Statistical Analysis Plan
for
final Analysis

Version 3.0

Study:	Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treatment for patients with COVID-19
Study-ID:	APN01-01-COVID19 EUDRACT Number: 2020-001172-15 IND: 151312
Sponsor / Contact:	APEIRON Biologics AG Campus-Vienna-Biocenter 5 1030 Vienna, Austria
Evaluation:	FGK Clinical Research GmbH
FGK code	3570
Version:	3.0 of 11Jan2021
Previous versions:	1.0 of 13Oct2020 2.0 of 02Nov2020

Revision history

Version	Author	Date	Reason for Revision
1.0	N. Semenenko	13Oct2020	1st final version
2.0	N. Semenenko	02Nov2020	2nd final version
3.0	N. Semenenko	11Jan2021	3rd final version (update due to detected inconsistences during programming)

Table of Contents

List of Abbreviations

In the following abbreviations are listed as used within this statistical analysis plan or which might occur within the tables, listings and graphs outputs:

AE	Adverse event
ATC	Anatomical therapeutic chemical
BDRM	Blind data review meeting
BID	bis in die, i.e. twice daily
BMI	Body mass index
CM	Concomitant medication
CRF	Case report form
CS	Clinically significant
DSMB	Data safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full analysis set
IMP	Investigational medicinal product
LDH	Lactate dehydrogenase
MedDRA	Medical dictionary for regulatory activities
MH	Medical history
N	Number of patients
NCS	Not clinically significant
PE	Physical examination
PP	Per protocol set
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SD	Standard deviation
SOC	System organ class
SOFA	Sequential organ failure assessment
mSOFA	Modified sequential organ failure assessment
SUSAR	Suspected unexpected serious adverse reaction
TLG	Tables, listings, graphs
VFD	Ventilator-free days
WHO	World health organization
WHO-DD	World health organization drug dictionary

1 General

This Statistical Analysis Plan (SAP) was defined by the Sponsor and the responsible Statistician without knowledge of the randomization code. It is based upon the Study Protocol (version 7.0 of 10Aug2020) and contains detailed description of the statistical methods described therein.

The SAP describes prospectively the analyses to be performed on study data for final analysis. It was finalized prior to data base lock and unblinding.

This SAP serves as SAP for final analysis and includes relevant endpoints for final analysis only. Details of outputs are given in Appendix A.

The DSMB analyses are described in a separate 'SAP for DSMB'.

Methodology

This is a Phase II 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 in patients with severe COVID-19 and to evaluate if treatment with APN01 on top of standard of care is superior to placebo (NaCl 0.9%) on top of standard of care.

Eligible patients will be centrally allocated using a dynamic randomization (1:1) at baseline (day 1) to Group A or B to receive the treatment or placebo. Dynamic randomization factors will be age in years (<65 years vs. >=65 years), presence of at least one relevant co-morbid condition (hypertension, diabetes, coronary artery disease) for study protocol versions prior version 6.0 and center.

After screening at day -1 and randomization at day -1 or day 1, 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 in the evening until day 7 (14 doses). If a patient will be discharged from hospital before day 7 treatment can be stopped at day of discharge.

Periods and duration

The study will consist of three periods: screening (day -1), treatment period (day 1 to day 7) and follow-up period (day 10, day 14 and day 28). Study duration is up to 29 days per patient. Total study duration is up to 5 months, with 2-4 months recruitment period per country.

Number of patients planned

The planned sample size is 200 treated patients. Approximately 40 sites in Europe, Russia and US are planned, hence for a 1:1 (APN01:Placebo) randomization scheme. 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.

DSMB Meetings

The regular DSMB will be performed after randomization of 8-10, 20, 50, 100 (if necessary), and 150 (if necessary) patients. Furthermore an ad hoc meeting of the DSMB may be called at any time by the DSMB Chair, coordinating investigator, medical monitor or sponsor imminent for any significant reason.

Study objectives

The primary study objective is to assess clinical efficacy of APN01 using a composite outcome of all cause-death or need of invasive mechanical ventilation up to 28 days.

The secondary study objectives are 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 and to monitor other biomarker changes (e.g. IL-6, Ang II) in patient with severe COVID-19 treated with APN01.

