APL-9

PROTOCOL APL9-COV-201, AMENDMENT 3

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

US IND No.: 148361

Phase: 1/2

Date: 09 November 2020

APPROVAL SIGNATURE

Sponsor's Approval

The protocol has been approved by Apellis Pharmaceuticals, Inc.

Responsible Medical Director:

PPD

PPD

Date

Apellis Pharmaceuticals, Inc
100 5th Avenue
Waltham, MA 02451

INVESTIGATOR'S AGREEMENT

I have received and read the investigator's brochure for APL-9. I have read Protocol APL9-COV-201 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 3 (09 November 2020)

Updates to the protocol implemented in this amendment are provided in the table below. Additions to the protocol are marked in underline; deletions are marked by strikethrough.

Description of change	Section(s) affected by change
Nonsubstantial changes that did not impact content of the document have been made for clarity.	Entire document
Protocol Amendment Summary of Changes: Moved Amendment 2 Summary of Changes to Appendix 3, Amendment History	Protocol Amendment Summary of Changes, Appendix 3
Synopsis Part 1 (Open-Label Period): The DMC will recommend to the sponsor whether: • 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; ~~extended treatment will be allowed only in subjects who still have mild or moderate ARDS at Day 7 with at least a 20-mm Hg increase in PaO_2 from baseline.)~~ refer to Part 2 [Randomized Double-Blind Period].)	Synopsis, Section 7.1
Update regarding Part 2 treatment period: ~~*Subjects may continue treatment for up to 21 days (only in subjects who still require respiratory support at Day 7 with at least a 20-mm Hg increase in PaO_2 from baseline) per DMC recommendation and PI discretion (treatment may be modified at any point during Part 2)~~ *Subjects are eligible to continue treatment for up to and including 21 days if they still require respiratory support at Day 7 with an improved PaO_2/FiO_2 ratio of at least 20 mm Hg from baseline if ABG test results are available for comparison. If ABG test results are not available, an improvement in FiO_2 of at least 4% in nonventilated subjects (eg, those on nasal cannula) and 10% in mechanically ventilated subjects is needed. FiO_2 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 per DMC recommendation and PI discretion (treatment may be modified at any point during Part 2).	Figure 2
Update regarding arterial blood gas test result availability: … extended treatment will be allowed only in subjects who still require respiratory support (oxygen supplementation or mechanical ventilation) at Day 7 with ~~at least a 20-mm Hg increase in PaO_2 from baseline~~ a PaO_2/FiO_2 ratio improved by at least 20 mm Hg from baseline if arterial blood gas (ABG) test results are available for comparison. If ABG test results are not available, an improvement in FiO_2 of at	Synopsis, Section 7.1, Table 1 (footnote a), Section 9.1.1, Section 10.1

Description of change	Section(s) affected by change
least 4% in nonventilated subjects (eg, those on nasal cannula) and 10% in mechanically ventilated subjects is needed. FiO_2 should be weaned following the site's protocol to keep oxygen saturation at 89% or above.	
Add the following exploratory objective: • CCI [redacted]	Section 6.1.3
Deleted the following secondary endpoints: • 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, CCI [redacted] -and inflammatory cytokines (C-reactive protein, tumor necrosis factor α, IL-1β, and IL-6).	Synopsis, Section 6.2.2
Added the following exploratory endpoints: CCI [redacted]	Section 6.2.3
Updated inclusion criterion 3: a. The arterial blood gas (ABG) test is used to determine the PaO_2/FiO_2 ratio. An ABG test should be performed for every subject, but if an ABG test result cannot be obtained, the peripheral oxygen saturation (SpO_2) can be measured and the SpO_2/FiO_2 ratio can be used. b. If the SpO_2/FiO_2 ratio is used for inclusion in the study, it must be >89. See Appendix 1 for more details.	Synopsis, Section 8.1
Updated exclusion criterion 4: Current participation in ~~an interventional~~ a clinical study with an investigational drug or biologic. NOTE: Participation in studies with the following therapies is NOT excluded: a. Therapies approved (indicated) for COVID-19 by the applicable health authority b. Therapies with emergency use authorization for COVID-19 by the US Food and Drug Administration or equivalent authorization by the applicable health authority c. Therapies approved (indicated) by the applicable health authority and used for COVID-19 as part of standard care	Synopsis, Section 8.2
Updated and clarified dosing time frame: • Dosing must occur on Day 1, on the same day as randomization. • In Part 2, subjects will receive treatment up to and including the DMC-approved treatment duration, discontinuation of respiratory	Synopsis, Table 1 (footnote a), Section 7.1, Figure 2, Section 9.1.1, Section 11

Description of change	Section(s) affected by change
support (oxygen supplementation or mechanical ventilation), or hospital discharge (whichever occurs ~~earlier~~ latest). • Through Part 2, the DMC may review efficacy and safety data and recommend changes to the study conduct on an ongoing basis, but it will be required to review efficacy and safety data after the 10th and 30th subjects reach the DMC-approved treatment duration, discontinuation of respiratory support, or hospital discharge (whichever occurs ~~earlier~~ latest). • Subjects who reach the end of the approved treatment duration, discontinuation of respiratory support, or hospital discharge (whichever occurs ~~earlier~~ latest) …	
Clarified end of treatment period: Subjects who reach the end of the approved treatment duration, discontinuation of respiratory support, or hospital discharge (whichever occurs earlier) must be assessed as indicated in the EOT visit column (for example, a subject who reaches the end of the approved treatment and achieves discontinuation of respiratory support ~~for example, a subject who achieves discontinuation of respiratory support~~ on Day 6 should be evaluated with a radiograph or CT scan even though it is not indicated as a Day 6 assessment).	Table 1 (footnote a)
Updated schedule of assessments footnote b: Those subjects who are fully eligible can have baseline and screening assessments on the same day ~~or may qualify for baseline assessments if they have met enrollment requirements within the previous 7 days~~ as baseline, which is defined as the day of initial study drug treatment.	Table 1
Updated schedule of assessments footnote c: ~~Any FDA-approved test may be used for confirmation of SARS-CoV-2.~~ Confirmation of SARS-CoV-2 infection may be completed more than 7 days before baseline. 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), viral antigen test, or other diagnostic method that is authorized, cleared, or approved by the US Food and Drug Administration or equivalent authority) for SARS-CoV-2 viral detection. Note: Serology-based antibody tests do not detect presence of virus and therefore are not considered diagnostic for active infection and cannot be used for study eligibility screening or for subsequent SARS-CoV-2 assessments.	Table 1
Updated schedule of assessments footnote j: Refer to the procedure for handling infusion-related reactions in Section 9.1.1.	Table 1
Updated schedule of assessments footnote k: ~~If confirmation of active SARS-CoV-2 infection has occurred within 7 days of screening, the viral RNA~~	Table 1

Description of change	Section(s) affected by change
~~or viral antigen test at screening/baseline is not mandatory.~~ Confirmation of SARS-CoV-2 infection for screening may be completed more than 7 days before baseline.	
Updated schedule of assessments EOT column to include discharge day and clarified timing of PK/PD samples at the end-of-treatment visit and discharge day visit: Schedule of assessments EOT column and footnote a: EOT and discharge day[a,n] Schedule of assessments footnote m: A PK/PD assessment will be done on the last day of treatment. If EOT and discharge day visit are on different days, a PK/PD sample will be collected on the discharge day visit as an unscheduled visit. Schedule of assessments EOT and discharge day column and footnote n: If EOT and discharge day visit are on different days, perform EOT assessments on the last day of treatment and repeat on the day of discharge as an unscheduled visit. Perform/record vital signs, ECG, concomitant medications/procedures, infusion site reactions, and AEs daily up to and including day of discharge. After EOT, record as unscheduled visits. Section 11.5: Blood will then be collected once daily between 1-2 hours after the first dose on Days 3, 5, 7, 11 (if treatment is ongoing), and 15 (if treatment is ongoing) and at the end-of-treatment visit. ~~(if the patient is discharged on a day not indicated for a clinical laboratory test sample).~~ If the subject is discharged after the end-of-treatment visit, another sample will be collected on the day of discharge. Section 11.6: These blood samples will be collected at the same time as the ~~pharmacokinetic~~ samples described in Section 11.5. ~~Blood will be collected 3 times on Day 1: (1) once prior to administration of the APL-9 bolus, (2) once as soon as possible following the bolus (within 5-10 minutes) prior to the continuous infusion, and (3) once at 2 hours after the beginning of the continuous infusion. If the subject discharges on a day not indicated for a clinical laboratory test sample, blood will be collected between 1-2 hours after first dose of the end-of-treatment (EOT) visit.~~	Table 1, Section 11.5, Section 11.6
Updated schedule of assessments row: Vital signs~~/SpO_2 saturation~~	Table 1
Updated schedule of assessments row: PK (APL-9)/PD (complement, coagulation, and inflammation)[m]	Table 1
Clarification of screening timeline for SARS-CoV-2 infection: Confirmation of SARS-CoV-2 infection may be completed more than 7 days before baseline. All other inclusion and exclusion criteria must be met within –7 days of baseline.	Section 8.4

Description of change	Section(s) affected by change
Clarified study drug administration: Dosing of subjects receiving APL-9 either as open-label treatment or by random, blinded assignment . . . will be initiated with an IV infusion of 180 mg APL-9 in 50 mL of saline over a 10-minute period, followed within 1 hour by continuous infusion of 180 mg APL-9 in 250 mL saline at the rate of 15 mg/h (approximately 21 mL/h) until the end of study drug administration as follows:~~at Day 7 (or approved treatment extension), discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge, whichever occurs earlier. (This results in the infusion of two 250-mL bags, each containing 180 mg of APL-9 every 24 hours.)~~ • Part 1: at Day 7 or until or resolution of ARDS (PaO_2/FiO_2 ratio >300 mm Hg), whichever occurs earlier • Part 2: at Day 7 or up to and including the approved treatment duration, discontinuation of respiratory support (supplemental oxygen or mechanical ventilation), or hospital discharge, whichever occurs latest This results in the infusion of two 250-mL bags, each containing 180 mg of APL-9, every 24 hours.	Section 9.1.1
Clarified study drug administration: Treatment with study drug (APL-9 IV or matching vehicle IV infusion) will terminate ~~either on Day 7 or at hospital discharge (whichever occurs earlier).~~as follows: • Part 1: at Day 7 or until or resolution of ARDS (PaO_2/FiO_2 ratio >300 mm Hg), whichever occurs earlier • Part 2: at Day 7 or up to and including the approved treatment duration, discontinuation of respiratory support (supplemental oxygen or mechanical ventilation), or hospital discharge, whichever occurs latest In Part 2, the ~~The~~ DMC may decide …	Section 10.1
Clarified time points for data collection: See the schedule of assessments (SoA) for data to be collected at the time of discontinuation of study treatment, discharge, and safety follow-up and for any further evaluations to be completed.	Section 10.1
Updated "Lost to Follow-up": A subject will be considered lost to follow-up for failure to complete ~~the study end-of-treatment assessments and are unable to be contacted by the study site through the 30-day follow-up period.~~ safety follow-up assessment 30 days after the last dose of study drug (up to Study Day 51 with a +7-day window). The following actions must be taken if a subject fails to complete the required ~~study end-of-treatment assessments~~ safety follow-up assessment 30 days after the last dose of study drug (up to Study Day 51 with a +7-day window):	Section 10.3

Description of change	Section(s) affected by change
Update study end-of-treatment assessments: • ~~The study end-of-treatment assessments are to be conducted on the day of hospital discharge.~~ The study end-of-treatment assessments are to be conducted at the end of treatment or on the day of hospital discharge, whichever occurs later.	Section 11
Updated Sequential Organ Failure Assessment score variables: • PaO_2/FiO_2 ratio (mm Hg) or SpO_2/FiO_2 ratio—collected and entered into the database locally … [g] SOFA score variables (PaO_2/FiO_2 ratio or SpO_2/FiO_2 ratio,	Section 11.1.1, Table 1 (footnote g)
Clarified adverse event recording time frame: Adverse events and SAEs will be collected from the signing of the consent form ~~until the safety follow-up assessment, or 30 days after the last dose of study treatment, up to Study Day 51 (+7).~~ up to and including the safety follow-up assessment 30 days after the last dose of study drug (up to Study Day 51 with a +7-day window).	Section 11.2.5
Clarified treatment-emergent adverse event time frame: As described in Section 11.2, TEAEs are defined as those AEs that develop or worsen after the first dose of study medication until ~~study end-of-treatment or the early termination follow-up visit.~~ up to and including the safety follow-up assessment 30 days after the last dose of study drug (up to Study Day 51 with a +7-day window).	Section 12.4
CCI [redacted]	Table 2
Calculation of PaO_2/FiO_2 ratio: For the purpose of calculating PaO_2/FiO_2 ratio… 3. ~~If radial artery needle puncture attempt is unsuccessful then attempt radial artery needle puncture in contralateral upper extremity unless contraindicated for any reason.~~ If ABG sampling remains unsuccessful for any reason, then SpO_2 (peripheral oxygen saturation) will be measured and the SpO_2/FiO_2 value will be derived, and the corresponding PaO_2/FiO_2 ratio will be used to determine the SOFA respiratory score according to Table 6. 4. ~~If radial artery puncture unsuccessful or contraindicated, then obtain ABG by placing arterial line, or puncture of femoral artery, or puncture of brachial artery, by qualified provider.~~ ~~5. In the event that ABG sampling remains unsuccessful for any reason, then SpO_2/FiO_2 value will be derived, and the corresponding of PaO_2/FiO_2 ratio will be used to determine the SOFA respiratory score according to Table 6.~~	Appendix 1

2. SYNOPSIS

Name of Sponsor/Company: Apellis Pharmaceuticals, Inc	
Name of Investigational Product, Dosage, and Mode of Administration: APL-9, 30 mg/mL in 6-mL vials for intravenous (IV) infusion in isotonic saline	
Name of Reference Product or Comparator, Dosage, and Mode of Administration: Reference treatment is IV infusion of isotonic saline as vehicle control.	
Name of Active Ingredient: APL-9	
Protocol Number: APL9-COV-201	**Phase: 1/2**
Title of Study: 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	
Objectives: **Primary:** • To evaluate the safety of APL-9 compared with that of vehicle control (as add-on therapy to standard of care [SOC]) in subjects with coronavirus disease 2019 (COVID-19) who have respiratory failure, including mild to moderate acute respiratory distress syndrome (ARDS) **Secondary:** 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 • Assessment of pharmacokinetics and pharmacodynamics	
Endpoints: **Primary:** • Cumulative incidence of treatment-emergent serious adverse events and treatment-emergent adverse events **Secondary:** • Hospital length of stay (measured in days) • 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 (by continuously worn mask or nasal cannula, measured in days)
- APL-9 PK parameters
- Observed values and changes from baseline in markers of complement activation (C3, C3a, C4, C4a, Bb, C5a, terminal complement complex, and alternative complement pathway hemolytic activity), coagulopathy (reticulocyte count, presence of schistocytes, lactate dehydrogenase, D-dimer, ferritin, haptoglobin, fibrinogen), and inflammatory cytokines (C-reactive protein [CRP], tumor necrosis factor α [TNFα], IL-1β, and IL-6)

Overall 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 SOC in subjects with respiratory failure 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 SOC from Day 1 through Day 7 or resolution of ARDS (PaO_2 [partial pressure of oxygen]/FiO_2 [fraction of inspired oxygen] ratio >300 mm Hg), whichever occurs earlier.

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 (PaO_2/FiO_2 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 subjects still hospitalized) or by telephone call (for subjects discharged).

Part 2 (Randomized Double-Blind Period):

Part 2 of the study will be initiated only 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 laboratory tests. All subjects will receive SOC independent of their randomization. Approximately 60 subjects will be randomly assigned in 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 (or up to and including the approved treatment duration), 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 only in subjects who still require respiratory support (oxygen supplementation or mechanical ventilation) at Day 7 with a PaO_2/FiO_2 ratio improved by at least 20 mm Hg from baseline if arterial blood gas (ABG) test results are available for comparison. If ABG results are not available, an improvement in FiO_2 of at least 4% in nonventilated subjects (eg, those on nasal cannula) and 10% in mechanically ventilated subjects is needed. FiO_2 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.

