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STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Vehicle-Controlled, Multicenter, Parallel-Group Study of APL-9 in Mild to Moderate Acute Respiratory Distress Syndrome Due to COVID-19

IND Number:	148361
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Phase:	Phase I / II
Sponsor:	Apellis Pharmaceuticals, Inc
Analysis Plan Version:	2.0
Analysis Plan Date:	11MAY2021

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	30OCT2020	New Document
2.0	11MAY2021	1, Updated the signatories. 2, Updated languages for clarity per protocol amendment 3. CCI [redacted] 4, Clarified full analysis set definition in section 4.4. 5, Removed per protocol set. 6, Added stratified Log-rank test and Cox regression method for analysis of time-to-event endpoints in section 6.2.1.

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SIGNATURE PAGE

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the study, and all applicable regulatory guidance and guidelines.

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Prepared by: Date

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Reviewed and Approved by: Date

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Apellis Pharmaceuticals, Inc

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AH50	Complement Alternative Pathway Assay
ATC	Anatomical Therapeutic Chemical
ARDS	Acute Respiratory Distress Syndrome
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
ICF	Informed Consent Form
ITT	Intent-to-Treat
KM	Kaplan-Meier
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
SAE	Serious Adverse Event

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Abbreviation	Term
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard deviation
SOA	Schedule of Assessments
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment
TEAE	Treatment-Emergent Adverse Event
TCC	Terminal Complement Complex
WHO	World Health Organization

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1. INTRODUCTION

This statistical analysis plan (SAP) describes detailed statistical methods to be used for data handling procedures, analysis and data presentation for Apellis study protocol APL9-COV-201: A Randomized, Double-Blind, Vehicle-Controlled, Multicenter, Parallel-Group Study of APL-9 in Mild to Moderate Acute Respiratory Distress Syndrome Due to COVID-19.

This document has been prepared according to study protocol version 1.0, Amendment 3.0 dated 09 November 2020 and eCRF version 6.0 dated 25 November 2020. The analyses specified in this document supersede the analysis plan described in the study protocol.

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2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is to evaluate the safety of APL-9 compared with that of vehicle control (as add-on therapy to standard of care) in subjects with coronavirus disease 2019 (COVID-19) who have respiratory failure, including mild to moderate acute respiratory distress syndrome (ARDS).

2.1.2 Secondary Objectives

The secondary objectives of this study are to evaluate the effect of APL-9 on:

- Hospital length of stay
- Overall survival
- Change in Sequential Organ Failure Assessment (SOFA) score
- Time on mechanical ventilation
- Time on oxygen therapy (i.e., time on mechanical ventilation or supplemental oxygen therapy)
- APL-9 pharmacokinetics (PK)
- APL9 pharmacodynamics (PD; the effect of APL9 on complement, and inflammation biomarkers)

2.1.3 Exploratory Objectives

The exploratory objectives of this study are to evaluate:

- The effect of APL-9 on presence of active SARS-CoV-2 infection
- The effect of APL-9 on new oxygen therapy use during the study (re-initiation 24 hours or more after cessation of prior oxygen therapy)
- The effect of APL9 on new mechanical ventilation use (re-initiation 24 hours or more after cessation of prior mechanical ventilation)
- CCI [redacted]

2.2 Endpoints

2.2.1 Primary Objective Endpoint

- Cumulative incidence of treatment-emergent serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs)

2.2.2 Secondary Objective Endpoints

- Hospital length of stay (measured in days)

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- Any-cause mortality (measured from beginning of treatment until the safety follow-up assessment 30 days after last study treatment [up to and including Study Day 51 with a +7-day window])
- SOFA score
- Total duration of mechanical ventilation (measured in days)
- Total duration of oxygen therapy (on mechanical ventilation or supplemental oxygen)
- APL-9 PK parameters
- Observed values and changes from baseline in markers of complement activation (C3, C3a, C4, C4a, Bb, C5a, TCC, and alternative complement pathway hemolytic activity [AH50]), coagulopathy (reticulocyte count, schistocytes, lactate dehydrogenase, D-dimer, ferritin, haptoglobin, fibrinogen,), and inflammatory cytokines (C-reactive protein, tumor necrosis factor α, IL-1β, and IL-6)

2.2.3 Exploratory Objective Endpoints

- Presence of active SARS-CoV-2 infection at the end-of-treatment visit. Presence of SARS-CoV-2 viral RNA or viral antigen may be detected in respiratory specimens (collected using nasopharyngeal or oropharyngeal swabs) with a qualitative nucleic acid amplification test (such as reverse transcriptase polymerase chain reaction [RT-PCR]), viral antigen test, or other diagnostic method that is authorized, cleared, or approved by the US Food and Drug Administration (or equivalent local authority) for SARS-CoV-2 viral detection. Serology-based antibody tests do not detect the presence of virus and therefore are not considered diagnostic and cannot be used for study eligibility screening or for subsequent SARS-CoV-2 assessments.
- Incidence, duration, and extent of new oxygen therapy use (re-initiation 24 hours or more after cessation of prior oxygen therapy)
- Incidence, duration, and extent of new mechanical ventilation use (re-initiation 24 hours or more after cessation of prior mechanical ventilation)
- CCI [redacted]

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3. STUDY DESIGN

3.1 Overview of Study Design

This is a randomized, double-blind, vehicle-controlled, multicenter, parallel-group Phase 1/2 study (with an initial open-label period) evaluating the safety and efficacy of APL-9 versus those of vehicle as an add-on therapy to standard of care in subjects who have respiratory failure (including mild to moderate ARDS) due to COVID-19 infection.

