% died and 27% remained in hospital.

This description of COVID-19 demonstrates the importance of pandemic preparedness and the need to maintain readiness to launch research studies in response to outbreaks [4]

Current data for the participating countries regarding the coronavirus according to the John Hopkins University are for Great Britain 187.842 confirmed with SARS-CoV-2 infected inhabitants (cumulated inclusive decedents and convalescents) and an average daily increase of 4800 new daily infected over the last 7 days. 28.520 inhabitants died thereof with an average daily increase of 630 over the last 7 days.

The situation in Germany are: 165.664 confirmed with SARS-CoV-2 infected inhabitants (cumulated inclusive decedents and convalescents) and an average daily increase of 1100 new daily infected over the last 7 days. 6866 inhabitants died thereof with an average daily increase of 130 over the last 7 days.

In Denmark there are 9868 confirmed with SARS-CoV-2 infected inhabitants (cumulated inclusive decedents and convalescents) and an average daily increase of 140 new daily infected over the last 7 days. 484 inhabitants died thereof with an average daily increase of 9 over the last 7 days.

In Austria there are 15.597 confirmed with SARS-CoV-2 infected inhabitants (cumulated inclusive decedents and convalescents) and an average daily increase of 53 new daily infected over the last 7 days. 598 inhabitants died thereof with an average daily increase of 8 over the last 7 days.

Although the progression of SARS-CoV-2 within the mentioned countries seems to have a different dynamic nevertheless the situation described may be volatile and proofs the need for a possible treatment option and therefore justifies this clinical study [5].

6.2 Pharmacological Classification

The investigational medicinal product (IMP) APN01 is a recombinant human (rh) soluble angiotensin converting enzyme 2 (ACE2).

Mode of action: APN01 is believed to be the cleavage of Angiotensin II of the renin angiotensin system to Angiotensin 1-7. Competitive binding by exogenous ACE2 may block viral entry and decrease viral replication in ACE2 expressing organs and protect the lung and distal organ from injury induced by SARS-CoV-2. Furthermore, preliminary studies in cell culture and multiple organoids have shown that ACE2 can decrease viral replication [6].

6.3 Clinical Use

The following clinical studies were performed with APN01: a placebo-controlled, Phase I, single dose escalating and repeat-dose study in healthy volunteers; a Phase IIa study in patients with acute respiratory distress syndrome (ARDS); a Phase IIb single dose escalation investigator sponsored study in patients with pulmonary arterial hypertension; a Phase I study examining the effects of APN01 on responses to acute hypoxia and exercise in healthy subjects; an ongoing Phase IIa, open-label, dose escalation study in patients with pulmonary arterial hypertension. APN01 is also referred in other study documents as GSK2586881.

In this study APN01 will be used for treatment of COVID 19 infected and hospitalized patients.

6.4 Human Pharmacokinetics

Following pharmacokinetic (PK) data were obtained from a placebo-controlled, Phase I, single dose escalating and repeat-dose study in healthy volunteers and a Phase IIa study in patients with acute respiratory distress syndrome (ARDS). For further information please see Investigators brochure chapter 5 [6].

Placebo-controlled, Phase I, single dose escalating and repeat-dose study in healthy volunteers:

Systemic ACE2 enzymatic activity was measured in plasma, and this measure was used to describe the exposure of GSK2586881 (APN01). Determination of rhACE2 content in plasma samples using a “sandwich” enzyme-linked immunosorbent assay (ELISA) was also conducted and the results showed good correlation, and yield similar results up to about 10 µg/ml. There was however a slight difference at higher values, where the ELISA figures become smaller than ACE2 enzymatic activity, but the difference was relatively small with approximately 20 % lower at around 20 µg/ml range. The summary of systemic exposure of APN01 as measured by ACE2 enzymatic activity assay following single dose of APN01 from 0.1 mg/kg to 1.2 mg/kg, is shown in Table 2.

Table 2: Summary of systemic PK in healthy volunteers following single dose of GSK2586881 (APN01-1-01)

Cohort	**1**	**2**	**3**	**4**	**7**
Dose	0.1mg/k	0.2mg/	0.4mg/k	0.8mg/k	1.2mg/k
N	3	3	3	3	3
	AUC[1]				
Geometric (GEO) Mean	17.27	26.60	67.84	81.80	141.70
CI 95% Lower GEO Mean	7.84	17.41	53.81	57.45	75.55
CI 95% Upper GEO Mean	38.04	40.65	85.52	116.48	265.78
	Cmax [2]				
Geometric Mean	2.01	2.85	6.30	12.72	21.03
CI 95% Lower GEO Mean	1.42	1.85	5.58	7.00	16.76
CI 95% Upper GEO Mean	2.86	4.39	7.12	23.13	26.40

1. Area under the curve (AUC) for each subject was taken from Apeiron APN01CSR (Apeiron Biologics AG) and summarized in house
2. Cmax was calculated and summarized in house from raw data; Note: Cmax was not reported in Apeiron APN01 CSR

Systemic exposure of GSK2586881 appeared to increase with increasing dose, and the increase was approximately dose proportional. GSK2586881 cleared quickly from systemic, with median clearance of 589 mL/h and median half-life of 9.8 hours.

Exploration of PK profiles indicated that GSK2586881 showed a bi-exponential decline, with an initial quick distribution phase followed by a relatively slower elimination phase.

Six healthy volunteers received multiple dosage of GSK2586881 at 0.4 mg/kg once daily for three (3 subjects in cohort 5) and six (3 subjects in cohort 6) consecutive days [6].

Figure 1 shows the systemic ACE2 enzymatic activity of the healthy volunteers following repeated dosing of 0.4 mg/kg GSK2586881 (green and blue curves) in comparison to the respective values found in cohort 3, in which volunteers were treated only once at the same dosage (red curve):

1. Single dose cohort (0.4 mg / kg) (red curve)

2. Multiple dose cohort over 3 days (0.4 mg / kg) (green curve)

3. Multiple dose cohort over 6 days (0.4 mg / kg) (blue curve)

Different infusion time points applied between the two multiple dose cohorts resulting in different curves during the first three days:

Multiple dose- cohort 5 (3d) green curve:

D1-3: 6 time points: prior + end of infusion, 1, 2, 4 and 8h after, D4: 24h after, D5: 48h after, D6: 72h after

Multiple dose- cohort 6 (6d) blue:

D1: 6 time points: prior + end of infusion, 1, 2, 4 and 8h after, D2 to D5: 1 time point prior

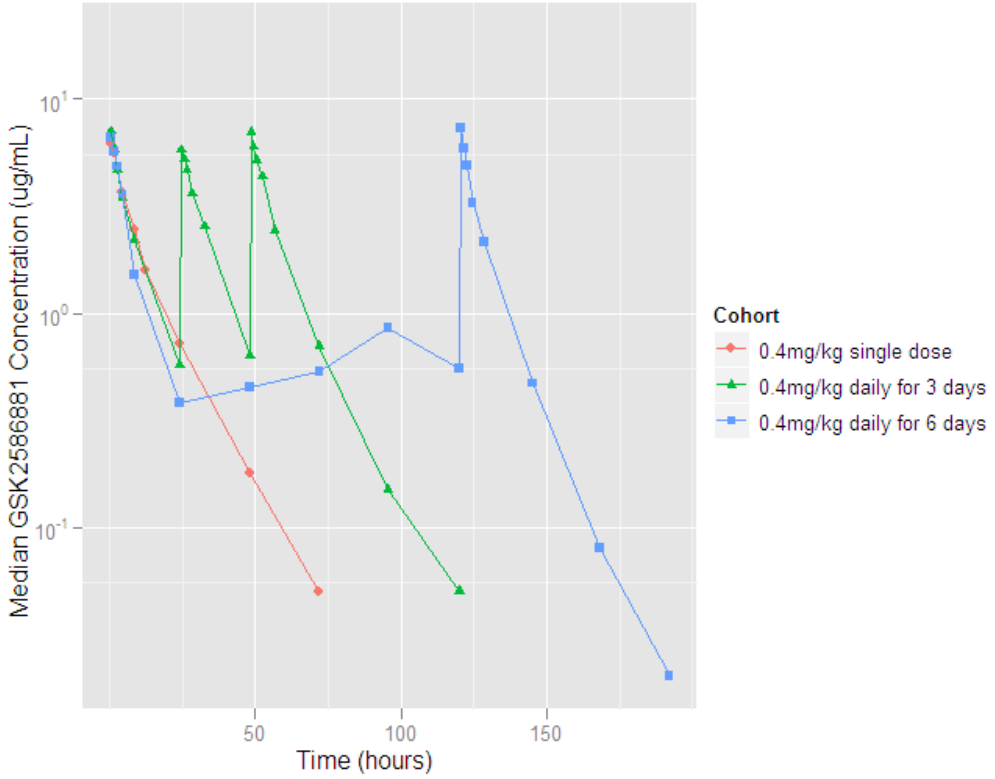
D6: 6 time points: prior + end of infusion, 1, 2, 4 and 8h after, D7: 24h after, D8: 48h after,

D9: 72h after

Sampling at different times (before and after infusion) explains the difference between the two curves of the multiple dose cohorts on day 2 and day 3. Sampling on day 6 of the blue curve was performed again after infusion and showed once again the increase in the GSK2586881 (APN01) concentration (comparable to the measured concentration of the green curve at the same time of taking the samples on days 2 and 3).

The shapes including the peaks and slopes of the curves were very similar indicating no changes in systemic PK following repeated dosing, and there was no marked accumulation of rhACE2 by repeated dosing for three and six consecutive days.

Figure 1 **Systemic ACE2 activity measured in plasma samples of healthy subjects with daily administrations of 0.4mg/kg GSK2586881 on three (green triangles) and six (blue squares) consecutive days, comparison to healthy subjects treated once with the same dosage (APN01-1-01)**



Phase IIa study in patients with acute respiratory distress syndrome (ARDS):

GSK2586881 concentrations were determined in plasma using a qualified analytical method based on sample dilution, followed by immunoassay analysis, and analyzed using population non-linear mixed effects modelling methods. Based on the population PK analysis the plasma GSK2586881 concentration time profile from n=24 ARDS patients (Parts A and B combined) was best described by a 1-compartment model with 1st order elimination. The only covariate found to be significant was study PART (Part A or B) on clearance. Population PK model parameters are described in Table 3.