2 Efficacy and Safety Endpoints

2.1 Primary Efficacy Endpoint

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

2.2 Secondary Efficacy Endpoints

The following secondary efficacy parameters will be analyzed:

- Log transformed levels of lactate dehydrogenase (LDH) at Day 5 as a surrogate marker for organ damage (powered secondary endpoint)
- 28-day mortality (all cause death)
- Ventilator-free days (VFD) (up to 28 days or hospital discharge)
- Proportion of responders, defined as >= 2 improvement in WHO's 11-Point Score system at Day 7, 10,14 and 28
- Time to death (all cause)
- Proportion of patients with any use of invasive mechanical ventilation (up to 28 days or hospital discharge)
- Time to first use of invasive mechanical ventilation (up to 28 days or hospital discharge)
- Absolute values and absolute change in PaO2/FiO2 ratio over time
- Absolute values and absolute change in modified Sequential organ failure assessment score (mSOFA score) over time
- Time to a 2-point decrease in WHO's 11-Point Score system
- Absolute values and absolute change in lymphocyte counts over time
- Absolute values and absolute change in C-reactive protein levels over time
- Absolute values and absolute change in D-dimer over time
- Absolute values and absolute change in log transformed levels of LDH over time
- Time to hospital discharge
- Change in viral RNA over time

2.3 Safety Endpoints

- Adverse events (AEs) and serious adverse events (SAEs)
- Vital signs: Systolic blood pressure, Diastolic blood pressure, Heart rate, Body temperature, Respiratory rate
- Oxygen saturation
- Clinical laboratory assessments:
  - Biochemistry
  - Inflammatory indicators
  - Myocardial enzymes
  - Hematology
  - Coagulation
  - Urinalysis
  - Stool routine and occult blood

- ECG parameters: Heart rate [bpm], RR interval [ms], PR interval [ms], QT interval [ms], QRS complex [ms], ECG evaluation
- Detection of viral nucleic acid or viral gene sequencing

2.4 Biomarker Endpoints

- Angiotensin II (Ang II), Angiotensin 1-7 (Ang 1-7), Angiotensin 1-5 (Ang 1-5), Plasma-Renin-Concentration (PRC), Aldosterone, Angiotensin-converting enzyme 2 (ACE2) activity and concentration, Angiotensin I (Ang I), Angiotensin 1-9 (Ang 1-9)
- Cytokines: Interleukin 6 (IL-6), Interleukin 8 (IL-8), soluble Tumor Necrosis Factor receptor type II (TNFR-II), Plasminogen Activator Inhibitor type-1 (PAI-1), von Willebrand factor (vWF-A2), Tumor necrosis factor-α (TNF-α)
- Alveolar epithelial markers: soluble Receptor for Advanced Glycation End products (RAGE), Surfactant protein-D (SP-D)
- Endothelial markers: Angiopoietin-2
- Change in clinical laboratory markers associated with poor outcome over time (e.g., lymphocyte counts, D-Dimer, CRP, hsTnI (high sensitivity troponin))
- NT-proBNP, Ferritin
- Immune function and COVID-19 antibodies
- Serology

3 Statistical Analysis Sets

3.1 Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients.

3.2 Safety Analysis Set (SAF)

The safety analysis set (SAF) consists of all randomized patients who received study medication (independent of whether it is APN01 or Placebo). If the application of any study medication is not certain, the patient will be included in the SAF.

3.3 Per-Protocol Analysis Set (PP)

The PP includes all subjects included in the SAF who had no major protocol deviations and completed through Day 28 or until discharge from the hospital (end of study follow-up). Protocol deviations will be identified and classified for each subject during a blind data review meeting (BDRM) (see section 4.8).

The following protocol deviations are a priori defined to have a “major” grade and will lead to an exclusion from the PP set:

- 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

3.4 Assignment of Analysis Sets to Analysis

The FAS serves as the primary efficacy analysis set (as randomized). All efficacy analyses are based on the FAS. The SAF will be used for the evaluation of the safety assessments (as treated) unless stated otherwise. All biomarker analyses are based on SAF (as treated) as well. The PP will only be analyzed for main efficacy outcome measures (as treated).

4 Statistical Evaluation

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.

The two different treatment groups (groups APN01 and Placebo) will be separately tabulated. Where appropriate total columns will additionally be displayed for the two treatment groups combined.

A detailed description of the planned tables, listings and graphs is given in Appendix A.

Baseline

Baseline is defined as last observation before treatment, i.e. Day 1 value or Screening value if Day 1 value is missing or if Screening and Day 1 is the same day, unless stated otherwise.

Visit terminology

Visit No.	Notation used on the case report form	Notation used for tables, listings and graphs
10	Screening (Day -1)	Screening
150	Unscheduled visit	Screening *
20	Day 1	Day 1
30	Day 2	Day 2
40	Day 3	Day 3
50	Day 4	Day 4
60	Day 5	Day 5
70	Day 6	Day 6
80	Day 7	Day 7
150	Unscheduled visit	Day 8 *
90	FU Day 10	FU Day 10
100	FU Day 14	FU Day 14
110	FU Day 28/EOS	FU Day 28/EOS
130	FU Day 28/EOS Phone Visit	FU Day 28/EOS
170	Russia only: Home Visit FU Day 28/EOS	FU Day 28/EOS
120	Early termination	ET
140	Early termination FU Day 28/EOS	ET
150	Unscheduled visit	Unscheduled visit

ET = Early termination

** IMP administration at Screening and at Day 8 as well as all related assessments (e.g. ECG, Vital signs, etc.) are documented in eCRF as IMP administration or assessment on Unscheduled visit and will be shown in TLGs as IMP administration or assessment on Screening and Day 8 respectively.*

Unscheduled visits will not be included in any tables or graphs, only in listings and will be displayed after all scheduled visits.