The study will be conducted in 2 parts:

Part 1 (Open-Label Period):
Initially, a cohort of 6 subjects will receive open-label treatment with APL-9 as add-on therapy to standard of care from Day 1 through Day 7 or resolution of ARDS (PaO2/FiO2 ratio >300 mm Hg), whichever occurs earlier. Resolution of ARDS in this study is defined according to the Berlin definition as PaO2/FiO2 ratio >300 mm Hg (ARDS Definition Task Force 2012).

An independent data monitoring committee (DMC) will review the clinical data available for all 6 subjects once the last subject in Part 1 reaches Day 7 or is discharged following the resolution of ARDS (PaO2/FiO2 ratio >300 mm Hg). The DMC will recommend to the sponsor whether:

- the study can proceed to Part 2, and
- the maximum allowed treatment duration in Part 2 can be extended. (The DMC can extend the treatment duration beyond Day 7 up to and including Day 21; refer to Part 2 [Randomized Double-Blind Period]).

Follow-up safety assessments for each subject will be collected 30 days following the last dose of APL-9 (with a +7-day window). These assessments will be conducted via inpatient assessment (for patients still hospitalized) or by telephone call (for patients discharged).

Part 2 (Randomized Double-Blind Period):
Part 2 of the study will only be initiated upon recommendation from the DMC. Required criteria for initiation of Part 2 will include 1) No fatal/life-threatening SAEs thought possibly related to APL-9 by the DMC, and 2) no more than 1 subject requiring premature treatment discontinuation by the investigator due to AEs or abnormal lab tests. All subjects will receive standard of care independent of their randomization. Approximately 60 subjects will be randomly assigned at a 1:1 ratio to blinded treatment with either APL-9 or saline vehicle. Subjects will receive treatment with APL-9 or vehicle from Day 1 through Day 7, discontinuation of respiratory support (supplemental oxygen or mechanical ventilation), or hospital discharge, whichever occurs latest.

Subjects may receive treatment beyond Day 7 if the DMC approves an extended treatment duration following the review of data from Part 1 or during the conduct of Part 2. The DMC may approve any extended treatment duration up to and including Day 21; extended treatment will be allowed

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only in subjects who still require respiratory support (oxygen supplementation or mechanical ventilation) at Day 7 with an improved PaO2/FiO2 ratio of at least a 20mm Hg from baseline if arterial blood gas (ABG) test results are available for comparison. If ABG test results are not available, an improvement in FiO2 of at least 4% in nonventilated patients (eg, those on nasal cannula) and 10% in mechanically ventilated patients is needed. FiO2 should be weaned following the site's protocol to keep oxygen saturation at 89% or above. Treatment beyond Day 7 and up to and including any DMC-approved extension will be at the discretion of the investigator.

Follow-up safety assessments for each subject will be collected 30 days following the last dose of study treatment (up to and including Study Day 51 with a +7-day window). Safety assessments may be performed any time during the 30-day follow-up period at the investigator's discretion but are required 30 days after the last dose of study drug (up to and including Study Day 51 with +7day window). These assessments will be conducted via inpatient assessment (for subjects still hospitalized) or by telephone call (for subjects discharged).

The DMC will perform safety and efficacy data reviews on an ongoing basis during Part 2. Two reviews will be required in Part 2:

1. After the 10th subject reaches the approved treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge, whichever occurs latest
2. After the 30th subject reaches the approved treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge, whichever occurs latest

If the DMC approves an extended treatment period following Part 1 or at any time through the conduct of Part 2, the DMC's safety and efficacy data reviews will be initiated when the 10th and 30th subjects reach the approved extended treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge, whichever occurs latest. For example, if, following Part 1, the DMC approves treatment through Day 14 in Part 2, the DMC will be required to review safety and efficacy after the first 10 patients reach Day 14 of treatment, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge, whichever occurs latest. Enrollment will not be suspended during the DMC reviews.

If a subject is treated up to the maximum allowed treatment duration and must discontinue treatment, treatment may not be reinitiated even if the DMC subsequently approves a longer treatment duration.

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3.2 Sample Size and Power Considerations

In Part 1 of the study, a cohort of 6 subjects will receive open-label APL-9 (as add-on therapy to standard of care), and safety data will be evaluated to determine initiation of Part 2. No formal sample size calculation was performed.