Table 3: Final Population PK Model (ACE114622)

Parameter	Esti-	SE	Relative SE
CL(L/h) – Part A	0.384	0.088	23.1
CL (L/h) – Part B	0.698	0.060	8.7
V (L)	5.79	0.521	9.0
IIV CL	0.094	0.030	32.7
IIV V	0 Fix	-	-
Residual Error	0.0596	0.013	22.8
IIV: Inter-occasion variability			

Based on the optimal model, the population mean estimate in Part A was lower (approximately 2-fold) than population mean estimate for Part B. However, the significance of this finding is unclear given the small subjects numbers in Part A (n=5).

Individual $AUC_{(0-24)}$ values, derived from individual post-hoc estimates of CL, are summarized by PART (Part A and Part B) in Table 4.

Table 4: Model Predicted CL and Systemic Exposure and Total Administered Dose (Geometric Mean [95% CI]) following administration of GSK2586881to ARDS subjects (ACE114622 Parts A and B)

PAR	N	Total GSK2586881 Dose	CL (L/h)	$AUC_{(0-24)}$
A	5	141 [118, 167]	0.391 [0.281,	359 [283, 456]
B	1	199 [184, 216]	0.703 [0.624,	284 [252, 320]

Based on visual inspection, concentrations of GSK2586881 (APN01) determined by immunoassay (ng/mL) generally reflected enzymatic activity measurements (ng/mL) [6].

6.5 Preclinical Results

In a pharmacology study, GSK2586881 (APN01) (IV at 1 mg/kg) when administered alone or co-administered with angiotensin type 1 receptor blocker losartan (10 mg/kg/d, p.o. via chow) or an ACE inhibitor, captopril (10 mg/kg/d, p.o.), to male spontaneously hypertensive rats (SHR) resulted in a decrease in BP of 7.92 mmHg when compared with rats treated with vehicle alone.

Minimal toxicity has been found in animal studies to date as shown in the Table 5 below.

In the 14-day repeated dose study in cynomolgus monkeys, one female monkey receiving the highest dose, 20.8 mg/kg/day, on Day 12 had 6 Ventricular Premature Complexes (VPCs) including an episode of non-sustained ventricular tachycardia (NSVT) consisting of 3 VPCs (triplet). This finding was considered adverse, and therefore the no observed adverse effect level (NOAEL) for this study was determined to be 8 mg/kg/day.

Table 5: Summarized NOAEL of the toxicology and safety-pharmacology studies

Model	Species	NOAEL (mg/kg/day)
Repeated dose toxicology (2 weeks)	HW rats	20.8 (highest dose tested)
Repeated dose toxicology (4 weeks)	Rhesus monkey	2.5 (highest dose tested)
Repeated dose toxicology (2 weeks)	Cynomolgus monkey	8.0
Cardiovascular & respiratory safety pharmacology	Cynomolgus monkey	8.0
Acute dose toxicology	CD rats	40
CNS interaction study (Irwin test)	CD rats	40

Further information can be found in the investigator's brochure [6].

6.6 Cautions and Tolerability

6.6.1 Contraindications

There are no specific disease-related contraindications known for the administration of APN01. However, APN01 should not be administered to pregnant women or nursing mothers. APN01 is contraindicated in subjects who are hypersensitive to APN01 or any of the excipients used.

6.6.2 Special Warnings and Preventive Measures for the Treatment

Patients receiving any Angiotensin-Converting-Enzyme inhibitor (ACEi) or Renin inhibitor within 7 days before giving informed consent are excluded from participating in this clinical trial with APN01.

6.6.3 Use during Pregnancy and Lactation

There is no clinical experience with the use of APN01 during pregnancy or lactation. Embryofetal developmental toxicity studies with the compound have not been performed. Therefore, APN01 may not be administered to pregnant or lactating females at this time. Women of childbearing potential may be included in clinical studies if they are enrolled under circumstances that would preclude the possibility of becoming pregnant during dosing.

6.6.4 Overdose

No specific antidote for APN01 is known. Patients should be observed and supported appropriately.

6.6.5 Drug Abuse and Dependency

No studies have been conducted to evaluate the potential for abuse and dependence. The mechanism of action and pharmacological activity provide no basis to suggest that APN01 has potential for abuse or dependence.

6.6.6 Side Effects

Adverse Reactions

In a study of critically ill patients with ARDS, serious adverse events (SAEs) and safety findings were consistent with a critically ill patient population with a wide range of underlying disease processes. More adverse events (AEs) of rash, hypernatremia, dysphagia and pneumonia were reported in patients on APN011 compared with placebo, although many of these events were reported in the follow-up period.

No adverse systemic hemodynamic effects have been observed in patients with pulmonary arterial hypertension (PAH), but clinical experience is limited to single doses.

No evidence of immunogenicity was found in the clinical studies to date, but further studies are needed to provide definitive information.

Further information can be found in the IB, Chapter 5.3 [6].

6.7 Risk-Benefit Considerations

Based on available information and the design of the clinical trial, the Sponsor considers the trial to be ethically acceptable.

In general, the adverse events in the first in human (FIH) Study (APN01-1-01) occurred with similar frequency between active and placebo treated subjects, without apparent dose-relatedness. In the Phase I-Study 204987 (Effects on the Response to Acute Hypoxia and Exercise) of APN01 with healthy subjects there were no serious adverse events, deaths or other significant adverse events. In the Phase Ib Study 204696 in patients with PAH, there were no SAEs associated with the infusion of GSK2586881 (APN01) or reported within the 2-week period of study observation [6].

In the ongoing open-labeled Phase II a-206246-Study with Patients with PAH there were no SAEs and no anti-ACE2 binding antibodies detected.

The hypernatremia reported with GSK258688 (APN01) in the Phase IIa-ACE114622-Study with patients with acute respiratory distress syndrome was mild and consistent with sodium levels in the placebo group, and a number of events occurred after discontinuation of drug. The episodes of pneumonia in subjects receiving GSK2586881 (APN01) in the same study were all considered nosocomial in origin and occurred between 5-36 days after the last dose of study drug.

During Part A of the Phase IIa-ACE114622-Study 3 subjects experienced a total of 9 SAEs that resulted in death, only one of which (acute renal failure), was considered to be related to study drug, and was reported 4 days after the last dose of study drug.

None of the fatal events in during Part B (3 fatal AEs - 2 in the placebo group due to multiple organ failure and septic shock and one in GSK2586881 (APN01) 0.4 mg/kg BID) was considered to be related to study treatment by the reporting investigator.

In general, the safety findings were consistent with a critically ill patient population with a wide range of underlying disease processes.

Fei Zhou et al. reported age, comorbidities, lymphocytopenia and elevated alanine aminotransferase, d-dimer, creatine kinase, high-sensitivity cardiac troponin I, prothrombin time, and disease severity to be associated with intensive care unit admission. In addition, angiotensin converting enzyme 2, the receptor for SARS-CoV-2, is expressed on myocytes and vascular endothelial cells, so there is at least theoretical potential possibility of direct cardiac involvement by the virus [7].

The maximum blood volume of approximately 215 mL (female) and 200 mL (male) is considered adequate and no undue risk for the patients especially as some of the laboratory analyses are within the clinical routine.

Giving the urgent need in the light of progression of infected people worldwide in comparison to so far known adverse events reported adverse events in study subjects on GSK2586881 like rash, hypernatremia, dysphagia and pneumonia the PI and Sponsor still consider the trial to be ethically acceptable.

7 STUDY OBJECTIVES

7.1 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.

7.1.1 Primary Endpoint

The primary endpoint is a composite endpoint of all cause-death or invasive mechanical ventilation up to 28 days or hospital discharge.

7.2 Secondary Objectives

- To assess efficacy of APN01 using log transformed levels of Lactate dehydrogenase (LDH) as a surrogate marker for organ damage.
- To evaluate the safety of APN01 in patients with severe COVID-19
- To monitor other biomarker changes (e.g. IL-6, Ang II) in patient with severe COVID-19 treated with APN01

7.2.1 Secondary Endpoints

1. Log transformed levels of Lactate dehydrogenase (LDH) at day 5 as a surrogate marker for organ damage (powered secondary endpoint)
2. 28-day mortality (all cause death)
3. Ventilator-free days (VFD) up to 28 days or hospital discharge
4. Proportion of responders, defined as ≥2 improvement in WHO's 11-Point Score system at day 7, 10,14 and 28
5. Time to death (all cause)
6. Proportion of patients with any use of invasive mechanical ventilation up to 28 days or hospital discharge
7. Time to first use of invasive mechanical ventilation up to 28 days or hospital discharge
8. Absolute values and absolute change in P/F ratio over time
9. Absolute values and absolute change in the modified Sequential organ failure assessment score (mSOFA score) over time
10. Time to a 2-point decrease in WHO scoring schema
11. Absolute values and absolute change in lymphocyte counts over time
12. Absolute values and absolute change in C-reactive protein levels over time

13. Absolute values and absolute change in D-dimer over time
14. Absolute values and absolute change in log transformed levels of LDH over time
15. Time to hospital discharge
16. Change in virus RNA over time

Biomarker endpoints: Absolute values and absolute changes in relevant biomarkers over time:

1. Angiotensin II (Ang II), Angiotensin 1-7 (Ang 1-7), Angiotensin 1-5 (Ang 1-5), renin and aldosterone, Angiotensin-converting enzyme (ACE), Angiotensin-converting enzyme 2 (ACE2); Angiotensin I (Ang I), Angiotensin 1-9 (Ang 1-9)
2. Cytokines: Interleukin 6 (IL-6), Interleukin 8 (IL-8), soluble Tumor Necrosis Factor receptor type II (sTNFrII), Plasminogen Activator Inhibitor type-1 (PAI-1), von Willebrand factor (vWF), Tumor necrosis factor-α (TNF-α);
3. Alveolar epithelial markers: soluble Receptor for Advanced Glycation End products (sRAGE), Surfactant protein-D(SP-D);
4. Endothelial markers: Angiopoietin-2
5. Change in clinical laboratory markers associated with poor outcome over time (e.g., lymphocyte counts, D-Dimer, CRP, hsTnI (high sensitivity troponin))
6. NT-proBNP, Ferritin

Safety endpoints:

Frequency of AEs and SAEs, in vital signs, clinical laboratory assessments and in ECG parameters.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan-Description

The clinical trial is designed as a prospective, multi-centre, double-blind, randomized, placebo-controlled, interventional trial to assess clinical safety, tolerability, and efficacy of APN01 on top of best standard of care (SOC) in patients with severe COVID-19 and to evaluate if treatment with APN01 on top of SOC is superior to placebo (NaCl 0.9%) on top of SOC.