For each subject, follow-up safety assessments will be collected 30 days after the subject's last dose of study treatment (up to and including Study Day 51 with a +7-day window). Assessments between study drug discontinuation and the safety follow-up assessment may be conducted at the investigator's discretion. 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:

- After the 10th subject reaches the approved treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge, whichever occurs latest
- 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 review 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 up to and including Day 14 in Part 2, the DMC will be required to review safety and efficacy after the first 10 subjects 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 and including the maximum allowed treatment duration and must discontinue treatment, treatment may not be reinitiated even if the DMC subsequently approves a longer treatment duration.

Number of Subjects (Planned):

- **Part 1:** 6
- **Part 2:** 60

In Part 1, an initial cohort of 6 subjects will receive open-label APL-9 treatment for up to and including 7 days to assess safety. In Part 2, approximately 60 subjects will be randomly assigned 1:1 to APL-9 or vehicle in order to ensure that there are approximately 58 evaluable subjects.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria:

1. At least 18 years of age at time of informed consent.
2. Diagnosis of active SARS-CoV-2 infection. 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) or 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. Note: Serology-based antibody tests do not detect presence of virus, and therefore are not considered diagnostic for active infection and cannot be used for study eligibility screening or for subsequent SARS-CoV-2 assessments.
3. Have respiratory failure requiring oxygen supplementation **or** have either invasive or noninvasive mechanical ventilation with PaO_2/FiO_2 ratio >100 mm Hg. Respiratory failure cannot be fully explained by cardiac failure or fluid overload.
    a. The arterial blood gas (ABG) test is used to determine the PaO_2/FiO_2 ratio. An ABG test should be performed for every subject, but if an ABG test result cannot be obtained, the peripheral oxygen saturation (SpO_2) can be measured and the SpO_2/FiO_2 ratio can be used.
    b. If the SpO_2/FiO_2 ratio is used for inclusion into the study, it must be >89.
4. Written informed consent for study participation must be provided by the subject (or legally authorized representative) prior to any study-related procedures.

5. Subject (or legally authorized representative) is willing and able to comply with study procedures and assessments, including imaging assessments and venous blood sample(s) per protocol.
6. Each female subject of childbearing potential must have a negative serum pregnancy test at screening and must agree to use protocol-defined methods of contraception from screening through at least 90 days after receiving the last dose of APL-9.
7. Male subjects must agree to use protocol-defined methods of contraception and agree to refrain from donating semen from screening through a minimum of 90 days after receiving the last dose of APL-9.

Exclusion Criteria:

1. Female subjects being pregnant or breastfeeding
2. Active bacterial, fungal, or parasitic infection
3. History of neuromuscular degenerative disease (eg, amyotrophic lateral sclerosis, Duchenne muscular dystrophy, or multiple sclerosis)
4. Current participation in a clinical study with an investigational drug or biologic. NOTE: Participation in studies with the following therapies is NOT excluded:
    a. Therapies approved (indicated) for COVID-19 by the applicable health authority
    b. Therapies with emergency use authorization for COVID-19 by the US Food and Drug Administration or equivalent authorization by the applicable health authority
    c. Therapies approved (indicated) by the applicable health authority and used for COVID-19 as part of standard care
5. Treatment with immune checkpoint inhibitors, or other immunomodulators within 3 months prior to study enrollment (however, treatment with convalescent plasma, steroids, IL-6 inhibitors, and antiviral agents is NOT excluded)
6. Subjects who have, at screening, been on mechanical ventilation for >7 days
7. Evidence of kidney AND liver failure at screening (estimated glomerular filtration rate <45 mL/min/1.73 m^2 and alanine aminotransferase level >5× the upper limit of normal, as assessed by the local laboratory)
8. Subjects with a hereditary complement deficiency

Study Drug Treatments:

Part 1:

Subjects shall receive the institutional SOC to treat their conditions at the discretion of the investigator, including (but not limited to) supplemental oxygen, mechanical ventilation, fluid management, and required medication as provided by the hospital and allowed by the protocol.

All subjects will receive prophylactic broad-spectrum antibiotic therapy from baseline until discontinuation of APL-9. Treatment with antibiotics may be adjusted according to culture results and at the discretion of the investigator.

Dosing with open-label APL-9 will be initiated on Day 1 with an IV infusion of 180 mg APL-9 in 50 mL saline over a 10-minute period, followed within 1 hour by continuous infusion of 180 mg APL-9 in 250 mL saline at the rate of 15 mg/h (approximately 21 mL/h) until Day 7 or resolution of ARDS, whichever occurs earlier. (This results in the infusion of two 250-mL bags, each containing 180 mg of APL-9 every 24 hours.)

Part 2:

Subjects shall receive the institutional SOC to treat their conditions at the discretion of the investigator, including (but not limited to) supplemental oxygen, mechanical ventilation, fluid management, and required medication as provided by the hospital and allowed by the protocol.

All subjects will receive prophylactic broad-spectrum antibiotic therapy from baseline until discontinuation of study drug treatment. Treatment with antibiotics may be adjusted according to culture results and at the discretion of the investigator.

At Day 1 subjects will be randomized in a 1:1 ratio to APL-9 for infusion or matched vehicle control.

Study drug (APL-9 for infusion or matched vehicle control) will be prepared by an unblinded pharmacist at the study site and transferred to blinded site personnel for administration to subjects. One vial of APL-9 (180 mg in

6 mL buffer) will be diluted in a 50-mL saline bag for infusion to initiate the study or in a 250-mL saline bag for the maintenance therapy. Vehicle control will be 50-mL and 250-mL saline bags that are identical in appearance but do not contain APL-9.

The blinded site personnel will initiate therapy with study drug received from the pharmacists on Day 1 with an IV infusion of the 50-mL bag over a 10-minute period, followed within 1 hour by continuous infusion of the 250-mL bag at the rate of approximately 21 mL/h until the end of study drug administration on Day 7 (or longer if DMC allowed), discontinuation of respiratory support, or hospital discharge, whichever occurs latest. This results in the infusion of two 250-mL bags every 24 hours.

Statistical Methods:

All efficacy and safety analyses will be summarized by treatment group.

Continuous variables will be summarized using descriptive statistics (eg, median and mean); for categorical variables, the frequency and percentage in each category will be displayed. Time-to-event data (such as time to hospital discharge and time to mechanical ventilation discontinuation) will be summarized with Kaplan-Meier estimates accounting for censored observations (and analyzed using the Cox proportional hazard model if appropriate).

Treatment-emergent adverse events will be summarized by System Organ Class and Preferred Term, according to the Medical Dictionary for Regulatory Activities. The number of subjects reporting each adverse event Preferred Term will be tabulated for all treatment-emergent adverse events and for those considered by the investigator as being possibly related to study treatment. The number of subjects reporting serious adverse events will also be tabulated.

Independent DMC:

The DMC and its chair will be appointed by the sponsor and will operate according to a charter. The DMC will review safety data and will recommend to the sponsor whether the study may proceed beyond the open-label safety period (Part 1) and whether to continue, terminate, or modify the study during Part 2. Required criteria for initiation of Part 2 will include (1) no fatal/life-threatening serious adverse events 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 adverse events or abnormal laboratory tests. Specifically, the DMC may recommend to the sponsor that the duration of treatment with APL-9/vehicle be extended beyond Day 7 during Part 2. 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 review 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. Enrollment will not be suspended during the DMC reviews.

Treatment duration in Part 2 may be maximally extended up to and including Day 21; extended treatment will be allowed only in subjects who still require respiratory support (oxygen supplementation or mechanical ventilation) at Day 7 with a PaO_2/FiO_2 ratio improved by at least 20 mm Hg from baseline if an ABG test result is available for comparison. If an ABG test result is not available, an improvement in FiO_2 of at least 4% in nonventilated subjects (eg, those on nasal cannula) and 10% in mechanically ventilated subjects is needed. FiO_2 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.

Through the conduct of the study the DMC can recommend any changes to the protocol, including study termination for safety or futility reasons.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/specialist term	Definition
AE	adverse event
AH50	alternative complement pathway hemolytic activity
ARDS	acute respiratory distress syndrome
COVID-19	coronavirus disease 2019
CRF	case report form
CRP	C-reactive protein
DMC	data monitoring committee
eCRF	electronic case report form
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome coronavirus
PaO_2	partial pressure of oxygen
PD	pharmacodynamic
PEEP	positive end-expiratory pressure
PK	pharmacokinetic
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of assessments
SOC	standard of care
SOFA	Sequential Organ Failure Assessment
SpO_2	peripheral oxygen saturation
TCC	terminal complement complex

Abbreviation/specialist term	Definition
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor α

5. INTRODUCTION

The rapid spread of coronavirus disease 2019 (COVID-19), the disease caused by the emerging coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presents an increasing threat to human health globally. Patients with COVID-19 are at risk of progressing to severe complications including acute respiratory distress syndrome (ARDS), pneumonia, pulmonary edema, and organ failure (Chen et al. 2020). These pathologies are driven by massive local and systemic inflammatory events and can be linked intrinsically to overactivation of the complement system (Robbins et al. 1987).

5.1. Study Rationale

Complement overactivation can damage host tissue in numerous pathologies. In the 1970s, the chemoattractant C5a (a product of complement activation) was shown to facilitate neutrophil-mediated damage to the pulmonary endothelium (Craddock et al. 1977). In the 1980s, investigations showed that C5a concentration in plasma is a prognostic marker for ARDS (Hammerschmidt et al. 1980). Subsequently, multiple studies have correlated ARDS severity and progression with complement activation by various products, eg, C1rC1s-C1 inhibitor (Langlois and Gawryl 1988) and C3d/C3 ratio (Duchateau et al. 1984), further substantiating the temporal association between complement activation and ARDS.

Complement has been implicated in many viral respiratory infections, including respiratory syncytial virus (Bera et al. 2011) and influenza A subtypes H5N1 (Ng et al. 2006; Sun et al. 2013) and H7N9 (Sun et al. 2015). More recently, patients with ARDS secondary to SARS-CoV-2 infection have exhibited significant deposits of the terminal complement complex (TCC) C5b-9 in lung and skin specimens (Magro et al. 2020).

Therefore, complement has been postulated as a rational therapeutic target in severe COVID-19 (Campbell and Kahwash 2020). This strategy is supported by preclinical models of other coronaviruses that have caused notable outbreaks. When infected with a mouse-adapted form of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1; the virus that caused the 2003 severe acute respiratory syndrome outbreak), transgenic mice deficient in C3 ($C3^{-/-}$ knockout mice) had viral titers similar to but reduced lung injury and pulmonary inflammation compared with wild-type mice (Gralinski et al. 2018). In a murine model of Middle East respiratory syndrome coronavirus (MERS-CoV) infection (which caused a 2012 outbreak), C5aR blockade reduced lung and spleen damage (Jiang et al. 2018). APL-9 is an investigational drug for intravenous (IV) infusion containing 2 cyclic pentadecapeptides covalently attached at the end of a 10-kDa linear poly(ethylene glycol) chain that bind and inhibit C3 and C3b complement components and therefore block complement activation.

The proposed Phase 1/2 study includes an open-label safety period (Part 1), followed by a randomized, double-blind, vehicle-controlled period (Part 2). Part 2 of this study will assess the safety and efficacy of APL-9 in subjects treated with study intervention (APL-9 in addition to standard of care [SOC]) compared with those in a control group (subjects treated with vehicle in addition to SOC).

5.2. Complement and APL-9 Background

Complement proteins exist in systemic circulation at high concentrations and can undergo rapid activation in response to infection or tissue damage, triggering local and systemic inflammation.

The complement system is composed of 3 activation pathways: classical, lectin, and alternative. Initiation of each pathway generates proteolytic enzyme complexes (C3 or C5 convertases) that cleave peptide bonds in the C3 and C5 proteins. The C3 protein is central to the activation of all 3 pathways of the complement cascade. Proteolytic cleavage of C3 releases the anaphylatoxin C3a and activates C3b, which with the factor B fragment Bb forms C3bBb, an enzyme complex (C3 convertase) with the ability to cleave C3. The C4 protein plays a role in both the classical and lectin pathways of complement activation. Following activation of these pathways, proteolytic enzyme complexes cleave a peptide bond in C4, releasing the anaphylatoxin C4a and activating C4b, which assembles with C2b to form a different C3 convertase, C2bC4b. Downstream of C3 activation, the cleavage of the C5 protein results in the production of the anaphylatoxin C5a and C5b, leading to the formation of the surface-bound membrane attack complex (C5b-9) or its soluble form, the TCC.

APL-9 contains 2 cyclic pentadecapeptides covalently attached at the ends of a 10-kDa linear poly(ethylene glycol) chain. The cyclic peptides bind and inhibit C3 and its C3b fragment and are responsible for the bioactivity of APL-9. The compound is a potent inhibitor of all 3 complement activation pathways and blocks the formation of most associated effector functions, including formation of the membrane attack complex.

In a Phase 1, double-blind, randomized, placebo-controlled, single ascending dose study in healthy volunteers (Study APL9-101), 24 subjects were treated with a single dose of IV APL-9 and 10 subjects were treated with matching placebo. The results of this study confirmed the potent inhibition of complement and established the pharmacokinetic (PK) profile; no significant safety findings were observed.

APL-9 is manufactured under current Good Manufacturing Practices as outlined in the US Code of Federal Regulations (21 CFR §210, 211) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH Q7).

More detailed descriptions of the chemistry, pharmacology, efficacy, and safety of APL-9 can be found in the APL-9 Investigator's Brochure.

5.3. Benefit-Risk Assessment

This is an interventional study in COVID-19 subjects with respiratory failure, including mild to moderate ARDS, a life-threatening complication of SARS-CoV-2 infection. Based on the known pathological role of complement overactivation in ARDS, C3 inhibition by APL-9 may improve pulmonary function in subjects with COVID-19. If efficacious, APL-9 may also reduce COVID-19-associated morbidity and mortality and shorten the length of stay in intensive care and respiratory units, which may be in critical shortage during outbreaks.

Nonclinical studies of SARS-CoV-1 have indicated that complement inhibition had beneficial effects to reduce lung inflammation, and a healthy volunteer clinical study of IV APL-9, a C3 inhibitor, demonstrated acceptable PK and safety profiles. Subjects participating in this study will also receive SOC therapy independent from randomization.

The risks include local adverse effects from IV dosing, adverse effects that are currently unknown, additional infections secondary to COVID-19, possible increased risk of bacterial infection due to complement inhibition, and possible lack of efficacy. All subjects who are to receive study drug treatment will also receive a broad-spectrum antibiotic (see Section 9.5) to counter the theoretical concern of increased risk of bacterial infection due to complement inhibition. As a further subject safety mechanism, the study will initially enroll and treat 6 subjects in an open-label fashion with APL-9 (Part 1). A data monitoring committee (DMC) will review the clinical data collected in Part 1 before Part 2 of the study will be initiated. Required criteria for initiation of Part 2 will include (1) no fatal/life-threatening serious adverse events (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 adverse events (AEs) or abnormal laboratory tests. After Part 2 is initiated, the DMC will perform further reviews of clinical data after the 10th and 30th subjects have reached the approved treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge, whichever occurs latest.

6. OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. 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 SOC) in subjects with COVID-19 who have respiratory failure, including mild to moderate ARDS.

6.1.2. 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
- APL-9 PK
- APL-9 pharmacodynamics (PD; the effect of APL-9 on complement, coagulation, and inflammation biomarkers)

6.1.3. 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 use during the study (reinitiation 24 hours or more after cessation of prior oxygen therapy)
- The effect of APL-9 on new mechanical ventilation use (reinitiation 24 hours or more after cessation of prior mechanical ventilation)
- CCI [redacted]

6.2. Endpoints

6.2.1. Primary Objective Endpoint

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

6.2.2. Secondary Objective Endpoints

- Hospital length of stay (measured in days)
- 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 intervention (measured in days)
- Total duration of oxygen therapy (by continuously worn mask or nasal cannula, measured in days)
- 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, and fibrinogen), and inflammatory cytokines (C-reactive protein [CRP], tumor necrosis factor α [TNFα], IL-1β, and IL-6).