In Part 2 of the study, with approximately 30 subjects treated in each treatment group (APL-9 plus standard of care vs Vehicle Control plus standard of care), there is a greater than 95% chance of an SAE being reported if the true incidence is 10% or higher. Similarly, there is a 26%, 71%, or 89% chance of an SAE being reported if the true incidence is 1%, 4%, or 7%, respectively.

3.3 Randomization (Part 2 Only)

In Part 2, approximately 60 subjects will be randomly assigned to receive either APL-9 plus standard of care or vehicle control plus standard of care at 1:1 ratio. Randomization will be stratified by need of mechanical ventilation (yes vs no) and age (younger than 65 years vs at least 65 years).

3.4 Blinding (Part 2 Only)

All subjects or their legally assigned representatives, investigators, and all study personnel involved in the conduct of the study, including data management and biostatistics, will be blinded to treatment assignment. Study drug infusion bags are prepared by dilution of the study drug in isotonic saline for infusion by an unblinded pharmacist at the study site and transferred to site personnel for administration to subjects according to their assigned randomization number.

Unblinded tables, figures, and listings will be provided to the DMC for review. An unblinded, independent biostatistician will be assigned to prepare the randomization schedule and unblinded tables, figures, and listings for the DMC. The unblinded statistician will not otherwise participate in study procedures.

Unblinding is discouraged but will be permitted in a medical emergency that requires immediate knowledge of the subject's assigned treatment. All subjects should be treated as though they are receiving APL-9. Emergency unblinding will be acceptable only if it affects the medical management of the subject.

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4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The screened set will include all subjects who provide written informed consent. This set will be used only for the purpose of describing subject disposition.

4.2 Safety Set

The safety set will include all subjects who received at least 1 dose of study treatment. This set will be used for safety analyses. Subjects will be analyzed according to the actual treatment they received.

4.3 Intent-to-Treat Set

The intent-to-treat (ITT) set will include all randomized subjects. Subjects will be analyzed according to their assigned treatment, regardless of the actual treatment received. This set will be used for supportive efficacy analyses.

4.4 Full Analysis Set

The full analysis set (FAS) set will include all randomized subjects who receive at least one dose of study treatment. The analyses using the FAS will be based upon the actual treatment allocated. The FAS will be used for all efficacy analyses.

4.5 Pharmacokinetic Set

The pharmacokinetic (PK) set is defined as all subjects in the safety set and for whom at least 1 PK sample is evaluable.

4.6 Pharmacodynamic Set

The pharmacodynamic (PD) set is defined as all subjects in the safety set with at least 1 PD evaluation.

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5. STUDY SUBJECTS

Unless otherwise specified, study subjects will be summarized for each part. Study subjects will be analyzed by treatment group in Part 2.

Unless otherwise stated, listing will be provided for safety set for Part 1 and for ITT set for Part 2.

5.1 Subjects Disposition

The following disposition categories will be tabulated for screened set:

- Number of subjects with informed consent form signed
- Number of subjects with screen failure
- Number of subjects randomized (Part 2 Only)
- Number and percentage of subjects who received at least one dose of study treatment
- Number and percentage of subjects with ≥ 1 post-dose PK assessment
- Number and percentage of subjects with ≥ 1 post-dose PD assessment
- Number and percentage of subjects who completed the study treatment
- Number and percentage of subjects who discontinued study treatment and primary reasons of study treatment discontinuation
- Number and percentage of subjects who completed the study
- Number and percentage of subjects who discontinued from study and primary reasons of study discontinuation

Percentage will be calculated based on number of subjects in safety set. A separate listing will be provided for screen failures along with the reasons.

5.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for safety set including:

- Age at screening (years)
  If not collected, then it will be calculated as (year of informed consent form signed - birth year)
- Age in categories (<65 years and ≥ 65 years)
- Sex, Childbearing Potential, Race, Ethnicity
- Baseline Weight (kg), Height (cm), Body Mass Index (BMI, kg/m^2)
- Randomization Stratification Factors (Part 2 Only)
- Baseline use of mechanical ventilation, Baseline use of supplemental oxygen
- Baseline Respiratory Rate, Oxygen Saturations, Temperature, Blood Pressure (Systolic and Diastolic), Heart Rate
- Baseline Level of Consciousness
- Baseline Sequential Organ Failure Assessment (SOFA) score

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5.3 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. The frequency count and percentage of patients experiencing any medical conditions will be tabulated by system organ class (SOC) and preferred term (PT). If a preferred term or system organ class were reported more than once for a patient, the patient would only be counted once in the incidence for that preferred term or system organ class.

5.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary March 2020 version.

Prior medications are defined as any medications, other than study drug, with a stop date before the first dose of study drug.

Concomitant medications are medications, other than study drug, being taken on or after the first dose of study drug and up to the end of study. Medications that started before the first dose of study drug and were ongoing on the date of the first dose of study drug will be considered as concomitant medications. Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification system level 2 (therapeutic main group) and preferred name, using the numbers and percentages of patients who received the medications. A subject who takes more than one medication will be counted only once if these medications belong to the same extended ATC classification.

5.5 Prior and Concomitant Procedures

Prior and concomitant procedures will be coded using World Health Organization (WHO) Drug Dictionary March 2020 version.