4.1 Dispositions of Subjects and Analysis Sets

Disposition of patients and study discontinuation

The disposition of patients, patients per center, inclusion and exclusion criteria, the status of study completion / study discontinuation and survival (telephone contact) as well as the number and percentages of patients discharged from hospital by visit will be shown.

4.2 Demographics and Other Covariates

Demographic data

Demographic data (Age, Age group (< 65 years/ >= 65 years), Sex, Race, Ethnicity, Body weight, Body height, BMI (Body Mass Index)) will be tabulated and listed.

Other demographic data like history of smoking and alcohol use, if available, will be listed only.

Prior and concomitant medication (CM)

Prior and concomitant medications will be coded by WHO-DD valid version at the end of the study.

Concomitant medications are defined as all medications with stop date >= date of first study medication or ongoing if started before date of first study treatment.

Prior medications include all medications that started and stopped before the date of first study medication. Medications with insufficient date information to determine whether or not they were concomitant will be considered concomitant.

Concomitant medication will be tabulated by anatomical therapeutic chemical (ATC) level 1, ATC level 4, preferred name and listed as well. Prior medication will be listed only.

Comorbidity

Number and percentage of patients with at least one comorbidity (arterial hypertension, diabetes and coronary artery disease) will be shown.

All comorbidity data will be listed as well.

Medical history (MH)

MH events will be tabulated by system organ class and current treatment status (currently treated/ currently not treated). The number of events, as well as the number and rate of affected patients will be reported for each treatment group.

All medical history data will be listed as well.

Respiratory condition (arterial blood gas analysis or pulse oximetry)

Arterial blood pH, PaO2 and PaCO2 will be presented using basic statistics of absolute values for all visits and change from baseline for all post-baseline visits.

All respiratory data will be listed as well.

Pregnancy test

The proportion positive or negative pregnancy test results will be tabulated by visit for females with childbearing potential.

All pregnancy test data will be listed as well.

Physical examinations (PEs)

The frequencies of changes (Evaluation (Normal / Abnormal – CS / Abnormal – Not CS)) in PEs (all body systems) since baseline will be shown for all visits using shift tables.

All physical examination data will be listed as well.

Patient status assessment

Patient status assessment will be presented using frequency tables.

Patient status assessment data will be listed as well.

4.3 Study Drug Administration

IMP administration

Each patient should receive 14 doses of IMP (APN01 or Placebo). The first IMP administration will be performed after randomization at screening or at day 1. If the first IMP administration is performed at day 1 at the evening, patient will receive the 14th dose on day 8 in the morning. IMP administration at screening and at day 8 as well as all related assessments (e.g. ECG, Vital signs, etc.) are documented in eCRF as IMP administration or assessment on unscheduled visit and will be shown in TLGs as IMP administration or assessment on screening and day 8 respectively (instead of unscheduled visit, i.e. renaming of unscheduled visits in this cases).

Total study drug exposure and total study drug exposure complete will be tabulated and listed.

Therefore, the frequency tables in overall as well as by Age group (< 65 years/ >= 65 years to < 75 years/ >= 75 years to < 80 years/ >= 80 years), Sex, Race and Ethnicity will be provided.

Total study drug exposure [days] is calculated as sum of days with at least 1 administered dose (complete or not complete) of IMP (APN01 or Placebo).

Total study drug exposure complete [days] is calculated as sum of days with two complete administered doses of IMP (APN01 or Placebo).

All other IMP administration data will be listed only.

Total dose per day of study medication taken [mg] is calculated as sum of first and second administered doses of IMP (APN01 or Placebo).

Total volume per day of infusion [ml] is calculated as sum of first and second administered volume of infusion.

Total dose of study medication taken [mg] is calculated as sum of daily administered doses of IMP (APN01 or Placebo).

Total volume of infusion [ml] is calculated as sum of daily administered volume of infusion.

4.4 Efficacy Analysis

In case that the first IMP is given at night of Screening visit, the duration of the study might be 29 days as a maximum. Therefore, a time window of 27 to 29 days will be applied where applicable.

4.4.1 Analysis of Primary Efficacy Endpoint

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

The following null hypothesis will be tested:

- H_0: pAPN01 = pPlacebo

versus the alternative

- H_1: 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.

<u>All cause-death</u>

The percentage of patients who have died at Day 28 will be presented by treatment group.

Patients with death from any cause will be used for this endpoint as part of responder. Patients who are still alive at Day 28 will be considered as non-event.