6.2.3. Exploratory Objective Endpoints

- Incidence, duration, and extent of new supplemental oxygen use (reinitiation 24 hours or more after cessation of prior supplemental oxygen therapy)
- Incidence, duration, and extent of new mechanical ventilation use (reinitiation 24 hours or more after cessation of prior mechanical ventilation)
- CCI [redacted]
- 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.

7. STUDY DESIGN

7.1. Overall Study Design

This Phase 1/2 trial includes an initial open-label period (Part 1) before proceeding to a randomized, double-blind, vehicle-controlled, parallel-group period (Part 2). Part 1 of the study is designed to evaluate the safety of open-label APL-9 with SOC in a small number of subjects who have respiratory failure (including mild to moderate ARDS) due to COVID-19 and who require respiratory support (supplemental oxygen or mechanical ventilation). A DMC will analyze the data for Part 1 and decide whether Part 2 of the study will be initiated. 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 laboratory tests. Part 2 of the study is designed to evaluate the safety and efficacy of APL-9 with SOC compared with those of vehicle with SOC in a larger number of subjects who have respiratory failure (including mild to moderate ARDS) due to COVID-19 and who require respiratory support (supplemental oxygen or mechanical ventilation).

Subjects will participate only in either Part 1 or Part 2 of the study (ie, subjects who participate in Part 1 of the study will **not** participate in Part 2).

Further details on the study design for each part of the study are provided below.

Part 1 (Open-Label Period):

Initially, a cohort of 6 subjects will receive open-label treatment with APL-9 as add-on therapy to SOC (CDC 2020) from Day 1 through Day 7 or resolution of ARDS (PaO_2 [partial pressure of oxygen]/FiO_2 [fraction of inspired oxygen] ratio >300 mm Hg), whichever occurs earlier. Resolution of ARDS in this study is defined according to the Berlin definition as PaO_2/FiO_2 ratio >300 mm Hg (ARDS Definition Task Force 2012).

An independent 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 (PaO_2/FiO_2 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 subjects still hospitalized) or by telephone call (for subjects discharged).

Part 2 (Randomized Double-Blind Period):

Part 2 of the study will be initiated only 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 laboratory tests. All subjects will receive SOC independent of their randomization. Approximately 60 subjects will be randomly

assigned in 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 only in subjects who still require respiratory support (oxygen supplementation or mechanical ventilation) at Day 7 with an improved PaO_2/FiO_2 ratio of at least 20 mm Hg from baseline if arterial blood gas (ABG) test results are available for comparison. If ABG test results are not available, an improvement in FiO_2 of at least 4% in nonventilated patients (eg, those on nasal cannula) and 10% in mechanically ventilated patients is needed. FiO_2 should be weaned following the site's protocol to keep oxygen saturation at 89% or above. Treatment beyond Day 7 and through any DMC-approved extension will be at the discretion of the investigator. 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 a +7-day 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 up to and including Day 14 in Part 2, the DMC will be required to review safety and efficacy after the first 10 subjects 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.

7.2. Scientific Rationale for Study Design

This study is designed to evaluate the safety of APL-9 in subjects with respiratory failure due to COVID-19, the disease caused by SARS-CoV-2 infection. Secondary objectives include

assessments of efficacy of APL-9 (evaluating survival, length of hospital admission, and lung function), APL-9 PK results, and the effect of APL-9 on complement activation biomarkers.

This study is being executed during a worldwide outbreak of COVID-19 that has resulted in capacity issues at many medical facilities. Additionally, the highly contagious nature of COVID-19 (compounded by a shortage of personal protective equipment) has caused concerns about the safety of health care providers caring for these seriously sick patients. Consequently, this study is designed to minimize any additional burden on clinical sites, including minimizing the number of assessments and interventions that the study will require in addition to SOC, while still ensuring the safety of subjects.

The first portion of this 2-part study will entail initial DMC review and confirmation of product safety in 6 subjects under open-label treatment conditions. The second part will be a double-blind, vehicle-controlled comparison of safety and efficacy. The investigational product (APL-9 in saline vehicle for infusion) and reference product (vehicle control) will be prepared by unblinded pharmacists and will be indistinguishable to blinded study personnel to limit bias in study assessments. Either APL-9 or vehicle control will be administered as add-on therapy to SOC. Most interventions and assessments may be accomplished in conjunction with SOC, without requiring additional hospital visits or resources.

Subjects with active bacterial, fungal, or parasitic infection are excluded, and enrolled and treated subjects will also receive treatment with a broad-spectrum antibiotic to prevent the theoretical risk of bacterial infections due to complement inhibition. A DMC will conduct periodic reviews of safety and efficacy data to ensure the safety of study subjects and to advise the sponsor on futility.

7.3. Justification for Dose

A single bolus infusion of 180 mg of APL-9 followed by continuous infusion of 360 mg/day will be tested in this study. This will result in an initial dose of 540 mg of APL-9 in the first 24 hours of dosing (followed by 360 mg/day on all subsequent days). This dose and higher doses were well tolerated in a previous study in healthy volunteers and demonstrated comparable PK and complement inhibition to that in prior cynomolgus monkey studies. More detailed information can be found in the APL-9 Investigator's Brochure.

The purpose of this dosing scheme is to achieve rapid complement inhibition by APL-9 upon initiation of treatment, followed by a regimen selected to keep the complement system consistently suppressed for the duration of study drug administration. Discontinuation of dosing is expected to restore normal complement activity within 24 hours.

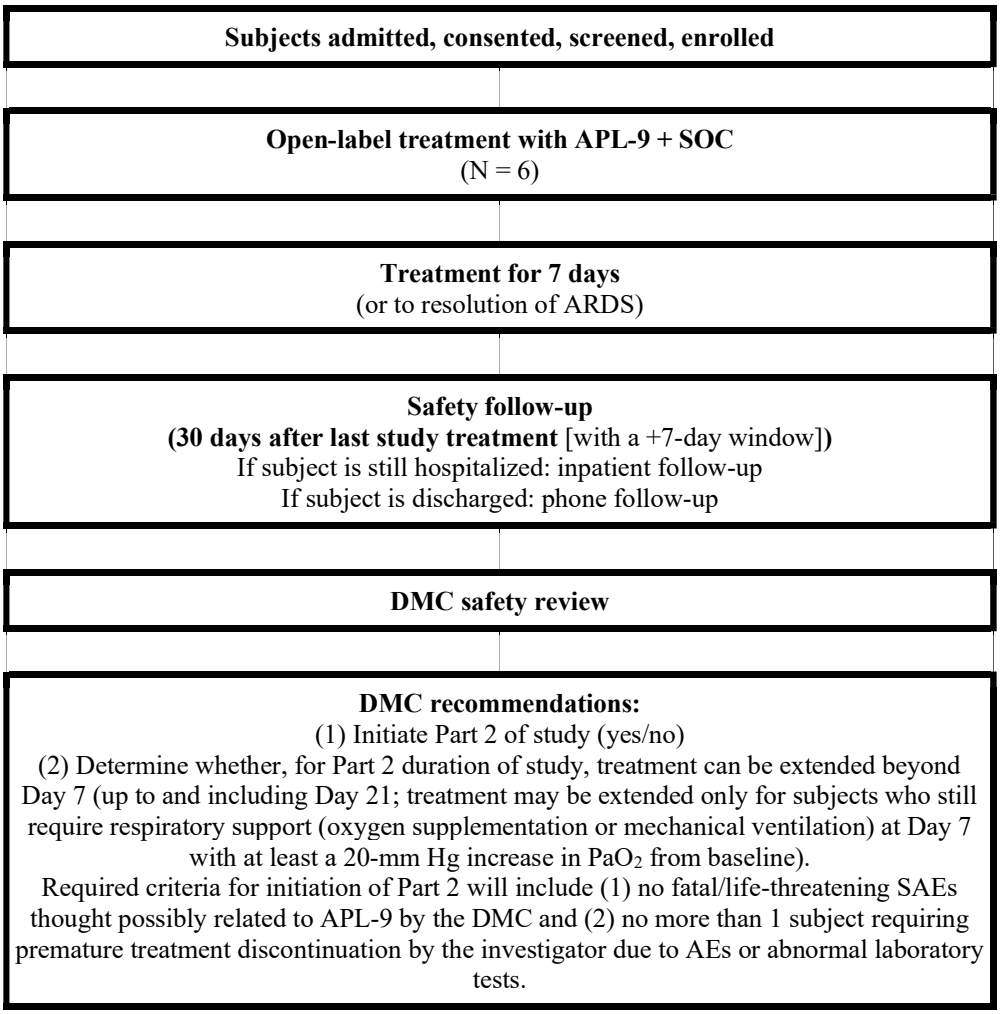
7.4. End of Study Definition

A subject is considered to have completed the study if all obtainable study assessments, including those at the day of discharge from the hospital and during follow-up, have been collected.

The end of the study is defined as the date of the safety follow-up assessment 30 days after the last dose of study drug (up to and including Study Day 51 with a +7-day window) for the last subject in the study.

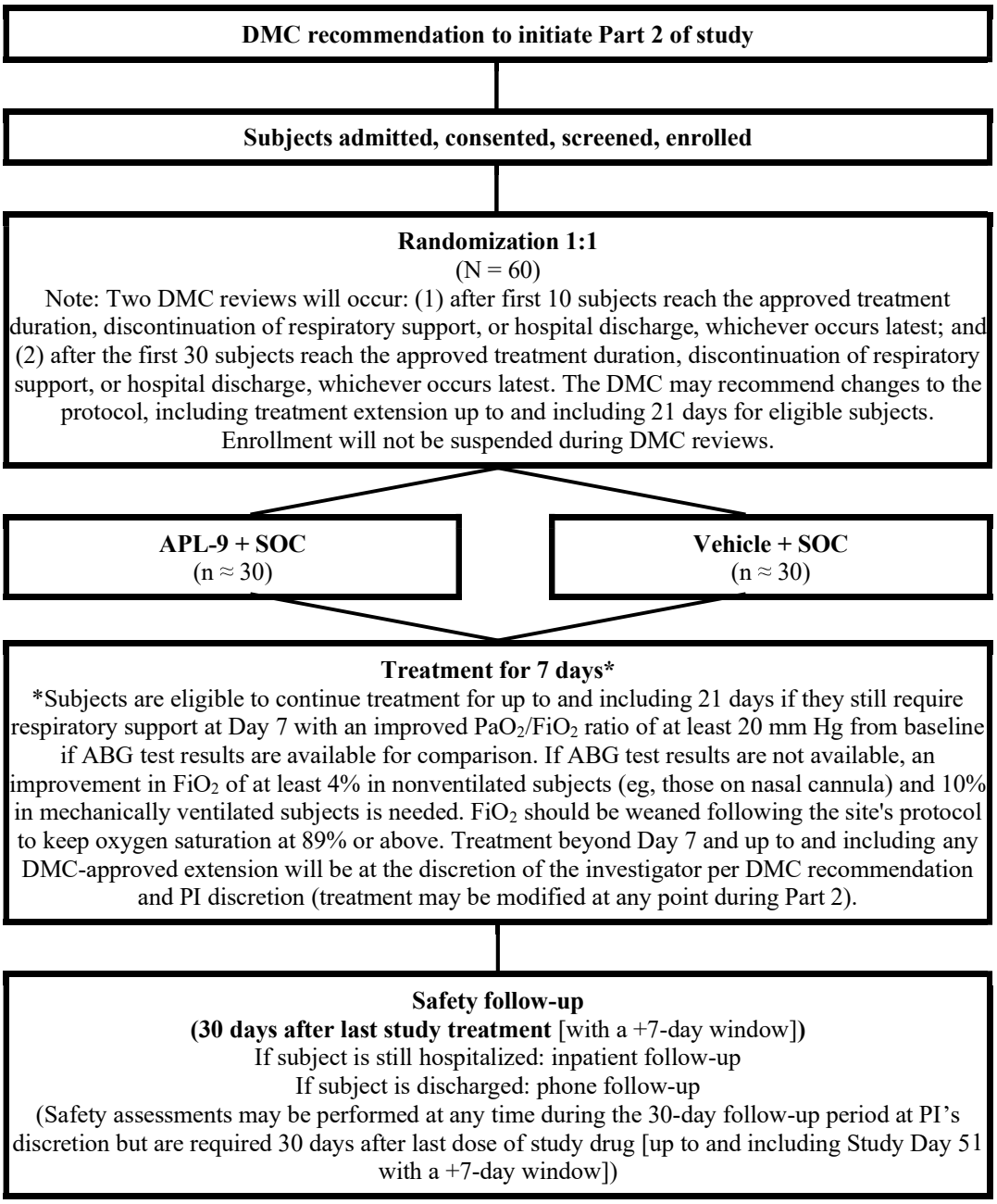
7.5. Study Design and Schedule of Assessments

Figure 1: Study Schema—Part 1



Abbreviations: ARDS = acute respiratory distress syndrome; AEs = adverse events; DMC = data monitoring committee; PaO_2 = partial pressure of oxygen; SAEs = serious adverse events; SOC = standard of care.

Figure 2: Study Schema—Part 2



Abbreviations: ABG = arterial blood gas; DMC = data monitoring committee; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of oxygen; PI = primary investigator; SOC = standard of care.

Table 1: Schedule of Assessments

	Study Day(s)[a]													
	Part 1 and Part 2[a]							Part 2 only [a]					Part 1 and Part 2[a]	
List of activities/assessments	**Screening/baseline –7 to 1[b]**	**2**	**3**	**4**	**5**	**6**	**7**	**8-10**	**11**	**12-14**	**15**	**16-21**	**EOT and discharge day[a,n]**	**Safety follow-up assessment[a] Up to and including Study Day 51 (+7)**
Informed consent[b]	X													
Inclusion/exclusion[b]	X													
SARS-CoV-2 confirmation[c]	X													
Medical history[l]	X													
Demographics	X													
eGFR/ALT	X													
Serum pregnancy test	X													
Height/body weight/BMI[d]	X													
Randomization (Part 2 only)	X													
Study drug administration[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Discharge card dispensation[e]													X	
SAFETY ASSESSMENTS														
Vital signs [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	
SOFA score[g]	X		X		X		X		X		X		X	
Clinical laboratory tests[h]	X		X		X		X		X		X		X	
Viral RNA or viral antigen assessment[k]	X						X				X		X	
Radiograph/CT scan (pulmonary consolidation)	X						X						X	
Concomitant medications and procedures[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infusion site reactions[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHARMACODYNAMIC AND PHARMACOKINETIC ASSESSMENTS														
PK (APL-9)/PD (complement, coagulation, and inflammation)	X		X		X		X		X		X		X [m]	

Abbreviations: ABG = arterial blood gas; AE = adverse event; ALT = alanine aminotransferase; ARDS = acute respiratory distress syndrome; BMI = body mass index; CT = computed tomographic; DMC = data monitoring committee; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOT = end-of-treatment visit; FiO_2 = fraction of inspired oxygen; GCS = Glasgow Coma Scale; ICU = intensive care unit; PaO_2 = partial pressure of oxygen; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOFA = Sequential Organ Failure Assessment; SpO_2 = peripheral oxygen saturation.

[a] Dosing must occur on Day 1, on the same day as randomization. The duration of subject participation in this trial may be variable. In Part 1, subjects may receive open-label treatment through Day 7 or resolution of ARDS (whichever occurs earlier). A DMC will review safety data from Part 1 and determine whether Part 2 can be initiated and whether Part 2 treatment can be extended beyond Day 7. 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 laboratory tests. In Part 2, dosing may be extended only in subjects who still require respiratory support (oxygen supplementation or mechanical ventilation) at Day 7 with an improved PaO_2/FiO_2 ratio of at least 20 mm Hg from baseline if ABG test results are available for comparison. If ABG test results are not available, an improvement of FiO_2 of at least 4% in nonventilated subjects (eg, those on nasal cannula) and 10% in mechanically ventilated subjects is needed. FiO_2 should be weaned following the site's protocol to keep oxygen saturation at 89% or above. Treatment beyond Day 7 and through any DMC-approved extension will be at the discretion of the investigator. In Part 2, subjects will receive treatment up to and including the DMC-approved treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge (whichever occurs latest). Through Part 2, the DMC may review efficacy and safety data and recommend changes to the study conduct on an ongoing basis, but it will be required to review efficacy and safety data after the 10th and 30th subjects reach the DMC-approved treatment duration, discontinuation of respiratory support, or hospital discharge (whichever occurs latest). Enrollment will not be suspended during the DMC reviews. Subjects who reach the end of the approved treatment duration, discontinuation of respiratory support, or hospital discharge (whichever occurs latest) must be assessed as indicated in the EOT and discharge day column (for example, a subject who reaches the end of the approved treatment and achieves discontinuation of respiratory support on Day 6 should be evaluated with a radiograph or CT scan even though it is not indicated as a Day 6 assessment). All subjects will be followed up at the safety follow-up assessment 30 days after last study treatment (up to and including Study Day 51 with a +7-day window), either in person (for subjects still hospitalized) or by phone (for subjects who have been discharged).