Prior procedures are defined as any procedures with a stop date before the first dose of study drug. Concomitant procedures are procedures performed on or after the first dose of study drug and up to the end of study. Procedures that started before the first dose of study drug and were still ongoing on the date of the first dose of study drug will be considered as concomitant procedures.

Prior and concomitant procedures will be summarized by the procedures performed, using the numbers and percentages of patients who received the procedures.

5.6 Exposure to Study Drug

The following parameters will be calculated and presented for safety set:

- Duration of treatment (days) defined as (the start date of last infusion – the start date of first infusion date + 1)
- Number of infusions received (1 infusion, 2 infusions, etc.)

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- Number of infusions completed
- Number of infusions interrupted
- Number and percentage of patients with any dose interruption
- Number and percentage of subjects with infusion related reaction

Details of study treatment exposure will be listed for safety set.

5.7 Measurements of Treatment Compliance

Compliance (%) = total dose administered (mg) / total dose prescribed (mg) x 100

Total dose administered (mg) is defined as the sum of the actual doses (mg) administered. Total dose prescribed (mg) is defined as the sum of the doses (mg) prescribed. If the investigator instructs the study staff to interrupt study medication for a time interval, e.g. due to an adverse event, then this period will not be included in the denominator for the compliance calculation.

Drug compliance will be summarized for the safety population by number and percentage of subjects in increments of 10% (e.g., $\geq$ 70% - $<$ 80%, $\geq$ 80% - $<$ 90% and $\geq$ 90 - $\leq$100%).

Treatment compliance will be listed for safety set.

5.8 Protocol Deviations

All protocol deviations will be reviewed and documented before database lock. Protocol deviations are recorded into Clinical Trial Management System (CTMS). Protocol deviations can be detected by (but not limited to) the subject, investigational site personnel, site management, data management, safety/pharmacovigilance, medical monitoring, biostatistics, auditors, and regulators. They may also be identified through programmable checks of the data.

Key protocol deviations include any violations of inclusion and exclusion criteria. This includes unknown violations at enrolment and on-study violations, such as taking a prohibited medication.

The CRO/Apellis will classify major and minor protocol deviations per the agreed protocol deviation management plan. The Apellis study team will review the protocol deviations and their classification throughout the study and before database lock.

Number and percentage of subjects with protocol deviation will be tabulated by importance of deviation for safety set in Part 1 and ITT set in Part 2.

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6. EFFICACY ANALYSIS

All efficacy analyses will be summarized for each study part. Efficacy data will also be analyzed by treatment group in Part 2. Hypothesis testing will be performed for part 2 between two treatment groups.

Unless otherwise specified, baseline for all efficacy analyses is defined as the last non-missing measurement recorded prior to taking the first dose of study drug.

All CIs will be presented as 2-sided 90% and/or 95% CIs. All statistical tests will be 2-sided hypothesis tests performed at the 10% level of significance.

The primary efficacy analyses will be performed for full analysis set (FAS). The supportive efficacy analyses will be performed for Intent-to-Treat (ITT) set.

6.1 Analysis of Primary Efficacy Endpoint

Not Applicable.

6.2 Analysis of Secondary Efficacy Endpoints

6.2.1 Time-to-event endpoints

The following time-to-event endpoints are defined as:

- Hospital length of stay: initiation of study drug (Day 1, for Part 1) or randomization date (for Part 2) to hospital discharge. For subjects with death of any cause or withdrawal of study participation, hospital length of stay will be imputed with the longest hospital length of stay observed in the study.
- Overall survival: initiation of study drug (Day 1, for Part 1) or randomization date (for Part 2) to death of any cause; censored at the last day known to be alive.
- Total duration of mechanical ventilation defined as days on mechanical ventilation during the study participation, calculated as follows:
    - For subjects with death of any cause (or withdrawal of study participation), total duration of mechanical ventilation will be imputed with the longest duration observed in the study.
    - For any subject who is on mechanical ventilation at the initiation of study drug (Day 1, for Part 1) or at the randomization date (for Part 2), total duration of mechanical ventilation is calculated from Day 1 or randomization date.
    - For any subject who is not on mechanical ventilation at the initiation of study drug (Day 1, for Part 1) or at the randomization date (for Part 2), patient will be excluded.
- Total duration of oxygen therapy defined as days on mechanical ventilation or supplemental oxygen during the study participation, calculated as follows:

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- For subjects with death of any cause (or withdrawal of study participation), total duration of oxygen therapy will be imputed with the longest duration observed in the study.
- For any subject who is on mechanical ventilation or supplemental oxygen at the initiation of study drug (Day 1, for Part 1) or at the randomization date (for Part 2), total duration of oxygen therapy is calculated from Day 1 or randomization date.
- For any subject who is not on mechanical ventilation or supplemental oxygen at the initiation of study drug (Day 1, for Part 1) or at the randomization date (for Part 2), patient will be excluded.