SOC treatment (such as Concomitant medication, remdesivir (if approved and available) and ventilation techniques) will be documented in the eCRF and considered for evaluation for study data. SOC treatment follows the national guidelines (https://www.ersnet.org/covid-19-guidelines-and-recommendations-directory).

The study will comprise two treatment groups as follows:

- Group A (active): APN01 (5 mg/ml, 4 ml/vial)
- Group B (placebo control): sterile, 0.9% sodium chloride

Eligible patients are centrally allocated using a dynamic randomization (1:1) to Group A or B to receive the treatment or placebo. Dynamic randomization factors will be age in years (continuous) and center. The entire study team will be blinded expect for an unblinded pharmacist or an unblinded study 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). . Randomization will be carried out centrally using the electronic case report form (eCRF).

After screening at day -1 and randomization at day -1 or 1, the patients will be treated with APN01 or Placebo intravenously twice daily (BID) every 12 hours (± 1 hour) over 3 to 30 minutes in the morning and the evening until day 7. Preparation of APN01 (0.4mg/kg BID for seven calendar days) and placebo (normal saline) will be carried out according to the Pharmacy Manual. The IMP will be administered in a double-blind manner (investigators, study team and patients will be blinded to the treatment administered).

In the treatment period (day 1 to day 7) daily visits will be performed. If a patient will be discharged from hospital before day 7 treatment can be stopped at day of discharge. After seven days of treatment or early discharge before day 7 the follow-up (FU) period starts. Three FU visits (day 10, 14 and 28) will be conducted to asses efficacy and safety. The study assessments will be performed according to the study schedule (Table 1).

8.2 Discussion of Study Design, including the Choice of Control Groups

The contagious coronavirus, named SARS-CoV-2 (formerly 2019-nCoV), which broke out at the end of 2019, has led to a medical emergency across the world, with the WHO officially declaring the novel coronavirus a pandemic on 11 March 2020 [1].

Whether or not the treatment with APN01 on top of SOC as approved in each country leads to a better outcome (assessed by using a composite outcome of all cause-death or invasive mechanical ventilation up to 28 days) is unclear. Therefore, this trial is of utmost importance.

To this end APN01 (on top of SOC) will be compared with placebo (NaCl 0.9%) therapy (on top of SOC) in a double-blind clinical trial setting. This is scientifically the strongest possible design and ethically appropriate given the limited evidence for therapeutic options in the treatment of patients with severe COVID-19.

8.3 Selection of Study Population

The treatment is symptomatic and oxygen therapy represents the major treatment intervention for patients with severe infection. Therefore, effective therapies are needed to treat patients with severe COVID-19.

Approximately 200 patients diagnosed to be COVID-19 POSITIVE will be enrolled in this study. Patients will be male or female and between ≥ 18 to ≤ 80 years of age.

The patients must not be treated before all inclusion criteria (including test results) and none of the exclusion criteria are confirmed. Patients meeting all of the inclusion criteria and no exclusion criteria listed below will be included in the study:

8.3.1 Inclusion Criteria

1. Hospitalised male or female, ≥ 18 to ≤ 80 years of age at the time of consent. The date of signing informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
2. Diagnosed to be COVID-19 POSITIVE (SARS-CoV-2 nucleic acid – qPCR)
3. Oxygenation criterion

- Oxygen saturation ≤93 % (either on Room Air or while the patient is on supplement oxygen)

4. ALT < 5xULN; bilirubin ≤ 1.5xULN
5. Signed informed consent form

8.3.2 Exclusion Criteria

1. Any patient for whom the investigator does not consider there is a reasonable expectation that they will be able to complete the study.
2. Known history of positive Hepatitis B surface antigen, Hepatitis C antibody or HIV antibody.
3. Current or chronic history of liver disease (Child Pugh score ≥ 10), or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
4. The patient has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
5. Patients requiring high doses of loop diuretics (i.e. > 240 mg furosemide daily) with significant intravascular volume depletion, as assessed clinically.
6. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
7. Pregnant females as determined by positive serum or urine hCG test prior to dosing.
8. Lactating females.
9. Unwillingness or inability to follow the procedures outlined in the protocol.
10. Unstable Hemoglobin (Hb < 7) at time of drug infusion (i.e. Hb must be > 7 mg/dL at the time of drug infusion. Transfusion is permitted to increase Hb levels to allow entry into the study.
11. Malignancy or other irreversible condition for which 6-month mortality is estimated to be >50%
12. Arterial blood pH less than 7.2 or serum HCO3- <15 (if arterial blood gas (ABG) not available) before infusion is started.
13. Known severe chronic pulmonary disease:
    - known FEV1/FVC less than 45% predicted, or
    - known chronic hypercapnia (PaCO2 > 45 mmHg) or chronic hypoxemia [(PaO2<55 mmHg) on FiO2 =0.21, or supplemental oxygen therapy prior to this admission], or
    - known FEV1 <15 ml/kg (e.g. 1L for 70 kg person), or
    - known radiographic evidence of chronic interstitial infiltration, or
    - known hospitalization within the past six months for respiratory failure (PaCO2 > 50 mmHg or PaO2 < 55 mmHg, or oxygen saturation <88% on FiO2 = 0.21),

- known chronic restrictive, obstructive, neuromuscular, chest wall, or pulmonary vascular disease resulting in severe exercise restriction (i.e. unable to climb stairs or perform household duties), known secondary polycythemia, severe pulmonary hypertension, or ventilator dependency

14. Known vasculitis with diffuse alveolar haemorrhage
15. Lung transplantation
16. Pre-existing renal failure, i.e. requiring renal replacement therapy with hemodialysis or peritoneal dialysis
17. There are other uncontrolled comorbidities that increase the risks associated with the study drug administration, that are assessed by the medical expert team as unsuitable
18. Patient in clinical trials with an IMP for COVID-19 within 30 days before signing informed consent form (ICF)
19. Unstable hemodynamics in the preceding 4 hours (MAP ≤ 65 mmHg, or SAP <90 mmHg, DAP < 60 mmHg, and vasoactive agents required)
20. Immunocompromised patients (chemotherapy, HIV, organ transplants, stem cell transplants)
21. Receive any Angiotensin-Converting-Enzyme inhibitor (ACEi) or Renin inhibitor treatment within 7 days before ICF

8.3.2.1 Reproductive Potential

The study population includes females of child-bearing potential (FOCP). A female is considered of childbearing potential, i.e. fertile, following menarche and until be-coming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. FOCP have to agree to comply with the applicable contraceptive requirements of the protocol as named below for the duration of the study or having post-menopausal status or be permanently sterilised (at least 6 weeks post-sterilisation).

Highly effective contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

Condoms are to be used with the mentioned acceptable contraceptives.

Male study participants need to comply with the contraceptive requirements given above as well.

FOCP with exclusively same-sex sex partners do not have to use highly effective/ acceptable birth control methods.

8.3.3 Removal of Patients from Therapy or Assessment

The study in its entirety may be discontinued prematurely by the Coordinating Investigator or Sponsor at any time (see below), and/or individual patients may terminate their participation prematurely, or have their participation be terminated by an Investigator.

8.3.3.1 Withdrawal of Patients from the Clinical Trial

The following circumstances may lead to discontinuation of the study by an individual patient who will then be recorded as a drop-out, include but are not limited to the following:

- Withdrawal for personal reasons
- AEs necessitating withdrawal from the clinical trial
- Occurrence of a severe adverse reaction (SAR)
- Sudden incidence of diseases
- Circumstances in which the health of the patient would be endangered upon continued participation in the clinical trial
- Lost to follow-up
- Other (must be specified)

If a patient withdraws from the study at any time either at his or her request or at the investigator's discretion, an "End-of-Study/Early Termination" visit should be performed and the "End of Study" eCRF section should be used to collect the relevant information. The visit may also be performed as a phone visit or in-home visit (in Russia). The reason(s) for withdrawal must be recorded on the relevant page of the patient's eCRF and the patient's source data. Patients discharged from hospital before day 28 will be contacted by telephone to asses if they are alive at day 28.

It is vital to obtain follow-up data for any patient withdrawn from the study because of an AE. Every effort must be made to undertake protocol-specific safety follow-up procedures. If a patient is discontinued due to an AE, the event should be followed up until resolution or until the event becomes chronic.

The Data Safety Monitoring Board may also recommend withdrawal of patients.

8.3.3.2 Premature Treatment Discontinuation

Patients must stop the IMP if the patient experiences any kind of hypersensitivity reaction. The patient may remain in the study and continue to attend study visits.

Patients may be withdrawn from the IMP after initiation of infusion if in the opinion of the investigator or of the Medical Monitor there is a risk to the patient's safety if they further receive IMP. If the patients are withdrawn from IMP, they may remain in the study and continue to attend study visits.

IMP treatment can be stopped early if a patient will be discharged before day 7.

8.3.3.3 Criteria for Termination of the Clinical Trial (Holding Rules)

The trial will be supervised by an independent Data Safety Monitoring Board (DSMB). All final decisions, however, regarding study termination or modification will be decided by the Sponsor and in agreement with the independent DSMB.

The clinical trial will be terminated if

- The DSMB requests termination of the clinical trial based on review of all clinical and laboratory data
- The Sponsor, Regulatory Agency or an EC requests the termination of the clinical trial
- 50% reduction in eGFR is observed. In addition, assessment of this parameter will be performed at the DSMB.

8.3.3.4 Study Termination

Individual study completion is defined as patients having finished the treatment period without early termination and reached the last visit within the specified window per the study schedule (Day 28; Table 1).

Overall End of Study is defined as the date of last patient last visit (LPLV). Within 90 days after the End of Study the Coordinating Investigator and the Sponsor must inform regulatory authorities and ethics committees about the completion of the trial.

The Sponsor may terminate the trial at any time for any reason and in particular if serious safety concerns rise for the patients. In the case of study termination, participating sites will be informed of the procedures to be followed to ensure that adequate consideration is given to the protection of the patient's safety.

The Sponsor has to inform the CAs and the ECs within 15 days.