The following cases may occur:

• Patient discharged from hospital **and** discontinued before Day 28, will be followed up by telephone interview to check whether they are alive or dead, if unclear as no telephone interview available, death is assumed (worst case) at last available date of early termination, hospitalization or hospital discharge

• No discharge from hospital, **but** early discontinuation before Day 28 will be followed up by telephone interview to check whether they are alive or dead, if unclear as no telephone interview available, death is assumed (worst case) at date of early termination

• Discharged from hospital, **but** no discontinuation before Day 28: No telephone interview, but regular entry at Day 28 about alive/death status

<u>Invasive mechanical ventilation (up to 28 days or hospital discharge)</u>

Invasive mechanical ventilation is defined as patients who are intubated or have a tracheostomy tube and are receiving positive pressure ventilation. Patients with at least one invasive mechanical ventilation (event with type of ventilation ‘Mechanical ventilation’) up to 28 days or hospital discharge will be used for this endpoint as part of responder.

<u>Chi-squared test</u>

Proportion of responder, i.e. those patients that died or having an invasive mechanical ventilation (up to 28 days or hospital discharge), as well as the p-value (two-sided) will be reported.

<u>Logistic regression</u>

A logistic regression with the responder (yes/no) as independent variable will be applied.

The following co-factors will be included in the logistic regression:

- ❑ Arterial hypertension

- Diabetes
- Coronary artery disease
- Age (<65 years vs. >=65 years)
- Center

The odds ratio along with its associated 95% confidence intervals will be reported.

4.4.2 Analysis of Secondary Efficacy Endpoints

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

Results of LDH will be converted to standard unit before any calculation if needed. Conversion of all lab values will be described in a separate document 'Conversion_3570 _VX-X_2020-MM-DD'. Standardized results will be log transformed for this endpoint.

Log transformed levels of LDH will be analyzed using linear regression adjusted for baseline log levels of LDH, center and age. 95% confidence intervals will be additionally calculated.

In protocol the wording of "minimization factors" is used: Stratification factors from the randomization are used in models as covariates.

Before application of the linear regression, it will be checked if the residuals are approximately normally distributed (QQ-Plot, Shapiro Wilk test). If there are no major violations of the normal distribution the model can be applied. If there are major violations available only descriptive analyses will be displayed.

Point estimate together with standard error and two-sided 95% confidence interval as well as p-value (two-sided) will be reported.

28-day mortality (all cause death)

The percentage of patients who have died at Day 28 will be presented by treatment group.

The following cases may occur:

• Patient discharged from hospital **and** discontinued before Day 28, will be followed up by telephone interview to check whether they are alive or dead, if unclear as no telephone interview available, death is assumed (worst case) at last available date of early termination, hospitalization or hospital discharge

• No discharge from hospital, **but** early discontinuation before Day 28 will be followed up by telephone interview to check whether they are alive or dead, if unclear as no telephone interview available, death is assumed (worst case) at date of early termination

• Discharged from hospital, **but** no discontinuation before Day 28: No telephone interview, but regular entry at Day 28 about alive/death status

Chi-squared test or Fisher's exact test

Proportion of responder, i.e. those patients that died, as well as the p-value (two-sided) will be reported.

Logistic regression

The following co-factors will be included in the logistic regression:

- Arterial hypertension
- Diabetes

- Coronary artery disease
- Age (<65 years vs. >=65 years)
- Center

The odds ratio along with its associated 95% confidence intervals will be reported.

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

VFD will be calculated as follows:

VFD = maximum((Duration in the study [days] - Duration of ventilation [days]); 0)
i.e. if the duration of ventilation is greater than the duration in the study, VDF is set to 0.

Duration in the study [days] = Date of study completion/ discontinuation - Date of randomization + 1.

Patients who died before or on Day 28 will be censored at the day before death (Date of death - 1).

Duration of ventilation [days] = Sum of days with all required ventilations.

If ventilation started before randomization, the duration will be counted from the date of randomization. If ventilation started and/or ended after study completion/ discontinuation, the duration will be counted until date of study completion/ discontinuation.

If ventilation is ongoing and/or no stop date is available, the duration will be calculated until date of study completion/ discontinuation or date of death respectively.

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/early termination. 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 by treatment group.

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

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

Proportion of responders, defined as >= 2 improvement in WHO's 11-Point Score system at Day 7, 10, 14 and 28

Patients who will be not assessed from any cause (e.g. discharge from hospital, early termination, death or in-home visit) will be considered as non-responder.

Chi-squared test or Fisher's exact test

Proportion of responder, i.e. those patients that have >= 2 improvement in WHO's 11-Point Score system, as well as the p-value (two-sided) will be reported for Day 7, 10, 14 and 28.

Logistic regression

The following co-factors will be included in the logistic regression:

- Arterial hypertension
- Diabetes
- Coronary artery disease

- Age (<65 years vs. >=65 years)
- Center

Separate models will be calculated for Day 7, 10, 14 and 28.

The odds ratio along with its associated 95% confidence intervals will be reported.