The p-values will be from a 2-sided unstratified Log-rank test and stratified Log-rank test by the randomization stratification factors [need of mechanical ventilation (yes vs no) and age (younger than 65 years vs at least 65 years)] at 0.1 significant level for evaluation of treatment difference. These time-to-event endpoints will be summarized via Kaplan-Meier (KM) methodology using the 25th, 50th (median), and 75th percentiles and pre-specified timepoints, each with associated 2-sided 90% confidence intervals. Point estimate of hazard ratio will be obtained from a Cox regression model with treatment and the randomization stratification factors as fixed factors and the 90% CI will be obtained using Wald method.

6.2.2 Sequential Organ Failure Assessment (SOFA) score

Organ failure status will be assessed using the SOFA score (see Table 1), which assesses 6 organ systems: respiration, coagulation, liver, cardiovascular, central nervous system, and renal (Ferreira et al., 2001). A subject will be defined as being free of organ failure when the SOFA score is zero. The SOFA score will be assessed at baseline on Day 1 and as listed in the schedule of assessment (SOA), based on worst daily values. SOFA score at each assessment and changes from baseline over time will be summarized using descriptive statistics.

Table 1: Sequential Organ Failure Assessment (SOFA) Scoring

Variables	0	1	2	3	4
Respiration					
PaO_2/FiO_2, mmHg	>400	≤400	≤300	≤200[a]	≤100[a]
or SpO_2/FiO_2, mmHg	≥512	≥357 to <512	≥214 to <357	≥89 to <214	<89
Coagulation					
Platelets × $10^3/\mu L$	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin, mg/dL[b]	<1.2	1.2 -1.9	2.0 -5.9	6.0 -11.9	>12.0
Cardiovascular					

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Hypotension	No hypo-tension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any dose)[c]	Dopamine >5, epinephrine ≤0.1, or norepinephrine ≤0.1[c]	Dopamine >15, epinephrine >0.1, or norepinephrine >0.1[c]
Central nervous system					
Glasgow Coma Scale score[d,e]	15	13 -14	10 -12	6 -9	<6
Renal					
Creatinine, mg/dL or urine output (mL/d)[f]	<1.2	1.2 to 1.9	2.0 to 3.4	3.5 to 4.9 or <500	>5.0 or <200

Abbreviations: FiO2 = fraction of inspired oxygen; MAP = mean arterial pressure.
[a] Values are with respiratory support
[b] To convert bilirubin from mg/dL to µmol/L, multiply by 17.1
[c] Adrenergic agents administered for at least 1 hour (doses are given in µg/kg/min).
[d] For subjects who are intubated, the verbal response is scored as:
5 – Seems able to talk
3 – Questionable ability to talk
1 – Generally unresponsive
[e] For subjects who are sedated, use an estimated score for Glasgow Coma Scale (the assumption is 15, if no other factors than sedation affect Glasgow Coma Scale score).
[f] To convert creatinine from mg/dL to µmol/L, multiply by 88.4
Source: Ferreira et al. 2001.

6.3 Analysis of Exploratory Endpoints

6.3.1 Presence of active SARS-CoV-2 infection on at the end-of-treatment visit

Viral RNA assessment will be performed at the end-of-treatment visit. In the case where viral RNA assessment data is unavailable or patient died during the study, that subject will be treated as having a positive viral RNA test result. Fisher exact and/or chi-square test will be used to compare the proportion of subjects who have negative viral RNA test result between two treatment groups.

6.3.2 Incidence, duration, and extent of new oxygen therapy use (re-initiation 24 hours or more after cessation of prior oxygen therapy)

The number and percentage of patients reporting new oxygen therapy use (i.e., mechanical ventilation or supplemental oxygen therapy) as well as types of new oxygen therapy use will be tabulated by treatment groups. The duration of new oxygen therapy use will be calculated from the re-initiation of oxygen therapy use. For subjects with death of any cause or withdrawal of study participation after the re-initiation of oxygen therapy use, the duration of new oxygen therapy use will be imputed with the longest duration observed in the study. The duration of new oxygen therapy use will be presented by descriptive statistics.

6.3.3 Incidence, duration, and extent of new mechanical ventilation use (re-initiation 24 hours or more after cessation of prior mechanical ventilation)

The number and percentage of patients reporting new mechanical ventilation use, and types of new mechanical ventilation use will be tabulated by treatment groups. The duration of new mechanical

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ventilation use will be calculated from the re-initiation of mechanical ventilation use. For subjects with death of any cause or withdrawal of study participation after the re-initiation of mechanical ventilation use, the duration of new mechanical ventilation use will be imputed with the longest duration observed in the study. The duration of new mechanical ventilation use will be presented by descriptive statistics.

6.3.4 CCI

[redacted]

7. SAFETY ANALYSIS

Safety endpoints include AEs, clinical laboratory variables, vital signs, and ECG variables.

Unless otherwise specified, all safety analysis will be performed by study part and treatment group for the safety set.

7.1 Adverse Events

Adverse events (AEs) will be coded using the most recent version of MedDRA (version 23.0). Adverse event severity level will be classified into mild, moderate, severe by investigators. For incidence summaries, a missing severity of an AE will be conservatively imputed as severe. Handling rules for missing severity of AEs are described in Section 12.6.5.