8.4 Treatments

8.4.1 Treatments Administered

8.4.1.1 Experimental Intervention

Administration of APN01 (on top of SOC) will be carried out according to investigators brochure (IB) and Pharmacy Manual. Dosing will be 0.4mg/kg twice a day (BID), administered for seven days, every 12 hours (± 1 hour). First dosing could either be in the morning of Day 1 or in the evening of Day -1. If a patient will be discharged before day 7, treatment can be stopped early at day of discharge.

The IMP should only be administered if the staff, trained to evaluate and manage anaphylactic reactions, is immediately available, and in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects following APN01 administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio-respiratory resuscitation and equipment for handling acute anaphylactic/ anaphylactoid reactions should be available. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

8.4.1.2 Control Intervention

Administration of Placebo (0.9% NaCl on top of SOC) is according to the dosing rules for APN01.

8.4.1.3 Follow-up per patient

After the treatment period of seven days or early discharge before day 7, a follow up period starts with visits on day 10, 14 and 28 to assess efficacy and safety. The study assessments will be performed according to the study schedule (Section 1, Table 1).

For patients who are unable to attend regular study visits within the set time frame, unscheduled visits can additionally be planned outside of the visit time frame.

If a patient is already discharged from the hospital, the follow-up visits could be performed on an out-patient basis or at patient's home provided the patient agrees to that.

8.4.1.4 Duration of Intervention per Patient

The patients will be randomized in a 1:1 ratio to the following groups:

- Group A (Test): APN01 (5 mg/ml, 4 ml/vial)
- Group B (Placebo): 0.9% sodium chloride, sterile

The treatment will be performed according to protocol and will be administered for seven days, BID every 12 hours (± 1 hour). In case patients will be discharged before day 7 treatment can be stopped early at day of discharge.

8.4.2 Identity of Investigational Medicinal Products

The IMP will be supplied by ABF Pharmaceutical Services GmbH, Austria.

8.4.2.1 Test Product

Active substances:	Recombinant human angiotensin-converting enzyme 2 (rhACE2) APN01
Strength	Injection, 5 mg/mL, 4.0 mL/vial, supplied as a frozen liquid
Dosage:	0.4 mg/kg IV BID (every 12 hours ±1 hour for seven days)
Route:	intravenous (i.v.) over 3 to 30 minutes
Administration:	Intravenously of undiluted IMP using a polypropylene syringe with a 0.22 micron filter, slow infusion
Storage:	-20°C (-15°C to -35°C), protected from light
EU QP Release	ABF Pharmaceutical Services GmbH Brunner Strasse 63/18-19 1230 Vienna, Austria

Additional information can be found in the IB.

8.4.2.2 Placebo

Active substance:	NaCl 0.9% (normal/ physiological saline)
Strength:	10 or 100 mL container with 10 or 100 mL physiological saline
Route:	intravenous (i.v.) over 3 to 30 minutes
Administration:	Intravenously of undiluted IMP using a polypropylene syringe with a 0.22 micron filter
Storage:	As indicated on the label

Additional information can be found in the Summary of Product Characteristics (SmPC) and the pharmacy manual.

8.4.2.3 Packaging & Labeling

ABF Pharmaceutical Services GmbH will supply the IMP for the study. Test product is labeled in accordance with the applicable laws and GCP guidelines. Syringe with infusion solution for dose application will be labeled according to the instruction in the pharmacy manual. The pharmacy manual contains detailed information about the necessary steps for preparation for individual dose preparation.

8.4.2.4 Dose preparation

A pharmacist or unblinded member of the study team will be responsible for preparation of the treatment infusions. IMP will be withdrawn from the vial for individual dose preparation. The prepared dose in the syringe is stable for 8 hours at room temperature or 24 hours at refrigerated conditions (2-8°C). Detailed information about preparation of IMP can be found in the pharmacy manual.

8.4.2.5 Storage

The PI at each study site has the responsibility for ensuring that the IMP is stored under appropriate conditions in a secure, limited-access location. IMP is distributed by the pharmacy or unblinded member of the study to a designed member of the study team.

Study medication must be stored in accordance with labeled storage conditions -20°C (-15°C to -35°C), protected from light. Temperature monitoring is required at the storage location to ensure that the study medication is maintained within an established temperature range.

8.4.2.6 Shipment

The IMPs will be provided by ABF, Austria and or designee.

8.4.2.7 Drug Accountability

The PI at each study site has the overall responsibility for administering the IMPs.

The investigator or a designee at the study sites will acknowledge receipt of the study medication documenting shipment content and condition. Damaged supplies will be replaced. Accurate records of all study medication received, dispensed, used, returned or destroyed must be maintained. No study medication may be destroyed or returned from the investigational site without prior knowledge and written consent by the Sponsor. If such transfer is authorized by the Sponsor, all applicable local, state and national laws must be adhered to for the transfer.

The PI, an investigator or a trained delegated member of the study team will administer the IMPs. All administrations will be documented in the site's drug accountability log or other study drug record. The PI at the study site is responsible for assuring the retrieval of all dispensed study supplies from patients.

At the end of the clinical trial or as instructed by the Sponsor all unused stock and empty used boxes are sent to a nominated contractor on behalf of the Sponsor. Study medication being returned to the Sponsor must be counted and verified by clinical investigational site personnel and the Sponsor or deputy. All certificates of delivery/drug receipts should be signed by the site representative to confirm contents of shipment. Shipment return forms must be signed prior to shipment by study site. Returned study medication must be packed in a tamper-evident manner to ensure product integrity. The Sponsor must give authorization to return any study medication prior to shipment. Shipment of all returned study medication must comply with local, state, and national laws.

Based on the entries in the site drug accountability logs, it must be possible to reconcile study medication delivered with those used and returned. One hundred percent of the study medication must be accounted for and all discrepancies investigated and documented.

8.4.2.8 Patient Compliance

Compliance must be assessed by an investigator

For study medication administration at study site, compliance must be assessed by observation of dosing. Designated members of the study team will record details on the drug accountability log or other appropriate source documents.

8.4.3 Method of Assigning Patient to Treatment Groups

Randomization will be performed based on a variance minimization algorithm (dynamic randomization). Patients will be assigned to a given treatment arm with a probability that takes in consideration the current arm assignments (8.4.8.1). Randomization will be done via the eCRF. Patients will be assigned a sequential randomization number by the eCRF.

8.4.4 Selection of Doses in the Clinical Trial

8.4.5 Dose selection is based on previous clinical experience.

In the Phase IIa-ACE114622-Study with patients with acute respiratory distress syndrome (not in patients with COVID-19) dosing was 0.4 mg/kg BID over three consecutive days. The dose of APN01 in that study was sufficient to observe biological effect in enrolled patients, as evidenced by decreased plasma ang-II and increased plasma ang1-7 and ang1-5. Moreover, decreases in plasma IL6 and increased SP-D and a trend to lower plasma IL-6 were observed in patients assigned to the study drug, further indicating effect on biological endpoints potentially relevant to ARDS. Regarding the dosing schedule, the half-life of rhACE2 is thought to be 9.6 hours, such that twice daily dosing seems reasonable.

The dose selected was largely based on previous experience with the drug, and more precisely on the study performed by Khan et al [8]. In addition, based on previous study findings no drug accumulation was observed with repeated dose administrations (either for 3 or 6 days; (Figure 15 of IB v 11.0). On this basis it seemed rational and safe to extend treatment duration to 7 days, as it appears that 7 days is the critical period for a potential recovery of lung functions in ARDS patients [9,10, 11]

The study by Khan gave drug for only 3 days because the goal of the study was different; 3 days of dosing was felt to be sufficient to assess the basic pharmacology of the compound, initial safety in patients with ARDS, and possibly demonstrate a physiological effect. In this study, our goal is longer term outcomes.

Looking to the antiviral activity described in Monteil et al (Cell, In Press) the virus can infect and replicate in human capillaries, and kidneys which likely explains shedding of the virus in these organs, potentially leading to multi-organ failure. While, it might be possible that a higher dose would be more effective in antiviral drug activity, the drug will be given to patients with varying degrees of viral load. In clinical practice during this pandemic, it is not possible to quickly measure the viremic viral load, and in fact many patients are not viremic. As such, we thought that from a safety perspective the dose given in the previous clinical trial would be the most appropriate for this Phase 2 trial.

8.4.6 Blinding and Unblinding

The entire study team will be blinded expect 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). IMP will be provided to the pharmacy or unblinded team in an unblinded manner. The PI will inform the pharmacist or unblinded member of the study team about the randomization of a new subject. The pharmacist or unblinded member of the study team will ascertain the treatment arm from the eCRF and provide the PI with the blinded treatment. In case of an emergency, patient treatment may be unblinded directly in the eCRF. The right to unblind treatment in the eCRF assigned to a given user role. Unblinding is performed by opening the patient in the eCRF and clicking the “Emergency unblinding” link to activate the unblinding workflow. The time, date and reason for unblinding are captured in the eCRF. In addition, the unblinding will be documented in the respective “unblinding form”. Unblinding should be restricted to cases of emergency where knowledge of thy type of treatment is considered necessary for adequate treatment of the patient. The sponsor must be notified about any patient unblinded immediately. Breaking of the emergency code leads to the exclusion of the respective patient.

The randomization list will be exported and provided to statistician as part of the final data transfer. The randomization list will be archived as part of the final database archival package.

8.4.7 Prior and Concomitant Therapy

Prohibited treatment: Patients receiving ACE inhibitors, or renin inhibitors

NOTE: angiotensin receptor blockers are not prohibited.

Concomitant treatment: Any concomitant treatment given for any reason during the course of the study must be recorded on the eCRF and in the patient’s medical records, including dosage, start and stop dates and reason for use.

8.4.8 Treatment Compliance

8.4.8.1 Enrolment to the Clinical Trial

A patient will only be enrolled in the trial if all inclusion and none of the exclusion criteria are met. A patient will only be admitted to the clinical trial if the ICF has been signed and all inclusion and none of the exclusion criteria are met. Should there be any doubts as to the state of health, a patient will not be admitted to the clinical trial.

8.4.8.2 Patient Identification

The PI of each site will keep a record relating the patient numbers and the names of all patient that have given their informed consent, to allow easy checking of data in patient files, when required. This record will also include the date of the patient’s enrolment and completion, as well as patients who could not be included in the study for whatever reason.