[b] Fully eligible subjects can have screening assessments on the same day as baseline, which is defined as the day of initial study drug treatment.

[c] Confirmation of SARS-CoV-2 infection may be completed more than 7 days before baseline. 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), viral antigen test, or other diagnostic method that is authorized, cleared, or approved by the US Food and Drug Administration or equivalent authority for SARS-CoV-2 viral detection. Note: Serology-based antibody tests do not detect presence of virus and therefore are not considered diagnostic for active infection and cannot be used for study eligibility screening or for subsequent SARS-CoV-2 assessments.

[d] Height/weight can be by subject assertion.

[e] Discharged subjects who are followed up by phone will be provided with emergency study cards that include a list of symptoms associated with infections. The study card also guides subjects with instructions to contact their study physicians or seek emergency medical care if they experience any of the listed symptoms.

[f] For continuous variables, the worst observed daily value will be recorded. Vital signs and ECG must be collected between the administration of the loading dose of study treatment and the initiation of the maintenance dose.

[g] SOFA score variables (PaO_2/FiO_2 ratio or SpO_2/FiO_2 ratio, platelets, bilirubin, hypotension/vasopressor use, GCS score, creatinine) are detailed in Section 11.1.1 and Appendix 1.

[h] A list of laboratory assessments is provided in Section 11.1.8. Blood will be collected 3 times on Day 1: (1) once prior to administration of the APL-9 bolus, (2) once as soon as possible following the bolus (within 5-10 minutes) prior to the continuous infusion, and (3) once at 2 hours after the beginning of the continuous infusion. Following that, assessments should be collected within the time frame of each calendar day. The use of silica reagents in coagulation panels should be avoided in subjects treated with APL-9.

[i] The concomitant procedures include recording the day that the subject was admitted to the ICU (or ICU-type environment), use of ventilatory support, use of oxygen therapy, date of ICU discharge, date of hospital discharge, and survival. The time and date of any changes to concomitant medications and procedures are to be recorded at the days indicated in the schedule of assessments. In case of early hospital discharge, the data is collected via phone interviews.

[j] Infusion-related reactions that occur during the administration of the 50-mL loading dose should be treated as follows: For mild infusion-related reactions: The 50-mL bag infusion time should be increased from 10 min to 20-40 min and the reaction should be monitored. Treatment with diphenhydramine may be required. The infusion time of the 250-mL bag should not be increased. For severe or persistent mild infusion-related reactions (instances in which the subject's symptoms do not respond to the increased infusion time), treatment should be discontinued, and the institution's emergency hypersensitivity protocol should be employed. Refer to the procedure for handling infusion-related reactions in Section 9.1.1.

[k] Confirmation of SARS-CoV-2 infection for screening may be completed more than 7 days before baseline.

[l] Vaccination history should be attempted to be collected as a component of medical history.

[m] A PK/PD assessment will be done on the last day of treatment. If EOT and discharge day visit are on different days, a PK/PD sample will be collected on the discharge day as an unscheduled visit.

[n] If EOT and day of discharge visit are on different days, perform EOT assessments on the last day of treatment and repeat on the day of discharge as an unscheduled visit. Perform/record vital signs, ECG, concomitant medications/procedures, infusion site reactions, and AEs daily up to and including day of discharge. After EOT, record as unscheduled visits.

8. STUDY POPULATION

8.1. Subject Inclusion Criteria (Part 1 and Part 2)

A subject must meet all the following criteria for enrollment:

1. At least 18 years of age at time of informed consent.
2. Diagnosis of active SARS-CoV-2 infection. 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 RT-PCR) or 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. Note: Serology-based antibody tests do not detect presence of virus, and therefore are not considered diagnostic for active infection and cannot be used for study eligibility screening or for subsequent SARS-CoV-2 assessments.
3. Have respiratory failure requiring oxygen supplementation **or** have either invasive or noninvasive mechanical ventilation with PaO_2/FiO_2 ratio >100 mm Hg. Respiratory failure cannot be fully explained by cardiac failure or fluid overload.
    a. The ABG test result is used to determine the PaO_2/FiO_2 ratio. An ABG test should be performed for every subject, but if an ABG result cannot be obtained, the peripheral oxygen saturation (SpO_2) can be measured and the SpO_2/FiO_2 ratio can be used.
    b. If the SpO_2/FiO_2 ratio is used for inclusion in the study, it must be >89. See Appendix 1 for more details.
4. Written informed consent for study participation must be provided by the subject (or legally authorized representative) prior to any study-related procedures.
5. Subject (or legally authorized representative) is willing and able to comply with study procedures and assessments, including imaging assessments and venous blood sample(s) per protocol.
6. Each female subject of childbearing potential must have a negative serum pregnancy test at screening and must agree to use protocol-defined methods of contraception from screening through at least 90 days after receiving the last dose of APL-9.
7. Male subjects must agree to use protocol-defined methods of contraception and agree to refrain from donating semen from screening through at least 90 days after receiving the last dose of APL-9.

Acceptable methods of contraception are described in Section 11.2.8. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

8.2. Subject Exclusion Criteria (Part 1 and Part 2)

Subjects are excluded from the study if any of the following criteria apply:

1. Female subjects being pregnant or breastfeeding

2. Active bacterial, fungal, or parasitic infection
3. History of neuromuscular degenerative disease (eg, amyotrophic lateral sclerosis, Duchenne muscular dystrophy, or multiple sclerosis)
4. Current participation in a clinical study with an investigational drug or biologic. NOTE: Participation in studies with the following therapies is NOT excluded:
    a. Therapies approved (indicated) for COVID-19 by the applicable health authority
    b. Therapies with emergency use authorization for COVID-19 by the US Food and Drug Administration or equivalent authorization by the applicable health authority
    c. Therapies approved (indicated) by the applicable health authority and used for COVID-19 as part of standard care
5. Treatment with immune checkpoint inhibitors or other immunomodulators within 3 months prior to study enrollment (however, treatment with convalescent plasma, steroids, IL-6 inhibitors, and antiviral agents is NOT excluded)
6. Subjects who have, at screening, been on mechanical ventilation for >7 days
7. Evidence of kidney failure AND liver failure at screening (estimated glomerular filtration rate <45 mL/min/1.73 m^2 and alanine aminotransferase level >5× the upper limit of normal, as assessed by the local laboratory)
8. Subjects with a hereditary complement deficiency

8.3. Lifestyle Considerations

Because of the nature of the study, no lifestyle considerations are applicable.

8.4. Screening Failures

Sites may initiate screening procedures prior to a subject's diagnosis of respiratory failure or ARDS. Confirmation of SARS-CoV-2 infection may be completed more than 7 days before baseline. All other inclusion and exclusion criteria must be met within –7 days of baseline. Screening failure is defined as the situation of a subject who consents to participate in the clinical study but does not receive study treatment. A minimal set of screening failure information is required to ensure transparent reporting of screening failures to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screening failure details, eligibility criteria, and any SAEs.

Subjects may be rescreened with approval from the sponsor.

9. TREATMENT OF SUBJECTS

9.1. Study Interventions

All subjects participating in this study independent of randomization shall receive the institutional SOC at the discretion of the investigator, to treat their conditions including (but not limited to) supplemental oxygen, mechanical ventilation, fluid management, and required medication as provided by the hospital and allowed by the protocol.

APL-9 is supplied in 6-mL glass vials. Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement, in advance, by Apellis Pharmaceuticals, Inc.

Labels containing study information and pack identification are applied to the investigational product containers.

All investigational product is labeled with a minimum of the following: protocol number, dosage form (including product name and quantity in pack), route of administration, directions for use, storage conditions, batch number and/or packaging reference, the statements "For clinical trial use only" and/or "CAUTION: New Drug—Limited by Federal (or US) Law to Investigational Use," and name and address of the sponsor.

Additional labels may, on a case-by-case basis, be applied to the investigational product in order to satisfy national, local, or institutional requirements but must not do any of the following: contradict the clinical study label, obscure the clinical study label, or identify the study subject by name.

Additional labels may not be added without the prior full agreement of Apellis Pharmaceuticals, Inc.

9.1.1. Study Drug Administration

APL-9 is provided in sterile vials, each containing 180 mg of APL-9 in 6 mL buffer (30 mg/mL). Study drug infusion bags are prepared by an unblinded pharmacist at the study site by dilution of the study drug in isotonic saline for infusion and transferred to site personnel for administration to subjects according to their assigned randomization numbers. Two types of infusion bags containing APL-9 will be prepared:

- 50-mL bag containing 1 vial of APL-9 (ie, 180 mg of APL-9 in 50 mL)
- 250-mL bag containing 1 vial of APL-9 (ie, 180 mg of APL-9 in 250 mL)

Dosing of subjects receiving APL-9 either as open-label treatment or by random, blinded assignment must occur on Day 1, on the same day as randomization, and will be initiated with an IV infusion of 180 mg APL-9 in 50 mL of saline over a 10-minute period, followed within 1 hour by continuous infusion of 180 mg APL-9 in 250 mL saline at the rate of 15 mg/h (approximately 21 mL/h) until the end of study drug administration as follows:

- Part 1: at Day 7 or until or resolution of ARDS (PaO_2/FiO_2 ratio >300 mm Hg), whichever occurs earlier

- Part 2: at Day 7 or up to and including the approved treatment duration, discontinuation of respiratory support (supplemental oxygen or mechanical ventilation), or hospital discharge, whichever occurs latest

This results in the infusion of two 250-mL bags, each containing 180 mg of APL-9, every 24 hours.

Dosing of subjects randomly assigned to vehicle control must occur on Day 1, on the same day as randomization, and will be initiated with an IV infusion of 50 mL of saline over a 10-minute period followed immediately (and up to and including within 1 hour) by continuous infusion of approximately 21 mL of saline per hour until the end of study drug administration at Day 7 (or approved treatment extension), discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge, whichever occurs latest. This results in the infusion of 2 bags of 250 mL saline every 24 hours.

Research nurses or other appropriately qualified personnel will administer the IV infusions.

The pharmacists and investigator can change the size of the infusion bags in the event that 50-mL and 250-mL isotonic saline bags are in short supply if:

- the infusion rates of a 180-mg loading dose of APL-9 in the initial 10 minutes and 15 mg/h thereafter to subjects receiving APL-9 are maintained and
- vehicle-only bags of identical size and appearance are given to the vehicle control group.

In the event that isotonic saline for infusion is not available, the pharmacists must contact Apellis Pharmaceuticals, Inc, to select an alternative vehicle.

The treatments are intended to continue to either Day 7 or until the subject no longer requires respiratory support (oxygen supplementation or mechanical ventilation) or is discharged from the hospital (whichever occurs later), except upon allowance by the DMC and by investigator discretion to administer treatment up to and including Day 21 (Part 2 only; extended treatment will be allowed only in subjects who still require respiratory support at Day 7 with an improved PaO_2/FiO_2 ratio of at least 20 mm Hg from baseline if ABG test results are available for comparison. If ABG test results are not available, an improvement in FiO_2 of at least 4% in nonventilated patients (eg, those on nasal cannula) and 10% in mechanically ventilated patients is needed. FiO_2 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. If treatment is interrupted for any reason for more than 24 hours, treatment may not be resumed.

A relapse of respiratory failure or ARDS due to COVID-19 must be reported as an AE. Under no circumstances can study drug be administered beyond the DMC-approved treatment window, and treatment may not be reinitiated if it is discontinued.

The SOC to be used at each study site will be determined by the investigator. A recent guideline for the treatment of critically ill patients with COVID-19 has been published and should be considered (CDC 2020).

Infusion-related reactions that occur during the administration of the 50- mL loading dose should be treated as follows:

- For mild infusion-related reactions: The 50 mL bag infusion time should be increased from 10 min to 20-40 min and the reaction should be monitored. Treatment with diphenhydramine may be required. The infusion time of the 250-mL bag should not be increased.
- For severe or persistent mild infusion-related reactions (instances in which the subject's symptoms do not respond to the increased infusion time): treatment should be discontinued, and the institution's emergency hypersensitivity protocol should be employed.

9.1.2. Empiric Antibiotic Treatment for Possible Infection

Body temperature, vital signs, relevant blood parameters, and bacterial cultures will be monitored regularly throughout the study to assess for signs of secondary bacterial infections. All enrolled subjects will receive a broad-spectrum antibiotic during the treatment period to cover possible additional serious bacterial infections (see Section 9.5 for details). Subjects who are discharged prior to the allowable treatment duration will have follow-up conducted by phone and will be provided with emergency study cards that include a list of symptoms associated with infections. The study card also guides subjects with instructions to contact their study physician or seek emergency medical care in the event they experience any of the listed symptoms.

9.2. Preparation, Handling, Storage, and Accountability

1. The investigational product should be stored frozen at a nominal temperature of –20 °C. Temperature monitoring is required at the investigator site (or documented storage location) to ensure that the investigational product is maintained within a defined and maintained temperature range.
2. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study intervention.
3. Only subjects enrolled in the study and assigned to active treatment may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Where allowed, the investigator may choose to delegate drug accountability responsibilities to a pharmacist or other appropriate individual.
5. Apellis Pharmaceuticals, Inc, or the clinical study sites may supply infusion sets and saline bags as required. Refer to the pharmacy manual for further details.

6. All unused and used study drug vials should be retained at the study site until they are inventoried by the study monitor. All used, unused, or expired study drug vials will be returned to Apellis Pharmaceuticals, Inc, or its designee for destruction, and destruction will be documented, or if authorized, disposed of at the study site per the site's standard operating procedures and documented. Please refer to the pharmacy manual for further guidance and information.
7. Please refer to the pharmacy manual for further guidance and information.

9.3. Measures to Minimize Bias: Randomization and Blinding

9.3.1. Randomization

The first 6 subjects enrolled will be assigned to open-label APL-9 treatment. For the remaining 60 subjects, approximately 30 subjects will be enrolled in each treatment arm for a total of approximately 60 subjects. Subjects will be randomly assigned (1:1) to receive either APL-9 in addition to SOC or vehicle control plus SOC. Randomization will be stratified by need of mechanical ventilation (yes vs no) and age (younger than 65 years vs at least 65 years).

9.3.2. 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.

9.4. Treatment Compliance

Subjects will receive study drug directly from the investigator or designee, under medical supervision. The date, time, and duration of each dose administered will be recorded in the source documents and in the electronic case report form (eCRF). If treatment is interrupted for any reason for greater than 24 hours, treatment may not be resumed.

9.5. Concomitant Medications

Any medications administered (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), and all procedures performed within 4 weeks of screening will be recorded as prior medications and procedures. Oral history is acceptable from the subject or

caregiver. Medications administered and procedures performed from the time of informed consent through the end-of-treatment visit must be recorded as concomitant, along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

All enrolled subjects will receive a broad-spectrum antibiotic during the treatment period to provide coverage for *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* unless contraindicated because of hypersensitivity or allergy. Treatment with antibiotics may be adjusted according to culture results and at the discretion of the investigator.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

9.5.1. Restricted and Prohibited Medications

The use of any approved or investigational anticomplement therapy other than APL-9 is prohibited within 5 half-lives of that product prior to screening. Use of corticosteroids is permitted. Treatment with immune checkpoint inhibitors or other immunomodulators is prohibited during the study (however, treatment with steroids, IL-6 inhibitors, and antiviral agents is NOT excluded).

9.6. Intervention After the End of the Study

There is no intervention following the end of the study. Any additional care provided to subjects after they complete or discontinue the study will be provided by the subjects' personal physicians according to what is normally expected for their conditions.

10. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

10.1. Discontinuation of Study Intervention

Treatment with study drug (APL-9 IV or matching vehicle IV infusion) will terminate as follows:

- Part 1: at Day 7 or until or resolution of ARDS (PaO_2/FiO_2 ratio >300 mm Hg), whichever occurs earlier
- Part 2: at Day 7 or up to and including the approved treatment duration, discontinuation of respiratory support (supplemental oxygen or mechanical ventilation), or hospital discharge, whichever occurs latest

In Part 2, the DMC may decide to allow treatment with study drug beyond Day 7. If allowed by the DMC, study drug infusions can be extended at the discretion of the investigator beyond Day 7 up to and including Day 21. In Part 2, dosing may be extended only in subjects who still require respiratory support (oxygen supplementation or mechanical ventilation) at Day 7 with a PaO_2/FiO_2 ratio improved by at least 20 mm Hg from baseline if ABG test results are available for comparison. If ABG test results are not available, an improvement of FiO_2 of at least 4% in nonventilated patients (eg, those on nasal cannula) and 10% in mechanically ventilated patients is needed. FiO_2 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. However, study drug administration must end at the DMC-allowed maximal time point or upon the subject's discharge from the hospital. The time of transfer and termination of study drug treatment must be recorded in the subject's medical records and eCRF. If treatment is interrupted for any reason for greater than 24 hours, treatment may not be resumed.

In rare instances, it may be necessary for a subject to permanently discontinue study treatment (definitive discontinuation). The date of and reason for treatment discontinuation must be determined by the investigator and recorded in the subject's medical record and on the appropriate eCRF. If it is determined that there was more than one reason for the discontinuation, each reason should be documented in the source document and the most clinically relevant reason, as determined by the investigator, should be entered on the eCRF (see also Section 10.2).

Any subject who discontinues treatment early or is withdrawn from the study early because of a TEAE, whether serious or nonserious, will be followed up until the TEAE resolves (returns to normal or baseline values) or stabilizes or until it is judged by the investigator to no longer be clinically significant.

If study treatment is definitively discontinued, the subject will remain in the study to be evaluated for safety. See the schedule of assessments (SoA) for data to be collected at the time of discontinuation of study treatment, discharge, and safety follow-up and for any further evaluations to be completed.

10.2. Subject Discontinuation/Withdrawal From the Study

- A subject may withdraw from the study at any time at his/her own request (or at the request of his/her legal representative) or at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, an end-of-treatment visit should be conducted, as shown in the SoA. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations to be completed. The subject will be permanently discontinued both from the study intervention and from the study at that time.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Subjects who withdraw from the study may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

10.3. Lost to Follow-up

A subject will be considered lost to follow-up for failure to complete the safety follow-up assessment 30 days after the last dose of study drug (up to Study Day 51 with a +7-day window).

The following actions must be taken if a subject fails to complete the required safety follow-up assessment 30 days after the last dose of study drug (up to Study Day 51 with a +7-day window):

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of final study assessments, and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Subjects who continue to be unreachable will be considered to have withdrawn from the study.

Closure of specific sites or of the study as a whole are described in Section 13.1.7.

11. STUDY ASSESSMENTS AND PROCEDURES

- Day 1 is defined as the day upon which study treatment is first administered.
- The last predose assessments will be considered as baseline assessments.
- Study procedures and their timings are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Significant safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the subject should continue or discontinue study participation.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided that the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).
- The study end-of-treatment assessments are to be conducted at the end of treatment or on the day of hospital discharge, whichever occurs later. The posttreatment follow-up assessment, conducted 30 days after the last dose of study drug (with a +7-day window), may be conducted either in the hospital or by telephone so that subjects do not have to be exposed to the hospital environment after hospital discharge.
- Discharged subjects will be provided with emergency study cards that include a list of symptoms associated with infections. The study card also guides subjects with instructions to contact their study physicians or seek emergency medical care in the event they experience any of the listed symptoms.

11.1. Safety and Efficacy Assessments

The safety and efficacy of APL-9 treatment will be assessed by objective endpoints and compared between treatment groups. These endpoints relate to AEs, overall hospitalization, use of mechanical ventilation and oxygen, assessments of organ failure, and overall survival. The SoA (Table 1) provides details of the scheduling of these assessments.

Assessments to be performed during the study are described below and in the SoA (Table 1). Every effort should be made to ensure that the protocol-required assessments are completed as described.

If deemed necessary, additional safety measurements will be performed at the discretion of the investigator.

11.1.1. SOFA Score

Organ failure status will be assessed using the SOFA score, 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 score will be assessed at baseline on Day 1 and as listed in the SoA based on worst daily values.

The SOFA score variables to be assessed are:

- PaO_2/FiO_2 ratio (mm Hg) or SpO_2/FiO_2 ratio—collected and entered into the database locally (see calculation instructions in Appendix 1)
- Platelets $\times 10^3/\mu L$—based on data provided by the local laboratory
- Bilirubin (µmol/L or mg/dL)—based on data provided by the local laboratory
- Hypotension/use of vasopressors—collected and entered into the database locally
- Glasgow Coma Scale score—collected and entered into the database locally (see Appendix 2)
- Creatinine (µmol/L or mg/dL)—based on data provided by the local laboratory

See Appendix 1 for additional information on calculating the SOFA score.

11.1.2. Computed Tomographic Scans/Radiographs: Pulmonary Consolidation

Pulmonary consolidation is defined as presence or absence of alveolar opacity observed in chest computed tomographic scans or radiographs in each of the 4 lung quadrants (left upper, left lower, right upper, and right lower), as determined by the investigator.

11.1.3. Demographic/Medical History

Relevant medical history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the subject's preexisting conditions, including all prior significant illnesses, up to and including 1 year before screening. Additional preexisting conditions present at the time when informed consent is given up to the time of first dosing are to be regarded as concomitant. Medical history will include alcohol consumption and smoking history, if applicable. Vaccination history should be attempted to be collected as a component of medical history.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 11.2.5.

Additionally, demographic data will be collected for all subjects, as allowed per applicable regulations.

11.1.4. Assessment of Kidney and Liver Failure

Evidence of kidney and liver failure will be assessed at screening using the following parameters:

- Estimated glomerular filtration rate <45 mL/min/1.73 m^2 AND
- Alanine aminotransferase more than 5 times the upper limit of normal

11.1.5. Vital Signs

Vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the SoA (Table 1). All vital signs will be measured after the subject has been resting in a sitting/prone position for at least 5 minutes, except when they are supine or semireclined because of study procedures and/or AEs, or if deemed necessary by the investigator. Blood pressure measurements are to be taken in the same arm for the duration of the study.

Vital signs measurements will be repeated if clinically significant or if machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements will be repeated at the investigator's discretion. Any confirmed, clinically significant changes in vital signs measurements must be recorded as AEs.

11.1.6. Weight and Height

Body weight and height will be noted at screening and can be as estimated by the subject.

11.1.7. Infusion Site/Pump Safety Assessment

Study drug will be administered by trained and qualified site staff. All clinically significant findings related to injection/infusion procedures will be recorded as AEs.

11.1.8. Clinical Laboratory Tests

Laboratory test samples (Table 2) are to be obtained at designated visits as detailed in the SoA (Table 1). Blood will be collected 3 times on Day 1: (1) once prior to administration of the APL-9 bolus, (2) once as soon as possible following the bolus (within 5-10 minutes) prior to the continuous infusion, and (3) once at 2 hours after the beginning of the continuous infusion. Following that, assessments should be collected within the time frame of each calendar day.

Blood samples will be analyzed at one or more central (or local) laboratory facilities, as defined in the laboratory manual. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that at minimum require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

Instructions for collection, handling, processing, storage, and shipping of samples will be provided in a separate laboratory reference manual prior to study initiation.

Table 2: Clinical Laboratory Tests

PARAMETERS ANALYZED AT THE LOCAL LABORATORY		
Blood/serum/plasma samples		
Hematology ABG Hb Hematocrit Platelet count RBC count Reticulocyte count Schistocytes WBC count with differential Coagulation panel[a] D-dimer Fibrinogen INR PT	Serum chemistry Albumin ALT ALP AST Bicarbonate Bilirubin (total, direct, and indirect) BUN C-reactive protein (CRP) C3 and C4 Calcium Chloride Creatinine Creatine kinase Cystatin C eGFR	Ferritin Glucose Haptoglobin HDL Iron LDH LDL Phosphorus Potassium Pregnancy Sodium Total cholesterol Total protein Triglycerides Troponin Uric acid
Urine samples		
Urinalysis Bilirubin Blood Glucose Ketones Leukocyte esterase Microscopic examination of urine sediment, including for presence of RBCs, WBCs, and casts, will be performed on all abnormal urinalyses		Nitrite pH Protein Specific gravity Urobilinogen
Respiratory swab		
Viral RNA or viral antigen assessment SARS-CoV-2		
PARAMETERS ANALYZED AT CENTRAL/SPECIALTY LABORATORIES		
Plasma samples		
Complement biomarkers Bb, C3a, C4a, C5a, TCC	Inflammation biomarkers TNFα IL-1β IL-6	CCI [redacted]
Serum samples		
PK concentrations AH50		

Abbreviations: ABG = arterial blood gas; ACR = albumin-to-creatinine ratio; AH50 = alternative complement pathway hemolytic activity; ALP = alkaline phosphatase; ALT = alanine aminotransferase; CCI [redacted] AST = aspartate aminotransferase; BCR = B-2 microglobulin:creatinine ratio; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; HDL = high-density lipoprotein; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; PK = pharmacokinetics; PT = prothrombin time; RBC = red blood cell; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TCC = terminal complement complex; TNFα = tumor necrosis factor α; WBC = white blood cell.

[a] The use of silica reagents in coagulation panels should be avoided in subjects treated with APL-9.

11.1.8.1. Pregnancy Screening

For women of childbearing potential, a serum pregnancy test will be performed at screening. Subjects with a positive test result will be excluded or discontinued from the study.

11.2. Adverse Events

11.2.1. Definition of AEs

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related. An AE can, therefore, be any unfavorable and unintended sign, including a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation and will be recorded during the study at the investigational site. All identified AEs must be recorded and described on the appropriate AE or SAE page of the eCRF.

Fluctuating or nonsignificant changes in laboratory values do not necessarily qualify for AE reporting. If these changes in laboratory values are assessed as clinically significant and/or lead to discontinuation of administration of investigational product, these should be reported as an AE. If these laboratory values are linked to a diagnosis, only the diagnosis should be reported as AE.

11.2.2. Serious Adverse Events

An SAE is any AE or suspected adverse reaction that, in the view of either the investigator or sponsor, results in any of the following outcomes: death; life threatening; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening*, or require hospitalization may be considered serious when, based upon appropriate medical judgment they may jeopardize the subject and may require medical/surgical intervention to prevent one of the outcomes listed in the above definition.

Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

**Life threatening* is defined as an AE or suspected adverse reaction, which, in the view of either the investigator or sponsor, places the subject at immediate risk of death as it occurred. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

11.2.3. Unexpected Adverse Events

An AE is considered "unexpected" if it is not listed in the Reference Safety Information section of the investigator's brochure in effect at that time of event onset.

11.2.4. Evaluation of AEs

All AEs that occur during this study will be recorded; however, only TEAEs will be analyzed and reported in the study report. The investigator or their medically qualified designee will review each event and assess its relationship to study drug treatment (not related, unlikely to be related, possibly related, or definitely related). The date and time of onset, time relationship to study drug dosing, duration, and outcome (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, or fatal) of each event will be noted.

Table 3 should be considered when evaluating the relationship of AEs/SAEs to study treatment.

Table 3: Definitions of Adverse Event Relatedness

Classification	Definition
Definitely related	Strong evidence of a causal relationship; the influence of other factors is unlikely
Possibly related	Some evidence of a causal relationship, but other factors may have caused or contributed to the event (eg, another illness or concomitant treatment)
Unlikely to be related	A causal relationship is not a reasonable possibility, but it cannot be completely ruled out with the available evidence
Not related	No evidence of a causal relationship

If the AE/SAE is determined to be possibly or definitely related to the study drug, the event will be considered to be related to the study drug for the purposes of expedited regulatory reporting.

Table 4 presents the definitions that should be considered when evaluating the severity of AEs and SAEs.

Table 4: Severity of Events

Severity	Definition/description
Mild	Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (eg, insomnia, mild headache).
Moderate	Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (eg, febrile illness requiring oral medication).
Severe	Event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention (eg, anemia resulting in blood transfusion).

11.2.5. Recording AEs

Adverse events and SAEs will be collected from the signing of the consent form up to and including the safety follow-up assessment 30 days after the last dose of study drug (up to Study Day 51 with a +7-day window).

Any events that occur prior to dosing will be categorized as pretreatment events; events occurring after dosing will be recorded as TEAEs (start date of dosing and, therefore, categorization of the event will be dependent on randomization assignment).

For each AE, the investigator will evaluate and report the onset date (and time if applicable), resolution date (and time if applicable), intensity, causality, action taken, serious outcome, and whether or not it caused the subject to discontinue the study.

If possible, the outcome of any AE that caused permanent discontinuation or was present at the end of the study should be reported, particularly if the AE was considered by the investigator to be related to the investigational product. Subjects experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the safety follow-up assessment (30 days after the last dose of APL-9), up to and including Study Day 51 (+7) should receive follow-up as appropriate.

All SAEs must be reported to the sponsor/Apellis Safety via eCRF immediately and within 24 hours of becoming aware of the event, whether or not the event is deemed treatment-related. If the electronic data capture system is not operational (or for paper-based study[ies]), the site must complete the paper SAE form and email to PPD, also within 24 hours of becoming aware of the event. The reported information submitted as a paper SAE must be entered into the electronic data capture system once it becomes operational.

Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.

11.2.6. Reporting AEs

The sponsor has the responsibility to inform concerned health authorities, ethics committees, and investigators about suspected unexpected serious adverse reactions in line with Good Clinical Practice (GCP) guidance and applicable regulatory requirements.

If required, specific SAEs should be reported to the concerned ethic committees in compliance with local requirements.

11.2.7. Pregnancy

Although pregnancy is not an AE, all pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring with a female subject or the female partner of a male subject must be followed to conclusion to determine their outcome and are considered immediately reportable events.

The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Apellis Safety within 24 hours of the investigator's awareness using the paper Pregnancy Report Form. The Pregnancy Report Form shall be signed and dated by the investigator and submitted via email to PPD.

The investigator must follow the subject until completion of the pregnancy and must report the outcome of the pregnancy (eg, delivery, termination, etc) and neonatal status up to and including 12 months post delivery. An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. In the event of an abnormal outcome, an SAE Report Form will be required.

11.2.8. Acceptable Methods of Contraception

Approved methods of contraception include:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral, injectable, or implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the trial subject who is a woman of childbearing potential and that the vasectomized partner has received medical assessment of surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments)
- Male condom with or without spermicide (for male study subjects with female partners of childbearing potential only)

Not all methods of contraception may be available in all of the countries in which this study is being conducted.

Note: Sexual abstinence is accepted only when it is the preferred and usual lifestyle of the subject.

Subjects must agree to use an approved method of contraception during the study and for 90 days after their last dose of study drug. Male subjects will be counseled to avoid donating semen during the time between the first screening and the final end-of-treatment visit and for 90 days after the last dose of study drug.

11.3. Drug Abuse, Misuse, Overdose, and Medication Error

Occurrences of events of drug abuse, drug misuse, drug overdose, and medication error must be reported to Apellis Safety.

Abuse of a medicinal product: Persistent or sporadic, intentional excessive use of medicinal products, which is accompanied by harmful physical or psychological effects.

Misuse: Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or not within the legal status of its supply.

Overdose: Administration of a quantity of study drug given per administration or per day, which is above the assigned dose.

Medication Error: An error made in prescribing, dispensing, administration and/or use of the study drug. Medication errors are reportable to the sponsor as defined below:

- The dispensing, administration, and/or use of the unassigned study drug.
- The administration and/or use of an expired study drug.

All AEs or SAEs associated with drug abuse, drug misuse, drug overdose, or medication error must be reported as appropriate.

11.4. SARS-CoV-2 Viral RNA/Viral Antigen Assessment

Presence of SARS-CoV-2 viral RNA or viral antigen will be detected in respiratory specimens (collected using nasopharyngeal or oropharyngeal swabs) with a qualitative nucleic acid amplification test (such as RT-PCR) or 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 for active infection and cannot be used for study eligibility screening or for subsequent SARS-CoV-2 assessments.