AEs are classified as related to study drug if AEs are definitely or possibly related to study drug. Any AEs with missing or unknown relationship will be considered as related to study drug (Section 12.6.6).

Treatment emergent adverse events (TEAEs) are defined as those AEs that develop or worsen in severity after the first dose of study drug and up to 30 (+7) days beyond the last dose of study drug.

All summaries of AEs described in this section will be on TEAEs. An overall summary of the number of subjects with TEAEs as well as the total number of events will be presented, including the number and percentage of subjects with

- any TEAEs,
- treatment-emergent serious adverse events (SAEs),
- treatment-related TEAEs,
- treatment-related SAEs,
- infusion site reaction TEAEs,

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- TEAEs leading to dose modification (dose reduction or interruption),
- TEAEs leading to treatment discontinuation,
- TEAEs leading to study discontinuation,
- TEAEs leading to death.

The number and percentage of patients reporting TEAEs will be tabulated by SOC and PT; by SOC, PT, and maximum severity.

In summary, the following types of tables will also be provided:

- TEAEs by SOC and PT
- TEAEs by SOC, PT and maximum severity
- Treatment-emergent SAEs by SOC and PT
- Treatment-related TEAEs by SOC and PT
- Treatment-related SAEs by SOC and PT
- Infusion site reaction TEAEs by SOC and PT
- TEAEs leading to dose modification by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT

If a SOC or PT was reported more than once for a subject, the subject would only be counted once in the incidence for that SOC or PT. For subjects experiencing the same PT at multiple severities, the occurrence of the AEs with the maximum severity will be counted in the analysis of incidence by severity. For subjects experiencing the same PT at multiple relationship levels, the occurrence of the AEs with the strongest relationship to study drug will be counted in the analysis of incidence by relationship to study drug.

The following listing will be provided for the Safety Population:

- All AEs
- Serious Adverse Events
- AEs leading to dose modification
- AEs leading to treatment discontinuation
- AEs leading to study discontinuation
- AEs leading to Death

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7.2 Clinical Laboratory Data

The detailed lab parameter list is summarized in Table 2 (Page 47) of study protocol APL9-COV-201 amendment 3. Continuous laboratory parameters will be normalized by converting values in original units to values in SI units and classified as normal, abnormal low, or abnormal high on normal ranges supplied by the local laboratories and upon employing standardization.

Observed values and change from baseline of clinical laboratory data (serum chemistry, hematology, coagulation, complement activation and inflammation, and continuous urinalysis parameters) will be summarized at each analysis visit. Categorical laboratory data will also be tabulated by the number and percentage of patients of each category at each analysis visit.

Frequency of abnormal (out-of-range) laboratory values will be tabulated by analysis visit.

If lab values are beyond detectable limit, the detectable limits will be used for analysis. The original collected values will be presented in the listings.

Clinical laboratory data will be presented in listings. Out of range laboratory results with their corresponding changes from baseline will be listed in separate listings.

7.3 Vital Signs

Observed value and change from baseline of vital signs (including systolic and diastolic blood pressure, respiration rate, oxygen saturations, heart rate, and temperature) will be summarized at each analysis visit.

Observed values and changes from baseline values will be listed. In the listing, values of potential clinical importance will be flagged. These are defined as:

Table 2: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria	
		Observed Value	Change from Baseline
Systolic blood pressure (mmHg)	High	≥180	Increase of ≥20
	Low	≤90	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	≥105	Increase of ≥15
	Low	≤50	Decrease of ≥15
Heart rate (beats per minute)	High	≥120	Increase of ≥15
	Low	≤50	Decrease of ≥15

7.4 Electrocardiogram (ECG)

Observed values and changes from baseline for ECG parameters (including heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval) will be summarized by analysis visit.

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Number and percentage of subjects with abnormal ECG interpretation will also be summarized at each analysis visit.

ECG data will also be presented in listing.

8. PHARMACOKINETIC ANALYSIS

8.1 Drug Concentration

The observed values and changes from baseline of APL-9 concentrations will be summarized for pharmacokinetic (PK) set at each scheduled time point using descriptive statistics (including at least mean, SD, CV, Min, Max, Geometric Mean, and %CV). The number and percentage of subjects with a BLQ value will also be tabulated. The handling of BLQ in the summary table is described in Section 8.2.

Linear and log-linear individual concentration profile plots against the actual study visit will be produced by study part and treatment group.

Linear and log-linear mean concentration plots against the actual study visit will be generated by study part and treatment group. The number of subjects contributing to each mean value at a visit will be presented above the x-axis.

A listing of concentration data will be presented by study part and treatment group. The actual time, deviation, and percent deviation from nominal time will be listed.

All summaries and analyses of the pharmacokinetic data will be based on the PK set.

8.2 Handling BLQ Values

APL-9 concentrations reported as below the limit of quantification (BLQ) will be taken as zero for linear plots, and equal to the lower limit of quantification (LLOQ) for semi-logarithmic plots. For the computation of descriptive statistics, BLQ will be taken as zero, except for the calculation of the geometric mean where the LLOQ will be used.