8.4.8.3 Early Termination

All enrolled patients who discontinue early, or withdraw from the clinical trial will have the follow-up assessments and procedures completed for their safety as outlined in Table 1. Patients who discontinue early or withdraw from the clinical trial will not be replaced as long as 200 patients complete the study according to the protocol.

In some cases, it may be necessary for patients to return to the study site or will be contacted for a phone visit or in-home visit (in Russia) for additional care, confinement, and/or follow-up. Circumstances in which this may be necessary are:

- Follow-up on abnormal laboratory evaluations
- Follow-up on an ongoing AE at the final visit (day 28) and or final phone visit

All additional safety follow-up visits will be at the discretion of the investigator, the PI and the Sponsor.

8.4.8.4 Unscheduled Visits

Unscheduled visits may be performed at any time during the clinical trial. Depending on the reason for the unscheduled visit (e.g., AE, abnormal laboratory values, ECG), appropriate assessments will be performed based on the judgment of the investigator. Results of the assessment and any changes in concomitant treatment will be recorded in the eCRF. After an unscheduled visit, the regular scheduled visits must continue according to the planned visit and assessment schedule.

8.5 Efficacy and Safety Variables

8.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

Details regarding scheduled assessments and procedures to be conducted in this clinical trial are provided below. For detailed assessment schedules refer to Table 1.

8.5.2 Appropriateness of Measurements

8.5.2.1 Screening Procedures

Written, signed, and dated informed consent from the patients prior to the performance of any clinical trial related procedures must be obtained by an investigator. A copy of the signed consent form and the information sheet must be given to the patient for their records after signature and before enrollment.

The time period between start of screening procedures and start of treatment must not exceed 24 hours. In case the required screening procedures take less time, randomization and start of treatment could be performed also on the same day then screening. Pre-dose events other than biomarker sampling and vital signs do not need to be performed if randomization and screening are on the same day. The following events will be performed: check of inclusion and exclusion criteria, obtaining medical history and demographics, score assessment of WHO's 11-point scale, PCR analysis, vital signs, physical examination, serum or urine pregnancy test, lab assessments, ECG, assessment of respiratory condition, mSOFA-score.

See Table 1 for a complete list of screening procedures to be performed.

Only an authorized and trained investigator may decide on the eligibility of the patient.

8.5.2.1.1 Screening Failure

A screening failure is defined as a patient who has given informed consent and failed to meet at least one inclusion or exclusion criteria or has not been administered IMP as defined by the protocol.

8.5.2.1.2 Re-Screening of Patients

Patients who fail to meet all inclusion/exclusion criteria will permitted to be re-screened once at a later timepoint.

8.5.2.2 Study Examinations

Assessments are to be performed according to the schedule shown in Table 1.

On Day -1/1 of the study schedule the assessments have to be performed prior dosing.

Follow-up visit on Day 28 may be performed as a phone visit or in-home visit , where applicable . If a patient is already discharged from the hospital, the follow-up visits could be performed on an out-patient basis or at patient's home provided the patient agrees to that.

8.5.2.2.1 Safety

Safety will be evaluated by collecting reported AEs at regular intervals throughout the clinical trial and by the assessment of physical examination findings, vital signs, clinical laboratory parameters, and ECGs.

8.5.2.2.2 Medical and Medication History

A complete medical and medication history as well as demographic information will be assessed at Screening. The medical history will be reviewed and recorded, including:

Medical and Medication History for the least 4 weeks

- Relevant recent ingestion of medication
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, musculoskeletal and other diseases

Demographic information

- Date of Birth
- Sex
- Height and weight
- History of allergies
- History of smoking and alcohol use
- Body mass index (BMI)
- Ethnicity

8.5.2.2.3 Vital Signs

The vital signs will be reviewed and recorded, including:

- Temperature
- Heart rate
- Respiration
- Blood pressure
- Oxygen saturation.

Vital signs need to be tested before and after each dose.

All measurements of vital signs must be recorded in the appropriate source documents.

8.5.2.2.4 Physical Examination

A complete physical examination will be performed at the time points described in Table 1.

The physical examination will include a review of the following body systems:

- General appearance
- Skin
- Head, Eyes, Ears, Nose and Throat
- Spine/Neck/Thyroid
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen (including liver and kidneys).
- Relevant Co-Morbidities

Any abnormalities or changes in intensity from the screening visit noted during the review of body systems should be documented in the medical record. If a new clinically significant abnormal finding (i.e. not noted at baseline) occurs after screening has been completed, it must be captured as an AE and documented on the source documents. In addition, resolution of any abnormal findings during the clinical trial will be noted in the medical record if clinically significant.

Physical examination could also be documented in the context of the general visit/health status e.g. during a general clinical review assessment.

8.5.2.2.5 Pregnancy test

Appropriately performed using blood (serum) or urine test.

8.5.2.2.6 Clinical Laboratory Assessments

All laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out-of-range pathological changes. The physician should assess out-of-range laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant (NCS) or clinically significant (CS). Abnormal laboratory values that are unexpected or not explained by the patient's clinical condition may be, at the discretion of the investigator, PI or Sponsor, repeated until confirmed, explained, or resolved as soon as possible.

Details are defined in the Laboratory Manual. The following laboratory assessments will be performed:

Bio-Chemistry

Blood samples for biochemistry will be collected at the time points described in Table 1. The following parameters will be assessed:

Aspartate aminotransferase (AST)	Potassium (K)
Alanine aminotransferase (ALT)	Sodium (Na)
Alkaline phosphatase (AKP)	Albumin (ALB)
Total bilirubin (TBI)	Urea nitrogen (BUN)
Total protein (TP)	Creatinine (Cr)

Uric acid (UA)	eGFR (assessment is calculated according to the formula used in local laboratory)

Hematology / Blood Routine

Blood will be drawn at the time points described in Table 1. The following parameters will be assessed:

Red blood cell (RBC) count	Hemoglobin (Hb)
Hematocrit (HCT) or hematocrit total	Platelet (PLT) count
Classification of white blood cells (WBC)	

Inflammatory Indicators

Blood will be drawn at the time points described in Table 1. The following parameters will be assessed:

C- reactive protein (CRP)	ESR
	Procalcitonin

Urinalysis

pH (PH)	
Urinary Protein (PRO)	Blood (red blood cells (BLD) and white blood cells (LEU))
Glucose (GLU)	Microscopic examination (if blood or protein is abnormal)

Stool routine and occult blood

The following parameters will be analyzed in fresh stool:

Red blood cells (RBC)	Occult blood
White blood cells (LEU)	

Myocardial enzymes

The following parameters will be analyzed:

creatine kinase (CK)	[alpha] - hydroxybutyrate dehydrogenase ([alpha]-HBD)
and isoenzyme (CKMB)	Troponin (cTnI)
lactate dehydrogenase (LDH)	

Coagulation function

To assess the coagulation function, the following parameter will be analyzed:

Prothrombin time (PT)	D-dimer
Activated partial thromboplastin time (APTT)	FIB

Assessment of Immune function

To assess the immune function the following parameter will be analyzed:

COVID-19 Antibodies	Immunoglobulin (IgG, IgA, IgM)

Serology

During the screening period only, 1 or 2 blood samples will be drawn to test for the presence of HIV, HBsAg, and HCV antibody.

HIV testing (HIV I and HIV II)	HCV antibody screen
HBV testing (HBsAg)	

8.5.2.2.7 Biomarker

Per collection of whole blood, the following biomarkers will be analyzed (12 ml):

<u>One Li-Heparin blood collection tube (5-6 ml):</u>

Plasma equilibrium angiotensin levels:

- Angiotensin II (Ang II)
- Angiotensin 1-7 (Ang. 1-7)
- Angiotensin 1-5 (Ang 1-5)
- Angiotensin I (Ang I)
- Angiotensin 1-9 (Ang 1-9)

Aldosterone

ACE2 Activity and ACE2 concentration

Cardiac pump function markers: NT-proBNP, Ferritin

Other exploratory indicators: specific exploratory indicators will be determined as needed.

<u>One EDTA blood collection tube (5-6 ml):</u>

Plasma-Renin-Concentration (PRC)

Cytokines:

- Interleukin- 6 (IL-6)
- Interleukin- 8 (IL-8)
- Soluble tumor necrosis factor receptor II (sTNFrII)
- PAI-1
- vWF
- Tumor necrosis factor - α

Alveolar epithelial markers:

- Soluble advanced glycation product receptor (sRAGE)
- Surface-active protein-D (SP-D)

Endothelial markers:

- Angiopoietin-2

Viral load

8.5.2.2.8 Electrocardiogram

A 12-lead ECG will be performed within 30 min after IMP administration (Table 1). Actual ECG assessment times will be monitored.

At a minimum, the date and time of when the event was performed, the investigator's assessment and the heart rate, RR, PR, QT, and QRS intervals are to be collected. All clinically significant abnormalities will be recorded on the appropriate source documents.

8.5.2.2.9 Assessment of Respiratory Condition

To assess the respiration of the patient a blood gas analysis (oxygenation index, blood lactic acid) or pulse oximetry will be performed (Table 1).

Detailed information is provided in the Investigator Manual.

8.5.2.2.10 WHO 11-point scale

The WHO Clinical Progression Scale (WHO-CPS) measures patient illness by tracking progress through the healthcare system. The WHO-CPS incorporates a number of explicit features that are advantageous for its use in in emerging infectious disease epidemic. It provides a measure of illness severity across an 11 point range from 0 (not infected) to 10 (dead) (Annex 1).

8.5.2.2.11 Modified Sequential Organ Failure Assessment (mSOFA) score

The mSOFA score [12] is made up of the following components:

- SpO2/FiO2 (mmHg)
- Central Nervous System: Glasgow coma score (GCS)
- Cardiovascular
- Liver
- Platelets
- Renal: Creatinine

Detailed information is provided in the Investigator Manual.

8.5.2.2.12 Patient status assessment

Patient status assessments includes the documentation of the following: no change, discharge from hospital, transition to critical illness, and death.

8.5.2.2.13 Adverse and Serious Adverse Events Assessments

The investigator is 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 will be recorded in the AE page of the eCRF using a recognized medical term or diagnosis that accurately reflects the event.

All AEs will be reviewed, confirmed, and classified (causality and seriousness) by a qualified, designated physician.

Pre-existing conditions that are present at screening are not defined as adverse events. These should be documented as medical history. Nevertheless, an AE will be documented in case of a worsening of severity of a pre-existing condition. AEs reported between screening and IMP application are defined as pre-treatment AE.