Time to death (all causes)

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

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

The following cases may occur:

• Patient discharged from hospital **and** discontinued before Day 28, will be followed up by telephone interview to check whether they are alive or dead, if unclear as no telephone interview available, death is assumed (worst case) at last available date of early termination, hospitalization or hospital discharge

• No discharge from hospital, **but** early discontinuation before Day 28 will be followed up by telephone interview to check whether they are alive or dead, if unclear as no telephone interview available, death is assumed (worst case) at date of early termination

• Discharged from hospital, **but** no discontinuation before Day 28: No telephone interview, but regular entry at Day 28 about alive/death status

Time to death (all causes) will be analyzed using Kaplan-Meier estimates and plots, log-rank test, and Cox proportional hazards model (adjusted for center and age to derive hazard ratios and corresponding 95% confidence intervals).

Kaplan-Meier estimates and Log-rank test

Kaplan-Meier table (product-limit “survival” estimates with 95%-CI, Standard error, Number of patient with event, Number of patient at risk) for Time to death [days], Kaplan-Meier Summaries of Event/Censoring (Number of patient with event, Number of patient censored, Total number of patients), Quartile Estimates (Median Time to Event,1st Quartile, 3rd Quartile, 95%-CI) and Kaplan-Meier table (“survival” estimates with 95%-CI) for Timepoint (28 days). Time to death [days] will be displayed by a Kaplan-Meier-curve. Treatments groups will be compared with Log-rank test.

Cox proportional hazards model

The hazards ratio along with its associated 95% confidence intervals as well as parameter estimate and p-value (two-sided) will be reported.

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

Requirement and type of ventilation will be presented using frequency tables.

Chi-squared test or Fisher’s exact test

Proportion of responder, i.e. those patients that having an invasive mechanical ventilation (up to 28 days or hospital discharge), as well as the p-value (two-sided) will be reported.

Logistic regression

The following co-factors will be included in the logistic regression:

- Arterial hypertension
- Diabetes
- Coronary artery disease
- Age (<65 years vs. >=65 years)
- Center

The odds ratio along with its associated 95% confidence intervals will be reported.

Time to first use of invasive mechanical ventilation (up to 28 days or hospital discharge)

Time to first use of invasive mechanical ventilation [days] = Start date of first ventilation - Date of randomization.

If ventilation started before randomization, the time to first use will be set to 0 (minimal possible duration).

Patients without documented invasive mechanical ventilation who completed the study or was early terminated or discharged from hospital before Day 28 will be censored at the date of study completion, discontinuation or discharge from hospital respectively.

Time to first use of invasive mechanical ventilation (up to 28 days or hospital discharge) will be analyzed using Kaplan-Meier estimates and plots, log-rank test, and Cox proportional hazards model (adjusted for center and age to derive hazard ratios and corresponding 95% confidence intervals).

Kaplan-Meier estimates and Log-rank test

Kaplan-Meier table (product-limit “survival” estimates with 95%-CI, Standard error, Number of patient with event, Number of patient at risk) for Time to first use of invasive mechanical ventilation [days], Kaplan-Meier Summaries of Event/Censoring (Number of patient with event, Number of patient censored, Total number of patients), Quartile Estimates (Median Time to Event,1st Quartile, 3rd Quartile, 95%-CI) and Kaplan-Meier table (“survival” estimates with 95%-CI) for Timepoint (28 days). Time to first use of invasive mechanical ventilation [days] will be displayed by a Kaplan-Meier-curve. Treatments groups will be compared with Log-rank test.

Cox proportional hazards model

The hazards ratio along with its associated 95% confidence intervals as well as parameter estimate and p-value (two-sided) will be reported.

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

The PaO2/FiO2 ratio = PaO2 [mmHg] / FiO2

This will be evaluated on each visit for ventilated patients only. If entries are not changed compared to previous entries, no entry will be done within the eCRF.

If ventilation is ongoing and/or no stop date is available, the PaO2/FiO2 ratio will be considered until date of study completion/ discontinuation or date of death respectively.

Baseline is defined as first observation of PaO2/FiO2 ratio (individual start value).Basic statistics for the PaO2/FiO2 ratio for both the absolute values and the absolute change from baseline will be tabulated by day of ventilation. Daily means will be used when more than one assessment is available per day.

Absolute values and absolute change in notified sequential organ failure assessment score (mSOFA score) over time

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

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

SOFA score (protocol version 4.0 and lower) will be listed only.

Time to a 2-point decrease in WHO's 11-Point Score system

Time to 2-point decrease [days] = Assessment date of first >= 2 improvement - Date of randomization.

Patients without documented 2-point decrease who completed the study or was early terminated or discharged from hospital before Day 28 will be censored at the date of last WHO assessment available.

Time to 2-point decrease will be analyzed using Kaplan-Meier estimates and plots, log-rank test, and Cox proportional hazards model (adjusted for center and age to derive hazard ratios and corresponding 95% confidence intervals).