11.5. Pharmacokinetics

The exposure of subjects to APL-9 will be evaluated in serum from blood collected in a serum separator tube. Two serum aliquots of at least 0.5 mL will be stored at –70 °C and shipped on dry ice. Blood will be collected 3 times on Day 1: (1) once prior to administration of the APL-9 bolus, (2) once as soon as possible following the bolus (within 5-10 minutes) prior to the continuous infusion, and (3) once at 2 hours after the beginning of the continuous infusion. Blood will then be collected once daily between 1-2 hours after the first dose on Days 3, 5, 7, 11 (if treatment is ongoing), and 15 (if treatment is ongoing) and at the end-of-treatment visit. If the subject is discharged after the end-of-treatment visit, another sample will be collected on the day of discharge.

11.6. Pharmacodynamics

The pharmacodynamic parameters evaluated in this study related to complement activation are levels of C3, C3a, Bb, C4, C4a, C5, and TCC) and AH50. The pharmacodynamic parameters evaluated in this study related to coagulopathy are reticulocyte count, presence of schistocytes, levels of D-dimer, ferritin, lactate dehydrogenase, haptoglobin, fibrinogen, CCI [redacted] The pharmacodynamic parameters evaluated in this study related to inflammation are levels of C-reactive protein (CRP), tumor necrosis factor α (TNFα), IL-1β, and IL-6. The complement activation markers and inflammatory cytokines will be analyzed in plasma from blood collected in K2 EDTA (dipotassium ethylenediaminetetraacetic acid) tubes with the exception of C-reactive protein,

which is measured from serum. The AH50 hemolytic assay will be measured in serum from blood collected in red plain top (no gel) tubes. The coagulopathy markers will be analyzed in plasma collected in sodium citrate tubes or serum. These blood samples will be collected at the same time as the samples described in Section 11.5.

11.7. Genetics

Genetic markers related to the complement system as well as the susceptibility to SARS-CoV-2 infection may be evaluated in this study as an optional post hoc analysis contingent upon initial study results.

11.8. Immunogenicity Assessments

Presence or absence of IgG/IgM against SARS-CoV-2 may be evaluated in this study on available samples as an optional post hoc analysis contingent upon initial study results.

12. STATISTICS

A formal statistical analysis plan (SAP) will be developed and finalized prior to locking the database. The full details of data presentations and analyses will be provided in the SAP. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP. Any deviations from the final SAP or from what is outlined in the protocol will be discussed in the final study report.

12.1. Determination of Sample Size

In Part 1 of the study, a cohort of 6 subjects will receive open-label APL-9 (as add-on therapy to SOC), 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, 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.

12.2. Analysis Set

12.2.1. 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.

12.2.2. 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 treatment they received.

12.2.3. Intent-to-Treat Set

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

12.2.4. Full Analysis Set

The full analysis set (FAS) set will include all 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.

12.2.5. Per-Protocol Set

The per-protocol set will include all subjects in the FAS who have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. Decisions concerning the exclusion of subjects from the per-protocol analysis set will be made and documented prior to database lock. Randomized subjects will be required to receive their randomized treatment to be included in the set so that analyses using this set will,

by default, be based upon the actual treatment allocated. This set will be used for supportive efficacy analyses.

12.2.6. 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.

12.2.7. Pharmacodynamic Set

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

12.2.8. Data Review for Analysis Set

After all data have been verified, coded, and entered into the database, a review will be performed. The purpose of this review will be to define the analysis populations. The review will also check the quality of the data, identifying outliers, and make decisions on how to deal with any data issues (eg, missing values, withdrawals, protocol deviations). After the preanalysis review, resolution of all issues, and documentation of all decisions, the database will be locked.

12.3. Efficacy Analysis

All efficacy analyses will be summarized by treatment group.

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

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

12.3.1. Analysis of Primary Efficacy Endpoint

Not applicable.

12.3.2. Analysis of Secondary Efficacy Endpoints

Continuous variables will be summarized using descriptive statistics (eg, median and mean); for categorical variables, the frequency and percentage in each category will be displayed. Time-to-event data (such as time to hospital discharge and time to mechanical ventilation discontinuation) will be summarized using Kaplan-Meier estimates accounting for censored observations (and analyzed using the Cox proportional hazard model if appropriate).

12.3.3. Analysis of Time-to-Event Data

The following time-to-event endpoints will be assessed by using the Kaplan-Meier method.

- Overall survival
- Hospital length of stay
- Duration of mechanical ventilation and/or oxygen therapy

Time-to-event curves between the 2 treatment groups will be compared by using a log-rank test along with the corresponding hazard ratio. Event rates (eg, mortality through the safety follow-up assessment) will be estimated along with the corresponding 2-sided 95% CI (or 2-sided 90% CI if appropriate).

12.3.4. Analysis of Exploratory Endpoints

Analyses of exploratory endpoints will follow the methods described in Section 12.3.2 considering the type of variables (ie, continuous, categorical, or time-to-event).

12.4. Safety Analysis

All safety analyses will be summarized for the safety set.

Adverse events will be coded using MedDRA. All AEs, including TEAEs, will be summarized by System Organ Class, Preferred Term, and treatment group for number of subjects and proportion reporting the event. A similar summary will be produced for SAEs, AEs leading to termination, severe AEs, and AEs related to the investigational product. The intensity of AEs and the relationship to investigational product will be summarized for each System Organ Class and Preferred Term by treatment group.

Withdrawals because of AEs will be summarized for each body system and Preferred Term by treatment group.

As described in Section 11.2, TEAEs are defined as those AEs that develop or worsen after the first dose of study medication up to and including the safety follow-up assessment 30 days after the last dose of study drug (up to Study Day 51 with a +7-day window).

AE summaries will be presented across all subjects. All AEs will be listed by subject, along with information regarding onset, duration, relationship, and severity to investigational product, action taken with investigational product, treatment of event, and outcome.

All laboratory assessments will be summarized by treatment group using appropriate descriptive statistics.

Changes from baseline in clinical laboratory tests will be summarized, using descriptive statistics, by visit and nominal time after dosing, and by treatment group. Baseline will be taken as the last predose assessment. Out-of-range values will be flagged in data listings.

Changes from baseline in vital signs will be summarized, using descriptive statistics, by treatment, visit, and nominal time after dosing. Baseline will be taken as the last predose assessment.

Values of potential clinical significance will be flagged in listings and summarized by treatment.

12.5. Other Analyses

Demographics, baseline characteristics, concomitant medication, medical history, and study medication exposure will be summarized by treatment group.

World Health Organization and MedDRA coding dictionaries will be used for the concomitant medications and medical histories, respectively.

12.6. Interim Analyses

Not applicable.

12.7. Independent Data Monitoring Committee

Data monitoring committee reviews on safety endpoints will be conducted after the 6 subjects in Part 1 reach Day 7. In Part 2, two reviews will be required:

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

These data reviews will be performed by an independent statistician external to the sponsor, and the results will be provided to the DMC by the independent statistician. The sponsor will remain blinded throughout these processes and will be unblinded if the study stops early or at the time of the final analysis. Enrollment will not be suspended during the DMC reviews.

The DMC for this study will be appointed by the sponsor in accordance with its standard procedures. The DMC chair will also be appointed by the sponsor, and the DMC will operate according to an approved charter.

Initially, the DMC will review the safety data obtained from open-label APL-9 treatment of the first 6 subjects. The DMC will review cumulative safety/tolerability data (eg, physical examinations, vital sign measurements, clinical laboratory tests, and AEs). Additional data may be reviewed that are related to efficacy, but the DMC will only be reviewing data for risk-benefit purposes. The DMC will have the responsibility to conduct a thorough safety assessment at regular predefined intervals during the treatment period of the study.

Data monitoring committee meetings will be held according to the schedule in the DMC charter. An ad hoc DMC data review may be recommended by the DMC or requested by Apellis Pharmaceuticals, Inc, at any time during the study.

The remit, roles, and responsibilities of the DMC will be specified in a separate DMC charter.

13. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

13.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following items:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH Good Clinical Practice Guidelines
  - Applicable laws and regulations
  - The Apellis Pharmaceuticals, Inc, policy on bioethics
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated. The investigator must provide a copy of the IRB/IEC approval to Apellis Pharmaceuticals, Inc, before enrollment of any subject into the study.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/IEC, European regulations for clinical trials (if applicable), and all other applicable local regulations

13.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative, including full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study, and answer all questions regarding the study. Subjects should have the opportunity to consider the information provided before providing their consent.
- Subjects must be informed that their participation is voluntary and that they are free to discontinue from the study at any time. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the

requirements of 21 CFR §50, local regulations, ICH GCP guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research, including testing for genetic markers related to the complement system as well as the susceptibility to SARS-CoV-2 infection. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

13.1.3. Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subjects must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the subject, who will be required to give consent for their data to be used as described in the informed consent.
- The subjects must be informed that their medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

13.1.4. Site Qualification and Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Apellis Pharmaceuticals, Inc, will contact the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of Apellis Pharmaceuticals, Inc, or its

representatives. This will be documented in a clinical study agreement between Apellis Pharmaceuticals, Inc, and the investigator.

During the study, a monitor from Apellis Pharmaceuticals, Inc, or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms (CRFs), and that investigational product accountability checks are being performed
- Perform source data verification as described in Section 13.1.5
- Record and report any protocol deviations not previously sent to Apellis Pharmaceuticals, Inc
- Confirm that all AEs and SAEs have been properly documented on CRFs and confirm that any SAEs have been forwarded to Apellis Pharmaceuticals, Inc, and those SAEs that met criteria for reporting have been forwarded to the IRB

The investigator must allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

13.1.5. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data; see Section 13.1.6) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. The investigator should contact Apellis Pharmaceuticals, Inc, immediately if contacted by a regulatory agency about an inspection.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checks of the data.

- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol, and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a period of 2 years after the last marketing application approval, or if not approved, for 2 years following the discontinuance of the test article for investigation, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

13.1.6. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the SAP.

13.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects at the first site.

The sponsor designee reserves the right to close any study site or terminate the study at any time, for any reason, at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected, and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or ICH GCP guidelines
- Inadequate recruitment of subjects by the investigator

- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up

13.1.8. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission to allow the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Both the use of data and the publication policy will be detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and Apellis Pharmaceuticals, Inc, or its designee. With respect to such rights, Apellis Pharmaceuticals, Inc, or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions, either to their institution or directly to Apellis Pharmaceuticals, Inc, or its designee, as will be set forth in the clinical study agreement.

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15. APPENDICES

APPENDIX 1. SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA)

Organ failure status will be assessed using the SOFA score, 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 score will be assessed at baseline on Day 1 and as listed in the SoA (Table 1) based on worst daily values. The SOFA score variables to be assessed are:

- PaO_2 (partial pressure of oxygen)/FiO_2 (fraction of inspired oxygen) ratio (mm Hg)—collected and entered into the database locally (see calculation instructions below)
- Platelets × $10^3/mm^3$—based on data provided by the central laboratory
- Bilirubin (µmol/L or mg/dL)—based on data provided by central laboratory
- Hypotension/use of vasopressors—collected and entered into the database locally
- Glasgow Coma Scale score—collected and entered into the database locally (see Appendix 2)
- Creatinine (µmol/L or mg/dL)—based on data provided by the central laboratory

Table 5 details the SOFA scoring requirements.

Table 5: Sequential Organ Failure Assessment (SOFA) Scoring

Variables	0	1	2	3	4
Respiration					
PaO_2/FiO_2, mm Hg	>400	≤400	≤300	≤200[a]	≤100[a]
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					
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: FiO_2 = fraction of inspired oxygen; MAP = mean arterial pressure; PaO_2 = partial pressure of oxygen.

[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.

Calculation of PaO_2/FiO_2 ratio:

For the purpose of calculating PaO_2/FiO_2 ratio, an arterial blood gas test (ABG) will be obtained from:

1. An arterial line if already present
2. A radial artery needle puncture unless contraindicated
3. If ABG sampling remains unsuccessful for any reason, then SpO_2 (peripheral oxygen saturation) will be measured and the SpO_2/FiO_2 value will be derived, and the PaO_2/FiO_2 ratio will be used to determine the SOFA respiratory score according to Table 6.

Table 6: Derivation of SpO_2/FiO_2 Values Corresponding to PaO_2/FiO_2 Ratios in the Combined Anesthesia and ARMA Database[a]

SOFA respiratory score	PaO_2/FiO_2	SpO_2/FiO_2
1	<400	<512
2	<300	<357
3	<200	<214
4	<100	<89

Abbreviations: ARMA = Acute Respiratory Management of ARDS; FiO_2= fraction of inspired oxygen; PaO_2 = partial pressure of oxygen; SOFA = Sequential Organ Failure Assessment; SpO_2 = peripheral oxygen saturation.

[a] Data derived from 4728 matched SpO_2/FiO_2 and PaO_2/FiO_2 measurements from the combined anesthesia and ARMA database.

Source: Pandharipande et al. 2009.

APPENDIX 2. GLASGOW COMA SCALE

Glasgow Coma Scale

Eye Opening Response

- Spontaneous—open with blinking at baseline **4 points**
- To verbal stimuli, command, speech **3 points**
- To pain only (not applied to face) **2 points**
- No response **1 point**

Verbal Response

- Oriented **5 points**
- Confused conversation, but able to answer questions **4 points**
- Inappropriate words **3 points**
- Incomprehensible speech **2 points**
- No response **1 point**

Motor Response

- Obeys commands for movement 6 points
- Purposeful movement to painful stimulus 5 points
- Withdraws in response to pain 4 points
- Flexion in response to pain (decorticate posturing) 3 points
- Extension response in response to pain (decerebrate posturing) 2 points
- No response 1 point

References

Teasdale G, Jennett B. Assessment of coma and impaired consciousness. *Lancet* 1974; 81-84.

Teasdale G, Jennett B. Assessment and prognosis of coma after head injury. *Acta Neurochir.* 1976; 34:45-55.

Categorization:

Coma: No eye opening, no ability to follow commands, no word verbalizations (3-8)

Head Injury Classification:

Severe Head Injury—GCS score of 8 or less

Moderate Head Injury—GCS score of 9 to 12

Mild Head Injury—GCS score of 13 to 15

(Adapted from: Advanced Trauma Life Support: Course for Physicians, American College of Surgeons, 1993.)

Disclaimer:

Based on motor responsiveness, verbal performance, and eye opening to appropriate stimuli, the Glascow Coma Scale was designed and should be used to assess the depth and duration of coma and impaired consciousness. This scale helps to gauge the impact of a wide variety of conditions such as acute brain damage due to traumatic and/or vascular injuries or infections, metabolic disorders (eg, hepatic or renal failure, hypoglycemia, diabetic ketosis), etc.

Education is necessary to the proper application of this scale (Teasdale G, Kril-Jones R, van der Sande J. Observer variability in assessing impaired consciousness and coma. *J Neurol Neurosurg Psychiatry*. 1978; 41:603-610. Rowley G, Fielding K. Reliability and accuracy of the Glasgow Coma Scale with experienced and inexperienced users. *Lancet.* 1991; 337:535-538). The predictive value of the GCS, even when applied early, is limited (Waxman K, Sundine MJ, Young RF. Is early prediction of outcome in severe head injury possible? *Arch Surg.* 1991; 126:1237-1242).

Despite these and other limitations (Eisenberg HM. Outcome after head injury: Part I: general Considerations, in Becker DP, Povlishock JR (eds): Central Nervous System Trauma Status Report, 1985. Washington, DC: U.S. Government Printing Office, 1988:271-280), health care practitioners continue to use this practical scale widely.

Source: Adapted from Glascow Coma Scale, Womack Army Medical Center, Fort Bragg, NC.