8.5.2.2.13.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (test) product, whether or not considered related to the medicinal product (ICH Guidance E2A 1995).

All AEs, including those associated with the IMP, are collected from the time of first dose administration, regardless of the relationship to the IMP. All AEs are to be recorded on the appropriate source documents and subsequently will be entered into the AE module of the eCRF. All AEs have to be recorded until the last trial day according to the clinical trial protocol. If the investigator becomes aware of a serious AE considered related to the IMP, it has to be reported (pharmacovigilance@ctc-north.com) even if it occurs after finalization of the clinical trial.

All AEs must be followed to closure (i.e. the patient's health has returned to his/her baseline status or all variables have returned to normal), an outcome is reached, stabilization (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained regardless of whether the patient is still participating in the clinical trial and clinical judgment indicates that further follow-up is not warranted. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

Moreover, elective procedures (planned at time of randomization, e.g. catheter intervention of a coronary stenosis) will be determined as expected AE.

8.5.2.2.13.1.1 Severity Categorization

The severity of AEs must be recorded. If the severity of an AE/SAE changes, or if there are any other changes they must be made within the same AE record. Also, only the highest severity needs to be recorded. Worsening of pre-treatment events from the medical history, after initiation of IMP treatment, must be recorded as new AEs.

The medical assessment of severity is determined by using the following definitions:

Mild: Symptom barely noticeable to patient; does not influence performance or functioning. Prescription drug not ordinarily needed for relief of symptom but may be given because of personality of patient.

Moderate: Symptom of a sufficient severity to make patient uncomfortable; performance of daily activities influenced: patient is able to continue in clinical trial; treatment for symptoms may be needed.

Severe: Symptom causes severe discomfort. May be of such severity that patient cannot continue in clinical trial: Severity may cause cessation of treatment with test drug; treatment for symptom may be given and/or patient hospitalized.

The term "severe" is here used to describe the severity/intensity of the specific event; it is not the same as "serious", which is based on patient/event outcome or action criteria.

8.5.2.2.13.1.2 Relationship Categorization

An investigator assesses each AE for its relationship to the IMP.

The assessment of the relationship of an AE to the administration of IMP is a clinical decision based on all available information at the time of and after the occurrence of the event. The factors which may be considered when evaluating the relationship of an AE to the IMP include: time from exposure to IMP until onset of the event; recovery or improvement on discontinuation of IMP; availability of alternative explanations such as underlying or intercurrent diseases; concomitant medications or treatments; pharmacology of the IMPs; known response pattern for this class of drug; recurrence on reintroduction of the IMP.

If there is no reasonable possibility for suggesting a relationship, then the AE should be classified as 'not related'. The adverse event should be classified as related if a reasonable possibility of a causal relationship between the event and IMP exists. This means that there are facts (evidence) or arguments to suggest a causal relationship. The causality must be documented in the source document and eCRF.

The following additional guidance may be helpful:

Term	Relationship	Definition
Related – Reasonable possibility	Yes	The temporal relationship between the event and the administration of the IMP is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the patient's medical condition, other therapies, or accident.
Not Related – No reasonable possibility	No	The event can be readily explained by other factors such as the patient's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the IMP and the event.

8.5.2.2.13.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the clinical trial in the eCRF. Outcomes are as follows:

- Recovered/Resolved
- Recovering/Resolving
- Not recovered/Not resolved/ongoing
- Recovered/Resolved with sequelae
- Fatal
- Unknown

8.5.2.2.13.1.4 Clinical Laboratory Evaluations

A change in the value of a safety laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the IMP, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the IMP, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

Changes in laboratory values that are clinically significant (cs) and are specific for COVID-19 do not need to be documented as adverse events (AE). Clinically significant changes in laboratory values that are not due to COVID-19 need to be documented as AEs.

The physician should decide, based on the above criteria and the clinical condition of a patient, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

8.5.2.2.13.1.5 Overdose and Medication Error

Overdose, or medication error (as defined below) must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE.

Overdose - Intentional or unintentional administration of a dose of study medication higher than the protocol prescribed dose for each patient.

Medication Error - A mistake made in administration, and/or use of the study medication. For studies, medication errors are reportable only as defined below.

Administration of an expired product should be considered as a reportable medication error when associated with an AE, or if otherwise appropriate.

Cases of patients missing doses of study medication are not considered reportable as medication errors.

8.5.2.2.13.2 Serious Adverse Event (SAE) Procedures

8.5.2.2.13.2.1 Reporting Procedures

All initial SAE reports must be reported by the investigator to the Sponsor's Pharmacovigilance Department immediately, without undue delay, under no circumstances later than 24 hours following the first awareness of the event. All SAE follow-up reports must be reported in a timely manner. The investigator must complete, sign, and date the SAE form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: source documents are not to be sent unless requested) and e-mail the form to the Sponsor's Qualified Person for Pharmacovigilance:

Name:	CTC North Safety Desk
Phone:	+49 40 524719-225
Email:	pharmacovigilance@ctc-north.com

8.5.2.2.13.2.2 Serious Adverse Event Definition

A SAE is any untoward medical occurrence (whether considered to be related to IMP or not) that follows the first IMP administration at any dose:

- Results in death
- Is life-threatening

  NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if was more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an Important Medical Event;

NOTE: Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

8.5.2.2.13.2.3 Pregnancy

Any report of pregnancy recorded for any female patient or for a female partner of a male patient should be reported to the Sponsor within the same timelines as an SAE, i.e. immediately (without undue delay, under no circumstances later than 24 hours following the first awareness/ within 30 days of IMP administration), but a separate form should be used. Pregnancy should be followed up at least until the birth or abort.

8.5.2.2.13.2.4 SAE Onset and SAE Stop Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The stop date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and SAE resolution dates, respectively.

8.5.2.2.13.2.5 Fatal Outcome

Any SAE that results in the patient's death (i.e. the SAE was noted as the primary cause of death) should have Outcome „Fatal" and the date of death recorded as the stop date of the SAE.

For all other events ongoing at time of death that did not contribute to the patient's death, the outcome should be considered unknown, with the SAE stop date (date of death) recorded.

For any SAE that results in the patient's death or any ongoing events at the time of death, the action taken with the IMP should be recorded as "dose not changed" or "not applicable" (if the patient never received IMP).

8.5.2.2.13.2.6 Regulatory Agency, Ethics Committee, and Investigative Site Reporting

The Sponsor is responsible for Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting to the relevant Regulatory Authorities/European Union (EU), central Ethics Committees and investigators participating in the clinical trial in compliance with the legal reporting obligations.

The expedited reporting will occur not later than 15 days after the Sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.5.3 Primary Efficacy Variable(s)

8.5.3.1 Outcome Measures

For the primary outcome a composite outcome of all cause-death or need of invasive mechanical ventilation up to 28 days is used. For the secondary outcome (powered secondary endpoint) log transformed levels of Lactate dehydrogenase (LDH) as a surrogate marker for organ damage are used.

8.5.3.2 Safety Variables

Assessment of safety is performed for the safety set. Safety data include:

- AEs (including changes from baseline in physical examination findings)
- Clinical laboratory results
- Vital signs
- 12-lead ECGs

The safety evaluation will be based upon the review of the individual values (potentially clinically important abnormalities) and descriptive statistics (summary tables, graphics).

8.5.3.2.1 Adverse Events

The AEs will be listed per patient using MedDRA terminology (lower level term, preferred term and system organ class) and will be reported in tables summarizing the frequency of patients with AEs and AEs by treatment and body system, the number of AEs and patients with AEs by treatments and the characteristics of AEs.

For the hematology, clinical laboratory and the urine analysis deviations from the reference ranges will be summarized in frequency tables.

8.5.3.2.2 Clinical Laboratory

All relevant clinical variables obtained during screening, final examination or the clinical trial periods will be reported in appropriate tables together with descriptive statistics. Clinical laboratory findings outside of the reference range will be flagged.

8.5.3.2.3 Vital Signs

For blood pressure and pulse rate descriptive statistics will be listed by sampling times (screening and follow-up) according to the data reported in the source documents.

8.5.3.2.4 ECG

The results of the 12-lead ECG will be listed by sampling times (screening and follow-up) according to the data reported in the source documents.

8.6 Data Quality Assurance

8.6.1 Quality Assurance System

Clinical trial management activities including medical writing, regulatory submission and communication, monitoring, data management and eCRF development and safety management will follow the Standard Operating Procedures (SOP) of the CTC North or CTC North subcontractors. Statistical analysis and clinical study report writing will follow the SOPs of FGK.

The quality management system of the CTC North and FGK has been repeatedly audited by sponsors as well as by local authorities.

Standard phases of the study may be subject to audits by the quality assurance unit (QAU) of the Sponsor or CTC North.

8.6.2 Monitoring

CTC North is responsible for the overall monitoring of the clinical trial. Local partners will be subcontracted to ensure source data verification in local languages (Denmark and UK). Local CROs will be responsible for the monitoring in the US and Russia. Site qualification and site initiation visits will be performed as phone visits. A combination of remote monitoring and regular on-site visits will be performed depending on the possibility for on-site visits due to the current COVID-19 pandemic. Close-out visits are planned as on-site visits. The frequency and kind of monitoring visits will depend on the study site's recruitment rate and current situation in each country/study site. The detailed extent of the monitoring and the risk based approach considering the COVID-pandemic situation and its influence on the daily life and the health system will be defined in the overall monitoring plan applicable for all countries and in Annex 2.

8.6.3 Documentation and Data Collection

An eCRF will be prepared to report all data required by the protocol.

Site staff will transfer the study data from the source documents into the eCRF and will check eCRF entries for completeness. Completed eCRF modules will be electronically signed by an Investigator in order to ensure data entry accuracy.

Corrections to source data documents will be dated and initialed. Reasons for the corrections should be given. Corrections to eCRF entries must be electronically signed and reasons for the corrections must be provided. The date on which the correction was performed is automatically recorded by the system's audit trail.

A study monitor will review source data and the eCRF data for completeness and accuracy during the monitoring visits (source data verification (SDV)). The study monitor will point out discrepancies between source data and the data captured in the eCRF. The monitor will issue electronic queries to site staff in order to initiate discrepancy resolution. Discrepancies which require eCRF data corrections have to be resolved by authorized site personnel by answering the queries and changing the respective eCRF entries. These query management and query resolution activities are also automatically recorded by the system's audit trail.