Kaplan-Meier estimates and Log-rank test

Kaplan-Meier table (product-limit "survival" estimates with 95%-CI, Standard error, Number of patient with event, Number of patient at risk) for Time to 2-point decrease [days], Kaplan-Meier Summaries of Event/Censoring (Number of patient with event, Number of patient censored, Total number of patients), Quartile Estimates (Median Time to Event,1st Quartile, 3rd Quartile, 95%-CI) and Kaplan-Meier table ("survival" estimates with 95%-CI) for Timepoint (28 days). Time to 2-point decrease [days] will be displayed by a Kaplan-Meier-curve. Treatments groups will be compared with Log-rank test.

Cox proportional hazards model

The hazards ratio along with its associated 95% confidence intervals as well as parameter estimate and p-value (two-sided) will be reported.

Absolute values and absolute change in lymphocyte counts over time

Results of lymphocyte counts will be converted to standard unit before any calculation if needed. Conversion of all lab values will be described in a separate document.

Basic statistics for both the absolute values and the absolute change from baseline will be tabulated by visit.

Absolute values and absolute change in C-reactive protein levels over time

Results of C-reactive protein will be converted to standard unit before any calculation if needed. Conversion of all lab values will be described in a separate document.

Basic statistics for both the absolute values and the absolute change from baseline will be tabulated by visit.

Absolute values and absolute change in D-dimer over time

Results of CD-dimmer will be converted to standard unit before any calculation if needed. Conversion of all lab values will be described in a separate document.

Basic statistics for both the absolute values and the absolute change from baseline will be tabulated by visit.

Absolute values and absolute change in log transformed levels of LDH over time

Results of LDH will be converted to standard unit before any calculation if needed. Conversion of all lab values will be described in a separate document. Standardized results will be log transformed for this endpoint.

Basic statistics for both the absolute values and the absolute change from baseline will be tabulated by visit.

Time to hospital discharge

Time to hospital discharge [days] will be calculated as Date discharge from hospital - Date of randomization.

The first discharge from hospital will be used for this endpoint. Patients without hospitalization or without documented hospital discharge who completed the study or was early terminated before Day 28 will be censored at the date of study completion or discontinuation respectively. Patients who have died before Day 28 will be censored at the date of death.

Time to hospital discharge will be analyzed using Kaplan-Meier estimates and plots, log-rank test, and Cox proportional hazards model (adjusted for center and age to derive hazard ratios and corresponding 95% confidence intervals).

Kaplan-Meier estimates and Log-rank test

Kaplan-Meier table (product-limit “survival” estimates with 95%-CI, Standard error, Number of patient with event, Number of patient at risk) for Time to hospital discharge [days], Kaplan-Meier Summaries of Event/Censoring (Number of patient with event, Number of patient censored, Total number of patients), Quartile Estimates (Median Time to Event,1st Quartile, 3rd Quartile, 95%-CI) and Kaplan-Meier table (“survival” estimates with 95%-CI) for Timepoint (28 days). Time to hospital discharge [days] will be displayed by a Kaplan-Meier-curve. Treatments groups will be compared with Log-rank test.

Cox proportional hazards model

The hazards ratio along with its associated 95% confidence intervals as well as parameter estimate and p-value (two-sided) will be reported.

Hospitalization data will be listed additionally.

Change in viral RNA over time

Basic statistics for both the absolute values and the absolute change from baseline will be tabulated by visit.

4.5 Safety Analysis

Adverse events (AEs) and serious adverse events (SAEs)

AEs will be coded by using the Medical dictionary for regulatory activities (MedDRA) version 23.0.

A treatment emergent adverse event (TEAE) is defined as an AE with AE onset date >= date of first study medication. If a date is unknown or incomplete and the AE cannot definitely be considered as started before date of first study medication, the AE will be considered as TEAE, unless the AE resolution date is before the date of first study medication.

An AE overview table will be prepared showing the number of patients with at least 1 AE and at least 1 TEAE, TEAEs related to IMP, TEAEs related to IMP procedure (infusion), serious TEAEs, serious TEAEs related to IMP and serious TEAEs related to IMP procedure (infusion) as well as the total number of events in each category.

TEAEs as well as serious TEAEs will be tabulated by system organ class and preferred term (MedDRA). The number of events, as well as the number and rate of affected patients will be reported for each treatment group. Additional tables will be provided for TEAEs (system organ class and preferred term) summarized by severity, by relationship to IMP and by relationship to IMP procedure (infusion).

AEs that occur with AE onset date < date of first study medication are defined as “pre-treatment” events. All AEs for patients without treatment will be considered as pre-treatment AEs. Pre-treatment AEs will be listed only.

Individual patient data listings will be provided for all SAEs as well as additionally for all deaths only (AEs with outcome ‘Fatal’), unexpected adverse drug reactions as confirmed by the sponsor’s drug safety manager (AEs of patients with primary reason for discontinuation ‘Occurrence of a severe adverse reaction (SAR)’), discontinuation of IMP due to AEs (AEs with action taken regarding IMP ‘Drug interrupted’ or ‘Drug withdrawn’), or premature trial termination due to AEs (AEs of patients with primary reason for discontinuation ‘Adverse events necessitating withdrawal from the clinical trial’).