For the estimation of PK parameters, concentrations that are recorded as BLQ prior to the first quantifiable value will be set to 0. Concentrations that are recorded at the end of the sampling period (i.e. no further quantifiable concentrations) will be set to missing and will not be used for the estimation of parameter values. If a BLQ value falls between two quantifiable concentrations the value will be set equal to the LLOQ, unless its exclusion can be justified (e.g. implausibility given the profile observed and known PK properties).

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9. PHARMACODYNAMIC ANALYSIS

9.1 Pharmacodynamic Data

The pharmacodynamic (PD) endpoints will be evaluated using the PD Population.

Observed values, changes from baseline and percentage changes from baseline in PD endpoints will be summarized by study part and treatment group at each protocol specified time point using descriptive statistics. PD markers include the following:

- complement activation (C3, C3a, C4, C4a, Bb, C5a, TCC, and alternative complement pathway hemolytic activity [AH50]),
- coagulopathy (reticulocyte count, schistocytes, lactate dehydrogenase, D-dimer, ferritin, haptoglobin, fibrinogen),
- inflammatory cytokines (C-reactive protein, tumor necrosis factor α, IL-1β, and IL-6).

Spaghetti plots for individual observed values and individual changes from baseline will be presented graphically. Actual sampling times will be used for the graphical presentation of individual data.

Observed values, changes from baseline, and percentage changes from baseline will also be presented graphically by study part and treatment group. Nominal sampling times will be used for the display in plots.

PD parameters will be listed together with changes from baseline and percentage changes from baseline by study part and treatment group.

10. INTERIM ANALYSIS

There is no planned interim analysis.

11. INDEPENDENT DATA MONITORING COMMITTEE

The independent data monitoring committee (DMC) for this study will be appointed by the sponsor in accordance with its standard procedures. The remit, roles, and responsibilities of the DMC will be specified in a separate DMC charter. The analysis will be performed based on a separate statistical analysis plan.

12. DATA HANDLING CONVENTIONS

12.1 General Data Reporting Conventions

Categorical variables will be tabulated as number of subjects and percentage of total number of subjects in the given analysis set as noted for each category. Percentages will be reported to one decimal place.

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Descriptive statistics will be used to summarize continuous variables including number of subjects, mean, standard deviation (SD), median, first quantile (Q1), third quantile (Q3), minimum, and maximum. Mean, median, Q1 and Q3 will be reported to 1 more decimal place than the raw data, while the SD will be reported to 2 more decimal places than the raw data. Minimum and maximum will be reported the same as the original data.

In general, all analyses will be performed by study part and treatment groups unless otherwise specified. Subject specific listings will be provided by study part, treatment, subject ID, visit and date, if applicable.

All summaries and statistical analysis will be performed by SAS v9.4 or later.

12.2 Definition of Study Days

Unless otherwise stated, study days of an assessment or event are defined as number of days relative to the patient's first dose date.

- For assessment/event on/after the first dose date, study days are calculated as
  Date of assessment/event – the first dose date + 1
- For assessment/event before the first dose date, study days are calculated as
  Date of assessment/event – the first dose date

12.3 Definition of Baseline

Unless otherwise stated, baseline is defined as the last non-missing measurement prior to or on the first administration of study drug (Study Day 1). Baseline can be on the same date as the first dose, given the measurement is expected prior to first dose when only date information is available. If there are repeated measurements with more than one evaluable result for the visit which could not be distinguished by time, mean value will be defined as baseline.

12.4 Definition of Visit Windows

Data will be summarized and analyzed based on the list of visits specified in the schedule of assessments (SOA) of the protocol. All the post-baseline records will be assigned to an appropriate analysis visit using the rules below:

- For the post-baseline visits, the lower and the upper bound for the analysis visit windows are defined as the midpoints of the target date of the scheduled visits.
- If the date of assessment falls in between the lower bound and the upper bound for a visit as specified in the schedule of assessments of the protocol, then it will be assigned to that visit.
- If the interval separating 2 scheduled visits is an even number of days, the middle day will be included in the lower bound of the next visit.

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- End of Treatment visit for subjects who discontinued the study early and unscheduled visits will be mapped to post-baseline scheduled visits if they fall in a scheduled visit window. If assessment result is available in the original post-baseline scheduled visit, then the record will be used in the analysis. If assessment from the original post-baseline scheduled visit is unavailable, then the assessment result mapped from unscheduled/end of treatment visit will be used for analysis. If there are more than one unscheduled/end of treatment visits mapped to the same window, the one closer to the target day will be used for analysis. If more than one visits have the equal distance to the target day, then the earlier one will be used for analysis. If more than one visits on the same day, the time or the sequence number will be used to select the earlier record. If more than one visits on the same day and could not be differentiated by the time or the sequence number, mean value will be used for analysis.