8.6.4 Data Management

Data management will check predefined eCRF entries as defined in the data management plan (DMP) and data validation plan (DVP).

Quality control (QC) and data validation procedures such as programmed automatic edit and consistency checks ensure data validity and accuracy immediately at the point of entry into the clinical database. The database application which is used to capture electronic clinical trial data is fully CFR part 11 compliant. Thus, it is access restricted, requires electronic signatures, maintains an electronic audit trail and provides appropriate back-up functionalities. Details of the application and eCRF configuration and all further data management procedures will be described in the DMP.

The database will only be locked after all queries and discrepancies have been resolved.

After database lock, the data in the study database will be exported and transferred electronically to the responsible biometrician for statistical analysis. The export will be used to generate the patient listings, tabulations, and analyses.

Upon request safety and other reports will be generated and provided by DM to the respective members of the DSMB.

8.6.5 Archival of Documents

Sponsor will maintain the trial documents as specified in the ICH-GCP guideline and take measures to prevent accidental or premature destruction of these documents.

All documents related to the clinical trial will be retained until at least 15 years after the end of the clinical trial.

8.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

8.7.1 Statistical and Analytical Plan

Details for the statistical evaluation of the results will be given in a separate statistical analysis plan.

8.7.1.1 Software to be used

All statistical calculations will be carried out using SAS language and procedures (SAS 8.2 or higher version SAS-Institute, Cary NC, USA).

8.7.1.2 Eligibility for Statistical Evaluation

Eligibility of patients will be determined within the data review meeting (blind data review meeting, DRM).

8.7.1.2.1 Safety Analysis Set (SAF)

All randomized patients who received study medication (independent of whether it is APN01 or placebo) will be valid for the SAF. The SAF will be used for the evaluation of the safety assessments (as treated).

8.7.1.2.2 Full Analysis Set (FAS)

The FAS includes all randomized subjects. The FAS serves as the primary efficacy analysis set (as randomized).

8.7.1.2.3 Per-Protocol Analysis Set (PP)

The PP includes all subjects included in the SAF who had no significant protocol deviations and completed through Day 28 or until discharge from the hospital (end of study follow-up). The PP will only be analyzed for main efficacy outcome measures (as treated).

8.7.1.2.4 Statistical Analysis

Continuous variables will be summarized with means, standard deviations, medians, lower and upper quartiles, minimums and maximums. Frequencies and percentages will be used to summarize categorical variables.

For time-to-event analyses censoring information will be used.

It is assumed that no patients will discontinue the study early prior to day 28 or hospital discharge in this Covid-19 setting. It is also assumed, that only very few missing values will arise due to not done evaluations. No imputation of missing values (e.g., no last observation carried forward (LOCF)) is planned, unless stated otherwise.

8.7.1.2.5 Primary and Secondary Endpoints

Analysis of primary efficacy endpoint

The primary endpoint of this trial is a composite of all cause-death or any use of invasive mechanical ventilation up to 28 days or hospital discharge.

Invasive mechanical ventilation is defined as patients who are intubated or have a tracheostomy tube and are receiving positive pressure ventilation. Patients who will be discharged from hospital before day 28 will be considered as non-event after confirmation by telephone interview that they are alive at day 28. Patients who will be discharged from hospital or early terminated before Day 28 will be considered having an event on the day of discharge or early termination, if a telephone interview was not possible and/or no information about alive/death status is known.

Hypothesis to be tested:

H0: pAPN01 = pPlacebo

H1: pAPN01 ≠ pPlacebo

H0 will be tested using a Chi-squared test. The level of significance is 5% (two-sided). In addition, logistic regression analyses will be conducted considering additional co-factors (will be detailed in the statistical analysis plan).

Analysis of secondary efficacy endpoints

Secondary efficacy variables will be tested descriptively and in an exploratory manner.

1. Log transformed levels of Lactate dehydrogenase (LDH) at day 5 as a surrogate marker for organ damage

   Log transformed levels of LDH will be analyzed using linear regression adjusted for baseline log levels of LDH, center and minimization factors.

   95% confidence intervals will be additionally calculated.

   Statistical procedures to check on a normal distributed of data, to be applied in case of non-normally distributed data, and to verify and handle minimization factors will be described in the statistical analysis plan, which will be finalized prior to unblinding.

2. 28-day mortality (all cause death)

   The percentage of patients who have died at Day 28 will be presented by treatment group. Patients who will be discharged from hospital or early terminated before Day 28 will be considered having an event on the day of discharge or early termination, if a telephone interview was not possible and/or no information about alive/death status is known. The Chi-squared or Fisher's exact test will be used to compare proportions. 95% CIs will be additionally calculated. Logistic regression analyses will be conducted considering additional co-factors (will be detailed in the statistical analysis plan).

3. Ventilator-free days (VFD) up to 28 days or hospital discharge

   VFD will be analyzed for both all patients as well as for the subgroup of patients who were alive at Day 28 or hospital discharge. For the analysis of all patients separate analyses will be conducted for patients who died: a) VFD will be set to 0, b) the observed VFD until death will be considered. Summary tables will be generated the VFD will be compared using Wilcoxon rank sum test. In addition, bootstrap methods will be applied to calculate 95% confidence intervals and two-sided p-values for the difference in means.

4. Proportion of responders, defined as ≥2 improvement in WHO's 11-Point Score system at day 7, 10, 14 and 28

Similar analyses as for 28-day mortality will be conducted.

5. Time to death (all cause) will be analyzed using Kaplan-Meier estimates and plots, log-rank test, and Cox proportional hazards model (adjusted for minimization factors to derive hazard ratios and corresponding 95% confidence intervals). Patients who will be alive at Day 28, or who will be discharged from hospital before day 28 with no information on death until day 28, will be censored at discharge if they cannot be reached at or after day 28 by means of a telephone interview. Further details will be described in the statistical analysis plan.
6. Proportion of patients with any use of invasive mechanical ventilation up to 28 days or hospital discharge

   Similar analyses as for 28-day mortality will be conducted.
7. Time to first use of invasive mechanical ventilation up to 28 days or hospital discharge
   Similar analyses as for time to death will be conducted. Patients without invasive mechanical ventilation will be censored on the last day of evaluation. For patients who died the observed time to first use of invasive mechanical ventilation will be considered; if a patient who died did not receive any mechanical ventilation, the patient will be censored on time of death.
8. Absolute values and absolute change in P/F ratio over time

   The PF ratio is defined as PaO2 [mmHg] divided by FiO2 in [%] and will be evaluated on each visit. Summary statistics for the PF ratio for both the absolute values and the absolute change from Baseline (day 1) will be tabulated.
9. Absolute values and absolute change in the modified Sequential organ failure assessment score (mSOFA score) over time

   Similar analyses as for the PF ratio will be conducted.
10. Time to a 2-point decrease in WHO scoring scheme.
    Similar analyzes as for 28-day mortality will be conducted. Patients without ≥2 improvement in WHO's 11-Point Score system will be censored on the last day of WHO scoring evaluation. For patients who died the observed time to a 2-point decrease until death will be considered; if a patient who died no 2-point decrease was observed, the patient will be censored on time of death.
11. Absolute values and absolute change in lymphocyte counts over time

    Summary statistics for both the absolute values and the absolute change from Baseline (day 1) will be tabulated.
12. Absolute values and absolute change in C-reactive protein levels over time

    Summary statistics for both the absolute values and the absolute change from Baseline (day 1) will be tabulated.
13. Absolute values and absolute change in D-dimer over time

    Summary statistics for both the absolute values and the absolute change from Baseline (day 1) will be tabulated (prognostic information: Zhou et al. Lancet 2020).
14. Absolute values and absolute change in log transformed levels of LDH over time

    Summary statistics for both the absolute values and the absolute change from Baseline (day 1) will be tabulated.
15. Time to hospital discharge

Similar analyses as for time to death will be conducted. Patients without hospital discharge will be censored on the last of hospital stay. Patients who died in the hospital will be censored on the day of death.

16. Change in viral RNA over time

    Summary statistics for both the absolute values and the absolute change from Baseline (day 1) will be tabulated.

8.7.1.2.6 Biomarker Endpoints

Biomarker endpoints will be analyzed using summary statistics at each scheduled measuring time point for absolute values and for absolute change from baseline values. No statistical testing procedures will be applied to Biomarker analyses.

1. Angiotensin II (Ang II), Angiotensin 1-7 (Ang 1-7), Angiotensin 1-5 (Ang 1-5), renin and aldosterone, Angiotensin-converting enzyme (ACE), Angiotensin-converting enzyme 2 (ACE2), Angiotensin I (Ang I), Angiotensin 1-9 (Ang 1-9),
2. Cytokines: Interleukin 6 (IL-6), Interleukin 8 (IL-8), Soluble tumor necrosis factor receptor type II (sTNFrII), Plasminogen activator inhibitor type-1 (PAI-1), von Willebrand factor (vWF), Tumor necrosis factor-α (TNF-α)
3. Alveolar epithelial markers: Soluble receptor for advanced glycation end products (sRAGE), Surfactant protein-D(SP-D)
4. Endothelial markers: Angiopoietin-2
5. Change in clinical laboratory markers associated with poor outcome over time (e.g., lymphocyte counts, CRP, D-dimers, hsTnI (high sensitivity troponin))
6. NT-proBNP

8.7.1.2.7 Safety Endpoint

The safety evaluations will include analyses of AEs and SAEs, changes in vital signs, clinical laboratory assessments and in ECG parameters. The analysis of safety will be based on the SAF.

AEs

Pre-treatment AEs will be analyzed separately based on all patients included into the trial. AEs will be summarized by system organ class and preferred term according to Medical Dictionary for Regulatory Activities (MedDRA). The number of events, as well as the number and rate of affected subjects will be reported. AEs (system organ class and preferred term) will also be summarized by seriousness, by severity and by relationship to study medication. No statistical testing procedures will be applied to the analysis of AEs.

Individual patient data listings will be provided for all deaths, patients with other SAEs, unexpected adverse drug reactions (as confirmed by the sponsor's drug safety manager), discontinuation of IMP due to AEs, or premature trial termination due to AEs.