APPENDIX 3. Amendment History

AMENDMENT 1: SUMMARY OF CHANGES FROM THE PREVIOUS VERSION **Updates to the protocol implemented in this amendment are provided in the table below. Additions to the protocol are marked in underline; deletions are marked by ~~strikethrough.~~**		
Protocol Versions		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 1	**Amendment Date** **07 May 2020**	**Global**
Description of Change		**Section(s) Affected by Change**
Nonsubstantial editorial and technical changes that did not impact content of the document have been made for grammar, clarity, and document usability.		Entire document
Inclusion criteria 6 and 7 were added to the Synopsis. These criteria were previously included in the body of the protocol: 6. Each female subject of childbearing potential must have a negative serum pregnancy test at screening and must agree to use protocol-defined methods of contraception from screening through at least 90 days after receiving the last dose of APL 9. 7. Male subjects must agree to use protocol-defined methods of contraception and agree to refrain from donating semen from screening through at least 90 days after receiving the last dose of APL-9.		Synopsis
Clarified that 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 patient requiring premature treatment discontinuation by the investigator due to AEs or abnormal lab tests.		Synopsis Section 5.3 Section 7.1 Section 7.5
Analysis of PK and PD parameters were elevated from exploratory objectives and exploratory endpoints to secondary objectives and secondary endpoints. PK and PD set definitions added to Section 12.		Synopsis Section 6.1.2 Section 6.1.3 Section 6.2.2 Section 6.2.3 Section 7.2 Section 12.2.6 (new section added) Section 12.2.7 (new section added)
The any-cause mortality secondary endpoint was modified for clarity, as follows: • Any-cause mortality (measured from beginning of treatment until the Day-30 follow-up assessment)		Synopsis Section 6.2.2 Section 12.3.3
Clarified that in Part 2 dosing will remain 7 days and may be extended only in patients who still have mild or moderate ARDS at Day 7 with at least a 20 mm Hg increase in PaO_2 from baseline.		Synopsis Section 7.1 Section 7.5 Section 9.1.1 Section 10.1
The safety follow-up duration was updated from a 7-day follow-up (-2/+7 days) to a 30-day follow-up (+ 7 days).		Synopsis Section 7.1 Section 7.4 Section 7.5, Table 1 Section 11

	Section 11.2.1
Exclusion criteria 2 was modified to exclude any active bacterial, fungal, or parasitic infection as follows: 2. Active bacterial, fungal, or parasitic infection ~~neisserial sepsis infection~~. Treatment with interleukin 6 inhibitors and hydroxychloroquine removed from exclusion criteria 5 as these treatments may be considered standard of care. 5. Treatment with ~~interleukin 6 inhibitors, hydroxychloroquine~~, immune checkpoint inhibitors, or other immunomodulators within 3 months prior to study enrollment (however, treatment with steroids, interleukin-6 inhibitors and antiviral agents is NOT excluded) Exclusion criteria 6 was modified to clarify that: 6. Treatment with convalescent plasma for COVID-19 within 3 months of baseline Exclusion criteria 8 was modified as follows: 8. Evidence of kidney and liver failure at screening (estimated glomerular filtration rate <45 mL/min/1.73 m^2 and alanine aminotransferase level ≥5× ~~>10x~~ the upper limit of normal, as assessed by the local laboratory) Exclusion criteria 9 was added to exclude: 9. Subjects with a hereditary complement deficiency	Synopsis Section 7.2 Section 8.2 Section 9.5.1
Clarified that a subject is considered to have completed the study if all obtainable study assessments, including those at the day of discharge from the hospital and during follow-up, have been collected. The end of the study was redefined as the date of the Day 30 follow-up assessment for the last subject in the study.	Section 7.4
Footnote "a" was modified to reflect the updates to the study design. Footnote "g" was added to indicate where the SOFA score variables are detailed in the protocol. Footnote "h" was modified to indicate where laboratory assessments are detailed in the protocol and to note that the use of silica reagents in coagulation panels should be avoided in subjects treated with APL 9 (this was previously included in the body of the original protocol). The previous footnote "g" detailing concomitant procedures is now footnote "i" due to the addition/modification of the previous footnotes. Footnote "j" was added to detail how infusion-relation reactions should be treated. Footnote "k" added to clarify that if confirmation of SARS-CoV-2 has occurred within 7 days of screening, the viral RNA at screening/baseline is not mandatory. Footnote "l" was modified to note that vaccination history should be attempted to be collected as a component of medical history.	Section 7.5, Table 1
Adverse Event collection added to the Schedule of Assessments ECGs added to the Schedule of Assessments	Section 7.5, Table 1 Section 7.5, Table 1
For clarity, the "exit visit" has been re-labeled as the "end-of-treatment visit." Subjects must receive all assessments indicated in the "end-of-treatment visit" on the last day they receive treatment, regardless of which study day that occurs on.	Section 7.5, Table 1 Section 9.5 Section 10.2 Section 10.3 Section 11 Section 11.2.3 Section 11.2.6 Section 11.5 Section 11.6 Section 12.4

Inclusion Criteria 3 was updated to allow for inclusion of patients that are not mechanically ventilated as follows: 3. Have: a. Respiratory failure requiring oxygen supplementation or either invasive or non-invasive mechanical ventilation with PaO2/FiO2 ratio >100 mm Hg but ≤300 mm Hg with end positive airway pressure (EPAP) or positive end-expiratory pressure (PEEP) b. Worsening of respiratory symptoms in the past week. c. Bilateral opacities present on a chest radiograph or computed tomographic scan. These opacities must not be fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules. d. Respiratory failure cannot be fully explained by cardiac failure or fluid overload. ~~3. Diagnosis of mild to moderate ARDS requiring mechanical ventilation according to the Berlin definition:~~ ~~a. Worsening of respiratory symptoms in the past week.~~ ~~b. Bilateral opacities present on a chest radiograph or computed tomographic scan. These opacities must not be fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules.~~ ~~c. Respiratory failure cannot be fully explained by cardiac failure or fluid overload.~~ ~~d. Mild or moderate ARDS with PaO_2/FiO_2 ratio >100 mm Hg but ≤300 mm Hg on ventilator settings that include positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥5 cm H_2O.~~	Synopsis Section 8.1
Instructions for treatment of infusion-related reactions were implemented in the protocol: Infusion-related reactions that occur during the administration of the 50 mL loading dose should be treated as follows: • For mild infusion-related reactions: The 50 mL bag infusion time should be increased from 10 mins to 20-40 mins and the reaction should be monitored. Treatment with diphenhydramine may be required. The infusion time of the 250 mL bag should not be increased. • For severe or persistent mild infusion-related reactions (instances in which the subject's symptoms do not respond to the increased infusion time): treatment should be discontinued and the institution's emergency hypersensitivity protocol should be employed.	Section 9.1.1 Section 7.5, Table 1
The following edit was made for clarity: Subjects who are discharged prior to the allowable treatment duration ~~study exit date~~ will have follow-up conducted by phone and will be provided with emergency study cards that include a list of symptoms associated with infections.	Section 9.1.2
Clarified that: Randomization will be stratified by need of mechanical ventilation (yes vs no) ~~severity of ARDS (mild vs moderate)~~ and age (younger than 65 years vs at least 65 years).	Section 9.3.1
Reference to specific antibiotics was removed as these are covered by the "broad-spectrum" antibiotic requirement. All enrolled subjects will receive a broad-spectrum antibiotic during the treatment period to provide coverage for *Neisseria meningitidis*,	Section 9.5

Streptococcus pneumoniae, and *Haemophilus influenzae* unless contraindicated because of hypersensitivity or allergy. ~~In that event, carbapenem, vancomycin, or aztreonam are the recommended alternates. Subjects with infection and cultures resistant to the prophylactic antibiotic should be switched to culture-specific antibiotic therapy.~~ Treatment with antibiotics may be adjusted according to culture results and at the discretion of the investigator.	
Treatment with interleukin 6 inhibitors and hydroxychloroquine removed from the list of prohibited medications.	Section 9.5.1
Noted that the SOFA score assessments will be conducted locally.	Section 11.1.1
It was noted that: Vaccination history should be attempted to be collected as a component of medical history.	Section 11.1.3 Section 7.5, Table 1
Liver failure criteria modified as follows: • Alanine aminotransferase more than 5 ~~10~~ times the upper limit of normal	Section 11.1.4
Reference to the following laboratory assessments being conducted locally was removed as noted below. These assessments were already included in the summary of labs (Table 2), and the laboratory manual will provide details of where laboratory values should be assessed. ~~**Local laboratory**: eGFR, pregnancy, arterial blood gas test~~	Section 11.1.8
An error was corrected to clarify that: Clinically significant changes in laboratory values, blood pressure, and pulse rate ~~need not~~ must be reported as AEs.	Section 11.2.3

AMENDMENT 2: SUMMARY OF CHANGES FROM THE PREVIOUS VERSION

Updates to the protocol implemented in this amendment are provided in the table below. Additions to the protocol are marked in underline; deletions are marked by strikethrough.

Amendment 2	Amendment Date 17 August 2020	Global
Description of Change		**Section(s) Affected by Change**
Nonsubstantial changes that did not impact content of the document have been made for clarity.		Entire document
Updated primary objective to reflect the study population, which was revised in Protocol Amendment 1 (07 May 2020) per FDA request to include patients with respiratory failure requiring nonmechanical respiratory support, in addition to patients with ARDS (respiratory failure requiring noninvasive or invasive mechanical ventilation). The primary objective was not updated accordingly in Amendment 1, so it is now updated as follows: • To evaluate the safety of APL-9 compared with that of vehicle control (as add-on therapy to standard of care [SOC]) in subjects with coronavirus disease 2019 (COVID-19) who have respiratory failure, including mild to moderate acute respiratory distress syndrome (ARDS)		Synopsis

Updated secondary endpoints

- Any-cause mortality (measured from beginning of treatment until the safety follow-up assessment 30 days after last study treatment (up to Study Day 51 with a +7-day window) ~~Day 30 follow-up assessment)~~
- Observed values and changes from baseline in markers of complement activation (C3, C3a, C4, C4a, Bb, C5a, TCC, and alternative complement pathway hemolytic activity) ~~thrombotic microangiopathy~~, coagulopathy (reticulocyte count, presence of schistocytes, lactate dehydrogenase, D-dimer, ferritin, haptoglobin, fibrinogen, von[CCI] and inflammatory cytokines (C-reactive protein, tumor necrosis factor α, IL-1β, and IL-6)

Updated overall 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 SOC in subjects with ~~mild to moderate ARDS~~ respiratory failure due to COVID-19 infection.

Revised Part 2 (Randomized Double-Blind Period)

Subjects will receive treatment with APL-9 or vehicle from Day 1 through Day 7 (or approved treatment duration), or ~~resolution of ARDS (PaO_2/FiO_2 ratio >300 mm Hg)~~ discontinuation of respiratory support (supplemental oxygen or mechanical ventilation), or hospital discharge, whichever occurs earlier.

The DMC may approve any extended treatment duration through Day 21 (extended treatment will be allowed only in subjects who still require respiratory support (oxygen supplementation or mechanical ventilation) at Day 7~~have mild or moderate ARDS~~ with at least a 20-mm Hg increase in PaO_2 from baseline). Treatment beyond Day 7 and through any DMC-approved extension will be at the discretion of the investigator.

For each subject, follow-up safety assessments will be collected 30 days after the subject's last dose of study treatment (up to Study Day 51 with a +7-day window). Assessments between study drug discontinuation and the safety follow-up assessment may be conducted at the investigator's discretion. These assessments will be conducted via inpatient assessment (for patients still hospitalized) or by telephone call (for patients discharged).

The DMC will perform safety and efficacy data reviews on an ongoing basis during Part 2. ~~Two reviews will be required: after the 10th subject enrolled in Part 2 reaches Day 7 (or is discharged following the resolution of ARDS) and after the 30th subject enrolled in Part 2 reaches Day 7 (or is discharged following the resolution of ARDS)~~ 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; and
2. After the 30th subject reaches the approved treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge.

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 review 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 achieve resolution of ARDS)~~, or hospital discharge. 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 ~~(or achieve resolution of ARDS)~~. Enrollment will not be suspended during the DMC reviews. Revised Study Drug Treatments – Part 2 The blinded site personnel will initiate therapy with study drug received from the pharmacists on Day 1 with an IV infusion of the 50-mL bag over a 10-minute period, followed within 1 hour by continuous infusion of the 250-mL bag at the rate of approximately 21 mL/h until the end of study drug administration on Day 7 (or longer if DMC allowed), ~~or resolution of ARDS~~ discontinuation of respiratory support, or hospital discharge. (This results in the infusion of two 250-mL bags every 24 hours.) Revised Independent DMC The DMC will perform safety and efficacy data reviews on an ongoing basis during Part 2. ~~Two reviews will be required: after the 10th subject enrolled in Part 2 reaches Day 7 (or is discharged following the resolution of ARDS), and after the 30th subject enrolled in Part 2 reaches Day 7 (or is discharged following the resolution of ARDS).~~ 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 2. After the 30th subject reaches the approved treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge. 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 review will be initiated when the 10th and 30th subjects reach the approved extended treatment duration ~~(or achieve resolution of ARDS),~~ discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge. Enrollment will not be suspended during the DMC reviews. Treatment duration in Part 2 may be maximally extended through Day 21; extended treatment will be allowed only in subjects who still ~~have mild or moderate ARDS~~require respiratory support (oxygen supplementation or mechanical ventilation) at Day 7 with at least a 20-mm Hg increase in PaO_2 from baseline.	
Revised Section 5.3, Benefit-Risk Assessment This is an interventional study in COVID-19 subjects with respiratory failure, including mild to moderate ARDS, a life-threatening complication of SARS-CoV-2 infection. ~~When~~After Part 2 is initiated, the DMC will perform further reviews of clinical data ~~when~~after the 10th and 30th subjects have reached the approved treatment duration, discontinued respiratory support (oxygen supplementation or mechanical ventilation), or been discharged from the hospital.	Section 5.3

Revised Section 6.1.1, 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 SOC) in subjects with COVID-19 who have respiratory failure, including mild to moderate ARDS.	Section 6.1.1
Revised Section 6.1.2, Secondary Objective • APL-9 pharmacodynamics (PD; the effect of APL-9 on ~~the~~ complement, coagulation, and inflammation ~~panel~~ biomarkers)	Section 6.1.2
Deleted pharmacokinetics and pharmacodynamics from exploratory objectives • ~~APL-9 PK~~ • ~~APL-9 pharmacodynamics (PD; the effect of APL-9 on the complement panel)~~	Section 6.1.3
Revised Secondary Objective Endpoints • Any-cause mortality (measured from beginning of treatment until the safety follow-up assessment 30 days after last study treatment (up to Study Day 51 with a +7-day window) ~~Day 30 follow-up assessment)~~ • 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]), ~~thrombotic microangiopathy~~ coagulopathy (reticulocyte count, schistocytes, lactate dehydrogenase, D-dimer, ferritin, haptoglobin, fibrinogen, CCI [redacted] and inflammatory cytokines (C-reactive protein, tumor necrosis factor α, IL-1β, and IL-6).	Section 6.2.2
Revised exploratory endpoints • ~~Presence of active SARS-CoV-2 infection assessed by qualitative reverse transcriptase polymerase chain reaction (RT-PCR), for SARS-CoV-2 on Day 28~~ • ~~APL-9 PK parameters~~ • ~~Observed values and changes from baseline in markers of complement activation (C3, C3a, C4, C4a, Bb, TCC, and AH50)~~ • 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.	Section 6.2.3
Revised Section 7.1 Overall Study Design to specify subjects who have respiratory failure and require respiratory support (supplemental oxygen or mechanical vent)	Section 7.1