The important risks such as multi-organ failure, hypersensitivity, adverse hemodynamic effects and cardiovascular effects will be documented as AEs and will be listed and tabulated by system organ class and preferred term (MedDRA) for treatment emergent adverse events. The number of events, as well as the number and rate of affected patients will be reported for each treatment group. Pre-treatment emergent adverse events will be listed only.

Vital signs

Vital signs include Systolic blood pressure, Diastolic blood pressure, Heart rate, Body temperature and Respiratory rate.

Basic statistics will be computed for absolute values and the absolute change from baseline.

Vital signs will be tested before and after each dose (within 30 min before/after IMP administration) and only once at the visits without IMP. Baseline is defined as Screening value. Daily mean values of assessments before/after IMP administration will be used for calculation of absolute change from baseline at visits with IMP administration.

Oxygen saturation (part of vital signs, but measured only once per visit)

Oxygen saturation will be presented using basic statistics of absolute values for all visits and change from baseline for all after baseline visits.

Clinical laboratory assessments

All continuous results of laboratory data will be converted to standard unit before any calculation if needed. Conversion of all lab values will be described in a separate document.

Value evaluation (Normal / Abnormal – CS / Abnormal – Not CS) will be summarized for all laboratory parameters using frequency table additionally.

Absolute values as well as absolute change from baseline for the following laboratory data will be analysed by visit using basic statistics:

- Biochemistry: AST (GOT), ALT (GPT), Alkaline Phosphatase (AP), Total bilirubin, Total protein, Uric acid, Potassium, Sodium, Albumin, Urea Nitrogen (BUN), Creatinine, eGFR

(assessment is calculated according to the formula used in local laboratory: CKD-EPI, Cockcroft-Gault or MDRD)

- Inflammatory indicators: C-reactive protein (CRP), ESR, Procalcitonin
- Myocardial enzymes: Creatine kinase (total), CKMB, LDH, [alpha] - hydroxybutyrate dehydrogenase ([alpha] -HBD), Troponin (cTnI), Blood lactic acid
- Hematology: Red blood cells (RBC), Hematocrit, White blood cells (WBC), Hemoglobin, Platelets
- Coagulation: Prothrombin time (PT), Activated partial thromboplastin time (APTT), D-dimer, FIB
- Urinalysis: pH, Microscopic examination Red blood cells (BLD), Microscopic examination White blood cells (LEU)
- Stool routine and occult blood: Red blood cells (RBC), White blood cells (LEU)

Frequencies will be provided for the following categorical laboratory results by visit:

- Urinalysis: Glucose, Protein, Red blood cells (BLD), White blood cells (LEU)
- Stool routine and occult blood: Red blood cells (RBC), White blood cells (LEU), Occult blood

All abnormal evaluations (CS as well as not CS) for all laboratory assessments collected in eCRF will be listed.

ECG parameters

ECG evaluation (Normal / Abnormal – CS / Abnormal – Not CS) will be summarized using frequency table.

All clinically significant abnormal ECG values inclusive all ECG parameters (Heart rate [bpm], RR interval [ms], PR interval [ms], QT interval [ms], QRS complex [ms]) will be listed as well.

Detection of viral nucleic acid or viral gene sequencing

Detection of viral nucleic acid or viral gene sequencing data will be presented using frequency tables and listing.

4.6 Biomarker Analysis

All continuous results of laboratory data will be converted to standard unit before any calculation if needed. Conversion of all lab values will be described in a separate document.

No statistical testing procedures will be applied to Biomarker analyses.

Absolute values as well as absolute change from baseline for the following biomarker data will be analyzed by visit using basic statistics:

- Li-Heparin blood collection tube (5-6 ml):
  - 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)
  - NT-proBNP, Ferritin
  - Aldosterone
  - Angiotensin-converting enzyme 2 (ACE2) activity and concentration
- EDTA blood collection tube (5-6 ml):
  - Plasma-Renin-Concentration (PRC)

- Cytokines: Interleukin 6 (IL-6), Interleukin 8 (IL-8), soluble tumor necrosis factor receptor type II (TNFR-II), Plasminogen activator inhibitor type-1 (PAI-1), von Willebrand factor (vWF-A2), Tumor necrosis factor-α (TNF-α)
- Alveolar epithelial markers: Soluble receptor for advanced glycation end products (RAGE), Surfactant protein-D (SP-D)
- Endothelial markers: Angiopoietin-2
- Immune function and COVID-19 antibodies: Immunoglobulin A (IgA), Immunoglobulin G (IgG) and Immunoglobulin M (IgM),)Anti-SARS-CoV-2 antibody

Serology

The proportion of patients with positive or negative test results for HIV, Hepatitis B and Hepatitis C will be tabulated.