12.5 Repeated or Unscheduled Assessments

For repeated measurements with more than one evaluable result at the same visit, mean value will be used for analysis. For repeated measurements with only one evaluable result at the same visit, then the evaluable assessment will be used for analysis. For unscheduled measurements, the records will be mapped to scheduled post-baseline visits according to visit windows described in section 12.4 above.

The repeated and unscheduled measurements will be presented in the listings.

12.6 Handling of Missing, Unused, and Spurious Data

12.6.1 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the safety set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date will be used in the calculation of treatment duration.

12.6.2 Missing or Partial Dates for Medications

When determining prior or concomitant medications, partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date.

- Medication start dates with a missing day and non-missing month and year will be assumed to have occurred on the first day of the non-missing month, except for medications occurring in the same month and year as the first dose of investigational drug, in which case the start date will be the first dose date.
- Medication start dates with missing day and month and non-missing year will be assumed to have occurred on the first day of the non-missing year (i.e., 01 January).
- A missing medication start date will be coded as the first dose date.

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- Medications that are not ongoing and have a medication stop date with a missing day and non-missing month and year will be assumed to have stopped on the last day of the non-missing month, except for medications stop in the same month and year as the last study date, in which case the stop date will be the last study date.
- Medications that are not ongoing and have a medication stop date with missing day and month and non-missing year will be assumed to have stopped on the last day of the non-missing year (i.e., 31 December), except for medications stop in the same year as the last study date, in which case the stop date will be the last study date.

Imputation of missing or partial dates for medications is used only to determine whether an event is prior or concomitant medication, data listings will present the missing or partial date as recorded in the eCRF.

12.6.3 Missing or Partial Dates for Procedures

For records with a missing or partial procedure date, the following steps will be employed to determine whether the procedure is prior or concomitant:

- Procedure start dates with a missing day and non-missing month and year will be assumed to have occurred on the first day of the non-missing month, except for procedures occurring in the same month and year as the first dose of study treatment, in which case the start date will be the first dose date.
- Procedure start dates with missing day and month and non-missing year will be assumed to have occurred on the first day of the non-missing year (i.e., 01 January).
- A missing procedure start date will be coded as the first dose date.
- Procedures that are not ongoing and have a procedure stop date with a missing day and non-missing month and year will be assumed to have stopped on the last day of the non-missing month, except for procedure stop in the same month and year as the last study date, in which case the stop date will be the last study date.
- Procedures that are not ongoing and have a procedure stop date with missing day and month and non-missing year will be assumed to have stopped on the last day of the non-missing year (i.e., 31 December), except for procedure stop in the same year as the last study date, in which case the stop date will be the last study date.

Imputation of missing or partial dates for procedures is used only to determine whether a procedure is prior or concomitant procedure, data listings will present the missing or partial date as recorded in the eCRF.

12.6.4 Missing or Partial Dates for Adverse Events

When the date of the adverse event is missing or partial for a subject in the safety set, all efforts should be made to resolve the full date from the investigator. The following conventions will be used to impute partial dates for adverse events. Note that the imputed values outlined here may not

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always provide the most conservative date. Under those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

1. Start Dates

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then: If the year matches the first dose date year, then impute the month and day of the first dose date. Otherwise, assign 'January'.
- If the day is unknown, then: If the month and year match the first dose date month and year, then impute the day of the first dose date. Otherwise, assign the first day of the month.

2. Stop Dates

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then assign 'December', except for the event stop in the same year as the last study date, in which case the stop date will be the last study date.
- If the day is unknown, then assign the last day of the month, except for the event stop in the same month and year as the last study date, in which case the stop date will be the last study date.

If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Imputation of missing or partial dates for adverse events is used only to determine whether an adverse event is treatment-emergent and calculation of duration of adverse events; data listings will present the missing or partial date as recorded in the eCRF.

12.6.5 Missing Severity Assessment for Adverse Events

- If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned.
- If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned.

The imputed values for severity assessment will be used for incidence summaries, while the actual values recorded in the eCRF will be used in data listings.

12.6.6 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned.

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12.6.7 Detectable Limits of Clinical Laboratory Variables

Lab results beyond the detectable limits will be reported as detectable limits for calculating descriptive statistics. Original values will be listed.

13. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

14. CHANGES TO ANALYSES

14.1 Changes to Analyses Specified in the protocol

Not applicable

14.2 Changes from Analyses Specified in the Previous Version of the SAP

CCI [redacted]

2, Clarified full analysis set definition in section 4.4.

"The full analysis set (FAS) set will include all subjects who receive at least one dose of study treatment." in SAP v1.0 has been updated to "The full analysis set (FAS) set will include all randomized subjects who receive at least one dose of study treatment.".

The sentence "The full analysis set is the same as the safety set in this study." In SAP v1.0 has been deleted.

3, Removed per protocol set and efficacy analysis based on per protocol set.

4, Added stratified Log-rank test and Cox regression method for analysis of time-to-event endpoints in section 6.2.1.

5, Updated the wording in section 6.3.1 for clarity per study team comments.

15. REFERENCES

ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-2533. doi: 10.1001/jama.2012.5669.

Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001;286(14):1754-1758. doi: 10.1001/jama.286.14.1754.