Vital signs

For vital signs, body temperature and body weight standard descriptive summary statistics will be calculated at each scheduled time point

Furthermore, standard descriptive summary statistics will be computed for the absolute change from baseline to each scheduled visit up to the last individual time point

Laboratory measurements

Laboratory data will be subjected to both a quantitative analysis (descriptive summary statistics) and qualitative analysis where frequencies of normal, above normal and below normal values will be computed.

The following analyses will be performed:

- Standard descriptive summary statistics will be calculated at each scheduled measuring time point
- Standard descriptive summary statistics will be calculated for the absolute change from baseline to each scheduled visit
- Frequencies of normal, above normal, and below normal values will be computed at each scheduled measuring time point
- Shift tables displaying changes with respect to the normal range between baseline and each scheduled visit will be provided
- A listing of all patients with abnormal (above normal or below normal) values at any time point will be given

Findings from ECG (12-lead)

Frequencies for the respective categories of (ab)normality will be tabulated.

A patient data listing of all clinically significant abnormal ECG values will be provided.

8.7.2 Determination of Sample Size

186 patients (93 per group) will yield 80% power to detect a 20% absolute risk reduction in the primary composite endpoint, from 50% in the placebo group to 30% in the APN01 group at a two-sided alpha of 0.05 when applying a two group Chi-Squares test. To consider patients who will be randomized but not treated a total of 200 patients (100 per group) will be enrolled.

9 CHANGES IN THE CONDUCT OF THE CLINICAL TRIAL OR PLANNED ANALYSIS

Modifications of the protocol are permitted only if they are authorized by the Sponsor and the PI in writing.

Deviations and changes to the study protocol will be classified by the Sponsor and the clinical trial center as:

Note-to-File: This refers to clarifications which are not considered changes of the protocol.

Study protocol amendment: This refers to changes of the protocol. If they fulfill the criteria as set out in the appropriate law, they need to be approved by the Ethics Committee(s) or the Competent Authority(ies) or both of them. Changes to the study protocol may also induce revision of the patient information sheet/informed consent form. Accordingly, patients undergoing trial assessment procedures at the time of implementation of the change have to be given the amended version and have to be asked for consent to continue in this amended trial.

9.1 Protocol Deviations

All protocol deviations will be tracked and actions will be defined, as feasible. All protocol deviations will be reviewed and classified in the DRM before data base lock and unblinding for the final analysis for assessment of their influence on the quality of the study analysis.

Protocol deviations (PD) are defined as follows:

Major PD:

- Informed consent procedure: ICF not signed and dated by patient/investigator
- Violation of an in- or exclusion criterion
- Randomization procedure
- Incorrect use of IMP (storage, preparation and administration)
- Use of forbidden concomitant medication
- Delayed reporting of serious adverse events

10 DSMB

A Data and Safety Monitoring Board (DSMB) will be established to protect the safety of study participants.

The DSMB will receive blinded CRF data in the form of tables and listings (prepared by an independent statistician), and adjudicate on patient status changes. Where appropriate, the DSMB may receive unblinded data (on a patient level) that should be reviewed in a closed session.

The data should include, but is not limited to, demographics, patient enrolment, baseline characteristics, AE data, SAE data (by severity and causality), laboratory data, protocol adherence, and patient withdrawals.

The DSMB will assess data quality and timeliness and patient's risk versus benefit. In addition, the DSMB will monitor external factors relevant to the trial, for example scientific and therapeutic developments that may affect participant safety or ethical status. Based on the observed benefits or adverse effects, the DSMB will make recommendations to the Sponsor concerning continuation, termination or modifications of the trial. Trial modifications may apply to an adjustment of dose and treatment duration, to the included trial population by adaptation of inclusion and/or exclusion criteria, to modifications on allowed or prohibited concomitant medications and medications to be considered for standard of care. The DSMB shall review overall diagnostic and therapeutic options available for COVID-19 patients and make recommendations whether the trial design needs to reflect these options through modifications in this trial.

The Sponsor will establish a DSMB charter document explaining the working procedures for the DSMB.

In addition, a DSMB meeting will be conducted whenever safety relevant data occur that might have an influence on the trial.

11 REPORTS

All reports to the Sponsor will be in English. The Sponsor will receive an electronic copy of all versions of the electronic CRFs.

11.1.1 Clinical Study Report

All clinical, analytical and statistical results will be presented in a clinical study report (CSR). The outline of this report will accord to the ICH-GCP E3 document "Structure and Content of Clinical Study Reports" of July 17, 1996.

The Sponsor will receive the original CSR.

All reports are the property of the Sponsor. Publication of the report or of part of it may only be allowed when authorized by the Sponsor in consultation with the clinical trial center.

11.1.2 Additional Reports

Within a year upon completion of the clinical trial, a summary of the CSR will be sent to the Ethics Committee and Competent Authorities as required by appropriated law.

12 REFERENCES

1 Joint statement ICAO-WHO on COVID-19“ (https://www.icao.int/Security/COVID-19/Pages/Statements.aspx from 11 March 2020

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3 Andrea Remuzzi, Guiseppe Remuzzi: COVID-19 and Italy: what next? The Lancet. Published online March, 12 2020.

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6 Investigator's Brochure for GSK2586881 (formerly known as APN01) A Soluble Recombinant Human Angiotensin Converting Enzyme 2 (rhACE2), Version 11 dated 17 Juni 2020.

7 Fei Zhou, Ting Yu, Ronghui Du at el.: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. Published online March, 9,2020.

8 Akram Khan, Cody Benthin, Brian Zeno et al.: A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Critical Care 21:234, 2017.

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12 Colin K. Grissom, Samuel M. Brown, Kathryn G. Kuttler et al.: A Modified Sequential Organ Failure Assessment (MSOFA) Score for Critical Care Triage. Disaster Med Public Health Prep. 4(4), 27: 7.84, 2010.

13 ANNEX 1

The WHO Working Group's on the Clinical Characterization of COVID-19 infection Proposed Core Outcome Measure Set for Clinical Studies of COVID-19 Infection.

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
	Symptomatic; Independent	2
	Symptomatic; Assistance needed	3
Hospitalized: Mild disease	Hospitalized; no oxygen therapy	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: Severe disease	Hospitalized; Oxygen by NIV or High flow	6
	Intubation & Mechanical ventilation, pO_2/FIO_2 ≥150 or SpO_2/FIO_2≥200	7
	Mechanical ventilation pO_2/FIO_2<150 (SpO_2/FIO_2 <200) **or** vasopressors	8
	Mechanical ventilation pO_2/FIO_2<150 **and** vasopressors, dialysis, or ECMO	9
Death	Dead	10

Notes:

1. If hospitalized for isolation only, record status as for ambulatory patient
2. If pO2 not available, use SpO2/FIO2 ratio with a cutoff of 200

14 ANNEX 2

Remote/Video monitoring visit

Due to the Corona-Pandemic on-site monitor and pharmacy visits may not be possible due to travel restrictions and/or access restrictions at the hospitals. For this reason, a combined remote and video monitoring visits may be the only possibility to monitor the site for an indefinite period.

The general goals of the remote/video on-site monitoring visits are the same as for the on-site monitor visits with the restriction that complete source data verification is not possible. For the remote/video monitoring a software certified for the use in the medical field and GDPR conform (i.e., CLICKDOC Videosprechstunde for Germany and Austria) is used.

Monitoring will only be conducted within the limits of site personnel (availability, workload, time) and technical capabilities to ensure secure video monitoring. Furthermore, essential data have to be entered into the database (eCRF) which includes the upload of corresponding documents (e.g. laboratory, physician's letter) in order to perform SDV remotely.

Study sites need to agree with the remote and video monitoring. Therefore, a written confirmation document will be provided to the sites and needs to be signed and collected by the CRA.

The following data according to recommendations of the European authorities are to be checked via remote/video monitoring:

- Verification of availability and correctness of signed informed consent forms
- data relevant for the inclusion and exclusion (including medical history)
- doses and dose regimens of IMP
- recording of (serious) adverse events
- concomitant medication

Video Monitoring: documents will be shown to the CRA by videoconference.

The following data should be checked during an on-site Visits.

- For 100% of all randomized patients: verification of availability and correctness of signed informed consent
- For 100% of all randomized patients:
  - data relevant for the inclusion and exclusion
  - data relevant for the primary objective
  - data relevant for the secondary objectives
  - IMP treatment
  - concomitant medication
  - safety-related data for AEs / SAEs

<u>Video Visits (blinded)</u>

The following documents will be reviewed per Video-Monitoring if available, i.e. the site needs to have documentation on paper.

Categorie	**Document**
Informed Consent Form	ICF
Physician´s letter/ Source Data Worksheets	In regard to I/E criteria, review of: - Medical History - Concomitant Medication - Age, Weight, - Oxygen Saturation Safety:

	AE/SAE Documentation
Laboratory values	In regard to I/E criteria review of: ALT, bilirubin, Hb, Hepatitis B+C, HIV COVID positive testing

In case one of the listed documents is only available as an electronic patient file, it cannot be reviewed per video-monitoring.

Documents listed below for remote monitoring will also be checked within the frame of video monitoring visit.

Remote Visits:

General requirements for provision of scanned documents for remote monitoring:

- Quality of scans should have at least minimum 200 dpi.
- Completeness of documents will be guaranteed by on the cover page of the document the complete number of pages of the document is indicated (for example 1-12), with initials and actual date.
- No scans of documents including personal data or data which can lead to the identity of the patients will be provided.
- Study personnel will be instructed to send the scans as a response to an email of the CRA and to just respond to the email without adding another recipient to the email to avoid that documents will be sent to unauthorized third parties by mistake.
- Documents received by the study site will be documented in the monitoring report.

Remote Visits (blinded)

The following documents should be provided (in case of any changes to previous visit) by the sites upon request via email and checked by remote monitoring:

- Patient enrolment log
- Site delegation log
- IMP handover form
- IMP drug accountability form
- Trainings logs
- Acknowledgments (Protocol, IB)
- Site Visit Log
- Site staff documents (FD, GCP, CV)
- Note to files

Remote Visits (unblinded)

The following documents should be provided (in case of any changes to previous visit) by the sites upon request via email and checked by remote monitoring:

- Handover forms
- IMP dispatch form
- Preparation of trial medication (APN01 or Placebo)
- IMP accountability logs (APN01 or Placebo)
- Investigational product stock on site/ Pharmacy
- Temperature Recording Log (APN01 or Placebo)
- Training Logs
- Note to files
- Print out randomization confirmation eCRF