All serology data will be listed as well.

Clinical laboratory markers associated with poor outcome over time

Clinical laboratory markers associated with poor outcome (e.g., lymphocyte counts, D-Dimer, CRP) is a part of safety analysis (clinical laboratory assessments) and secondary endpoints. Absolute values as well as absolute change from baseline for this endpoint will be presented together with other clinical laboratory assessments.

4.7 Missing Values

No missing value imputation methods will be applied.

4.8 Data Base Closure and Blind Data Review Meeting (BDRM)

A data base closure will be performed prior to the analysis. All parameters will be checked, as specified in the data validation plan, and all queries resolved before data base closure and analysis.

A data review will be conducted prior to unblinding based on all data to check for protocol deviations and to allocate the patients to the analysis sets. At least the following items will be discussed:

- Informed consent procedure: ICF not or too late signed and dated by patient/investigator
- Violation of any 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

These evaluations and assessments will be done together and in agreement with the Sponsor, however FGK in cooperation with CTC North will provide the Sponsor with the appropriate patient listings (as defined in Appendix A). Data review can be done via a telephone conference or in writing.

The affiliation of subjects to the SAF, FAS, and the PP set will be done prior to unblinding.

Data unblinding will be done after data base closure / data review. The unblinded data including formats will be provided from CTC North to FGK for final analysis.

4.9 Miscellaneous

For qualitative variables the frequencies (absolute and relative) are calculated. If no further remark is given in the description of the tables, following format will be used for all tables with qualitative variables (Note: In shift tables the percentages are based on the overall Total and not on the column Totals):

	Y-variable(s) (e.g., treatment group)					
	Category 1		Category 2		Total	
X-variable(s)	N	%	N	%	N	%
Category 1	xx	xx.x	xx	xx.x	xx	xx.x
Category 2	xx	xx.x	xx	xx.x	xx	xx.x
Missing	xx	xx.x	xx	xx.x	xx	xx.x
Total	xx	100.0	xx	100.0	xx	100.0

For this standard format the description of the tables in Appendix A determines only the X- and Y-variables. If another format of table is described in the details to the tables, the real design will be determined by the technical possibilities within SAS and may not look identical to the provided example. However, all information as displayed will be included.

Quantitative parameters will be described by declaring the mean value, standard deviation, minimum, first quartile, median, third quartile, and maximum. In the description of the tables this will be denoted by „basic statistics“. In general, minimum and maximum will be presented to the same level of precision as the raw data; means and medians, standard deviation, and quartiles will be presented to one further decimal place. P-values will be reported to four decimal places (i.e., 0.xxxx).

For frequency tables, all missing values (including user-defined missing values) will be combined in one category “missing” and included in the calculation of percentages. Percentages will be presented to one decimal place.

Tables and graphics will be presented only for scheduled visits.

The listings are always sorted by treatment group, center, and patient. If a different sorting order should be used for some listings this will be remarked separately. The variables for the special listings are explicitly given in the description of listings. All listings will be presented for the safety analysis set, if not stated differently, and indicator variables for further analysis sets, e.g., full analysis set, will be added if needed.

Enrolled but not treated patients (e.g. withdrawal before treatment) will be considered in tables and listings describing disposition of subjects, analysis sets as well as listings of PDs.

The following title will be used for all generated tables, listings, and graphs:

3570: APN01-01-COVID19 – final analysis Page # of #

<Table/Listing/Graph NNN: Description of contents>

<Subtitle for description of contents - if applicable>

<Analysis set>

The numbering NNN of the tables/listings/graphs will be stated in the detailed description (Appendix A).

Following footnote will be used for all generated tables, listings, and graphs:

Date: <Actual date(ddmmmyyyy)> Program: <Name of program>

All tables, listings, and graphs will be generated in A4 paper format.

The statistical evaluation will be performed using SAS version 9.4 or higher.

5 Changes from Protocol

In the following any changes on statistical aspects as described in the protocol are given:

- Wording of WHO's Proposed Core Outcome Measure Set for Clinical Studies of COVID-19 Infection for consistence (secondary endpoint):
  - Protocol: Time to a 2-point decrease in WHO scoring schema
  - SAP: Time to a to a 2-point decrease in WHO's 11-Point Score system
- Covariables used in statistical models and dynamic randomization
  - Protocol: Age as continuous variable
  - SAP: Age as dichotomous variable (<65 years vs. >= 65 years)

6 Signatures

Statistician:
Nataliia Semenenko FGK Clinical Research GmbH Heimeranstr. 35 80339 München Germany
11 Jan 2021 (Date (ddmmmyyyy)) — SN (Signature)

Sponsor:
Sonja Höller APEIRON Biologics AG Campus-Vienna-Biocenter 5 1030 Vienna, Austria
11 Jan 2021 (Date (ddmmmyyyy)) — (Signature)