Part 1 of the study is designed to evaluate the safety of open-label APL-9 with SOC in a small number of subjects who have respiratory failure (including mild to moderate ARDS) due to COVID-19 and who require respiratory support (supplemental oxygen or mechanical ventilation). Part 2 of the study is designed to evaluate the safety and efficacy of APL-9 with SOC compared with those of vehicle with SOC in a larger number of subjects who have respiratory failure (including mild to moderate ARDS) due to COVID-19 and who require respiratory support (supplemental oxygen or mechanical ventilation). Part 2 (Randomized Double-Blind Period): Subjects will receive treatment with APL-9 or vehicle from Day 1 through Day 7, ~~or resolution of ARDS (PaO_2/FiO_2 ratio >300 mm Hg)~~ discontinuation of respiratory support (supplemental oxygen or mechanical ventilation), or hospital discharge, whichever occurs earlier. ~~Resolution of ARDS in this study is defined according to the Berlin definition as PaO_2/FiO_2 ratio >300 mm Hg (ARDS Definition Task Force 2012).~~ The DMC may approve any extended treatment duration through Day 21; extended treatment will be allowed only in subjects who still require respiratory support (oxygen supplementation or mechanical ventilation) ~~have mild or moderate ARDS~~ at Day 7 with at least a 20-mm Hg increase in PaO_2 from baseline. Follow-up safety assessments for each subject will be collected 30 days following the last dose of ~~APL-9~~study treatment (up to 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 Study Day 51 with +7-day window). The DMC will perform safety and efficacy data reviews on an ongoing basis during Part 2. ~~Two reviews will be required: after the 10th subject enrolled in Part 2 reaches Day 7 (or is discharged following the resolution of ARDS) and after the 30th subject enrolled in Part 2 reaches Day 7 (or is discharged following the resolution of ARDS).~~ 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 2. After the 30th subject reaches the approved treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge 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 achieve resolution of ARDS~~), or hospital discharge. 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 ~~(or achieve resolution of ARDS)~~. Enrollment will not be suspended during the DMC reviews.	
Revised scientific rationale This study is designed to evaluate the safety of APL-9 in subjects with respiratory failure ~~mild to moderate ARDS~~ due to ~~confirmed~~ COVID-19, the disease caused by SARS-CoV-2 infection. Secondary objectives include assessments of efficacy of	Section 7.2

APL-9 (evaluating survival, length of hospital admission, and lung function), APL-9 PK results, and the effect of APL-9 on ~~the~~ complement ~~panel~~ activation biomarkers.	
Revised end of study definition The end of the study is defined as the date of the safety follow-up assessment 30 days after the last dose of study drug (up to Study Day 51 with +7-day window) ~~Day 30 follow-up assessment~~ for the last subject in the study.	Section 7.4
Revised Figure 1 Study Schema, DMC recommendation 2 treatment may be extended only for subjects who still require respiratory support (oxygen supplementation or mechanical ventilation) ~~have mild or moderate ARDS~~ at Day 7 with at least a 20-mm Hg increase in PaO_2 from baseline). Revised Figure 2: Randomization 1:1 Note: Two DMC reviews will occur: (1) after first 10 subjects reach the approved treatment duration, discontinuation of respiratory support, or hospital discharge; ~~(or resolution of ARDS)~~ and (2) after the first 30 subjects reach the approved treatment duration, discontinuation of respiratory support, or hospital discharge. ~~(or resolution of ARDS) and~~ The DMC may recommend changes to the protocol, including treatment extension up to 21 days for eligible subjects. Revised Figure 2: Treatment for 7 days Subjects may continue treatment for up to 21 days (only in subjects who still ~~have mild or moderate ARDS~~ require respiratory support at Day 7 with at least a 20-mm Hg increase in PaO_2 from baseline) per DMC recommendation and PI discretion (treatment may be modified at any point during Part 2) Revised Figure 2: Safety follow-up (Safety assessments may be performed at any time during the 30-day follow-up at PI's discretion but are required 30 days after last dose of study drug [up to Study Day 51 with +7-day window]) Revised column heading for Schedule of Activities, Part 1, and Part 2 Safety~~30-day~~ follow-up assessment~~period~~[a] Up to Study Day 51 (+7) Revised footnote a of Schedule of Activities, Table 1 a. In Part 2, dosing may be extended only in subjects who still require respiratory support (oxygen supplementation or mechanical ventilation~~) have mild or moderate ARDS~~ at Day 7 with at least a 20-mm Hg increase in PaO_2 from baseline. In Part 2, subjects will receive treatment through the DMC-approved treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge ~~or resolution of ARDS~~ (whichever occurs earlier). Through Part 2, the DMC may review efficacy and safety data and recommend changes to the study conduct on an ongoing basis, but it will be required to review efficacy and safety data after the 10th and 30th subjects reach the DMC-approved treatment duration, discontinuation of respiratory support, or hospital discharge, ~~or resolution of ARDS~~ (whichever occurs earlier). Enrollment will not be suspended during the DMC reviews. Subjects who ~~achieve resolution of ARDS or~~ reach the end of the approved treatment duration, discontinuation of respiratory support, or hospital discharge (whichever occurs earlier) must be assessed as indicated in the EOT visit column (for example, a subject who achieves ~~resolution of ARDS~~ discontinuation of respiratory support on Day 6 should be evaluated with a	Section 7.5

radiograph or computed tomographic scan even though it is not indicated as a Day 6 assessment). All subjects will be followed up 30 days after last study treatment (with a +7-day window), either in person (for subjects still hospitalized) or by phone (for subjects who have been discharged). All subjects will be followed up ~~30 days~~ at the safety follow-up assessment 30 days after last study treatment (up to Study Day 51 with a +7-day window), either in person (for subjects still hospitalized) or by phone (for subjects who have been discharged). Revised footnote f of Schedule of Activities, Table 1 Vital signs and ECG must be collected between the administration of the loading dose of study treatment and the initiation of the maintenance dose. Revised footnote h of Schedule of Activities, Table 1 A list of laboratory assessments is provided in Section 11.1.8. ~~Day 1 assessments should be collected within 1-2 hours of loading infusion.~~ Blood will be collected 3 times on Day 1: (1) once prior to administration of the APL-9 bolus, (2) once as soon as possible following the bolus (within 5-10 minutes) prior to the continuous infusion, and (3) once at 2 hours after the beginning of the continuous infusion. Revised footnote k of Schedule of Activities, Table 1 If confirmation of SARS-CoV-2 has occurred within 7 days of screening, the viral RNA or viral antigen test at screening/baseline is not mandatory.	
Revised subject inclusion criterion 2 2. Diagnosis of active SARS-CoV-2 infection. 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 RT-PCR) or 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. Note: Serology-based antibody tests do not detect presence of virus, and therefore are not considered diagnostic for active infection and cannot be used for study eligibility screening or for subsequent SARS-CoV-2 assessments. ~~2. Confirmed SARS-CoV-2 infection as determined by any method that is authorized, cleared, or approved by the US FDA (or equivalent local authority). Subjects may have previous confirmation of SARS-CoV-2 (within 7 days of screening) or may be assessed for SARS-CoV-2 at screening.~~ Revised subject inclusion criterion 3 ~~3. Have:~~ ~~a. Respiratory failure requiring oxygen supplementation or either invasive or non-invasive mechanical ventilation with PaO2/FiO2 ratio >100 mm Hg but ≤300 mm Hg with end positive airway pressure (EPAP) or positive end-expiratory pressure (PEEP)~~ ~~b. Worsening of respiratory symptoms in the past week.~~ ~~c. Bilateral opacities present on a chest radiograph or computed tomographic scan. These opacities must not be fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules.~~ ~~d. Respiratory failure cannot be fully explained by cardiac failure or fluid overload.~~	Synopsis, Section 8.1

3. Have respiratory failure requiring oxygen supplementation or either invasive or noninvasive mechanical ventilation with PaO_2/FiO_2 ratio >100 mm Hg. Respiratory failure cannot be fully explained by cardiac failure or fluid overload.	
Revised subject exclusion criterion 3 and criterion 5; deleted criterion 6 and renumbered subsequent exclusion criteria accordingly 3. History of neuromuscular degenerative disease ~~such as~~ (eg, amyotrophic lateral sclerosis, Duchenne muscular dystrophy, or multiple sclerosis) 5. Treatment with immune checkpoint inhibitors or other immunomodulators within 3 months prior to study enrollment (however, treatment with convalescent plasma, steroids, IL-6 inhibitors, and antiviral agents is NOT excluded) 6. ~~Treatment with convalescent plasma for COVID-19 within 3 months of baseline~~	Synopsis, Section 8.2
Revised Screening Failures Sites may initiate screening procedures prior to a subject's diagnosis of respiratory failure or ARDS.	Section 8.4
Revised study drug administration Dosing of subjects receiving APL-9 either as open-label treatment or by random, blinded assignment will be initiated with an IV infusion of 180 mg APL-9 in 50 mL of saline over a 10-minute period, followed within 1 hour by continuous infusion of 180 mg APL-9 in 250 mL saline at the rate of 15 mg/h (approximately 21 mL/h) until the end of study drug administration at Day 7 (or approved treatment extension), discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge, whichever occurs earlier.~~or resolution of ARDS~~. Dosing of subjects randomly assigned to vehicle control will be initiated with an IV infusion of 50 mL of saline over a 10-minute period followed immediately (and up to within 1 hour) by continuous infusion of approximately 21 mL of saline per hour until the end of study drug administration at Day 7 (or approved treatment extension), discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge, whichever occurs earlier.~~or resolution of ARDS~~. The treatments are intended to continue to either Day 7 or until the~~subject's ARDS is resolved (PaO_2/FiO_2 ratio >300 mm Hg)~~ subject no longer requires respiratory support (oxygen supplementation or mechanical ventilation) or is discharged from the hospital (whichever occurs earlier), except upon allowance by the DMC and by investigator discretion to administer treatment up to Day 21 (Part 2 only; extended treatment will be allowed only in subjects who still ~~have mild or moderate ARDS~~ require respiratory support at Day 7 with at least a 20-mm Hg increase in PaO_2 from baseline). If treatment is interrupted for any reason for more than 24 hours, treatment may not be resumed. A relapse of respiratory failure or ARDS due to COVID-19 must be reported as an adverse event. Under no circumstances can study drug be administered beyond the DMC-approved treatment window, and treatment may not be reinitiated if it is discontinued.	Section 9.1.1
Revised Discontinuation of Study Intervention	Section 10.1

In Part 2 dosing may be extended only in subjects who still require respiratory support (oxygen supplementation or mechanical ventilation) at Day 7 ~~have mild or moderate ARDS at day 7~~ with at least a 20-mm Hg increase in PaO_2 from baseline.	
Revised end-of-treatment assessments • The study end-of-treatment assessments are to be conducted on the day of hospital discharge. The ~~30-day (+7)~~ posttreatment follow-up assessment, conducted 30 days after the last dose of study drug (with a +7-day window), may be conducted either in the hospital or by telephone so that subjects do not have to be exposed to the hospital environment after hospital discharge.	Section 11
Revised wording for Day 1 Assessments Laboratory test samples (Table 2) are to be obtained at designated visits as detailed in the SoA (Table 1). ~~Day 1 assessments should be collected within 5 hours of loading infusion~~ Blood will be collected 3 times on Day 1: (1) once prior to administration of the APL-9 bolus, (2) once as soon as possible following the bolus (within 5-10 minutes) prior to the continuous infusion, and (3) once at 2 hours after the beginning of the continuous infusion. Revised Table 2, Clinical Laboratory Tests Additional laboratory tests were added to Table 2, which was reformatted to clearly indicate which tests would be performed at local and central/specialty laboratories.	Section 11.1.8
Updated definition of adverse events 11.2.1 Definition of Adverse Events An AE is any untoward medical occurrence associated with the use of a drug in humans whether or not it is considered drug related. An AE can, therefore, be any unfavorable and unintended sign, including a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related ~~causally~~ to the investigational product ~~(FDA Guidance for Industry). Any abnormal finding that is deemed not clinically significant is not an AE~~. Adverse events can be spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation and will be recorded during the study at the investigational site. All identified AEs must be recorded and described on the appropriate AE or SAE page of the eCRF. Fluctuating or nonsignificant changes in laboratory values do not necessarily qualify for AE reporting. If these changes in laboratory values are assessed as clinically significant and/or lead to discontinuation of administration of investigational product, these should be reported as an AE. If these laboratory values are linked to a diagnosis, only the diagnosis should be reported as an AE.~~Any medical condition that is present at the time when the subject is screened should be recorded on the medical history eCRF and not reported as an AE. However, if that condition deteriorates or severity changes at any time during the study, it should be recorded as an AE.~~ ~~Any AEs that occur prior to dosing on study Day 1 will be categorized as pretreatment events. Treatment-emergent adverse events will be defined as those AEs that occur or worsen in severity after initial dosing and during the 30-day (+7) posttreatment follow-up.~~	Section 11.2.1

~~A suspected adverse reaction (ADR) is any AE for which there is a reasonable possibility that the investigational product caused the AE. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the investigational product and the AE.~~	
Updated serious adverse events and moved to Section 11.2.2 ~~11.2.1.1~~ 11.2.2 Serious Adverse Event ~~If any AEs are serious, special reporting procedures will be followed, as described in Section 11.2.4.~~ ~~An SAE is any AE occurring during any study period (ie, baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator, or vehicle, that, in the view of either the investigator or Apellis Pharmaceuticals, Inc, fulfills one or more of the following criteria:~~ ~~• Results in death~~ ~~• Is immediately life threatening~~ ~~• Requires inpatient hospitalization or prolongation of existing hospitalization~~ ~~• Results in persistent or significant disability or incapacity~~ ~~• Results in a congenital abnormality or birth defect~~ An SAE is any AE or suspected adverse reaction that, in the view of either the investigator or sponsor, results in any of the following outcomes: death; life-threatening; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening*, or require hospitalization may be considered serious when, based upon appropriate medical judgment they may jeopardize the subject and may require medical/surgical intervention to prevent one of the outcomes listed in the above definition. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse. **Life-threatening* is defined as an AE or suspected adverse reaction, which, in the view of either the investigator or sponsor, places the subject at immediate risk of death as it occurred. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. Unexpected Adverse Event An AE is considered "unexpected" if it is not listed in the Reference Safety Information section of the investigator's brochure in effect at that time of event onset.~~Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, according to appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events may include infections that require antibiotic treatment, allergic bronchospasm requiring intensive treatment in an emergency~~	Section 11.2.2

~~room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.~~ ~~A *life-threatening AE* is defined as an AE or suspected ADR that, in the view of either the investigator or Apellis Pharmaceuticals, Inc, places the subject at immediate risk of death. It does not include an AE or suspected ADR that, had it occurred in a more severe form, might have caused death.~~ ~~An *unexpected AE* is defined as an AE or suspected ADR that is not listed in the investigator's brochure, is not listed at the specificity or severity that has been observed, or is not consistent with the risk information described in the general investigational plan or elsewhere in the current protocol, as amended.~~	
Moved evaluation of adverse events to Section 11.2.3 ~~11.2.2~~ 11.2.3 Evaluation of Adverse Events	Section 11.2.3
Updated recording of adverse events and moved to Section 11.2.4 ~~11.2.3~~ 11.2.4 Recording Adverse Events ~~Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse rate must be reported as AEs. However, abnormal values that constitute SAEs or lead to discontinuation of administration of study drug must be reported and recorded as AEs. Information about AEs and SAEs will be collected from the signing of the ICF until the study end-of-treatment visit. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, and serious outcome (if applicable) and whether or not the subject discontinued treatment as a result of the event.~~ ~~It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, as summarized in Table 4, whereas seriousness is defined by the criteria under Section 11.2.2. An AE of severe intensity may not be considered serious.~~ ~~Should a pregnancy occur, it must be reported and recorded on the Apellis Pharmaceuticals, Inc, pregnancy form. As described in Section 11.2.5, pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication~~ Adverse events and SAEs will be collected from the signing of the consent form until the safety follow-up assessment, or 30 days after the last dose of study treatment, up to Study Day 51 (+7). Any events that occur prior to dosing will be categorized as pretreatment events; events occurring after dosing will be recorded as TEAEs (start date of dosing and, therefore, categorization of the event will be dependent on randomization assignment). For each AE, the investigator will evaluate and report the onset date (and time if applicable), resolution date (and time if applicable), intensity, causality, action taken, serious outcome, and whether or not it caused the subject to discontinue the study. If possible, the outcome of any AE that caused permanent discontinuation or was present at the end of the study should be reported, particularly if the AE was considered by the investigator to be related to the investigational product. Subjects experiencing AEs that cause interruption or discontinuation of investigational	Section 11.2.4

product, or those experiencing AEs that are present at the safety follow-up assessment (30 days after the last dose of APL-9), up to study Day 51 (+7) should receive follow-up as appropriate. All SAEs must be reported to the sponsor/Apellis Safety via eCRF immediately and within 24 hours of becoming aware of the event, whether or not the event is deemed treatment-related. If the electronic data capture (EDC) system is not operational (or for paper-based study[ies]), the site must complete the paper SAE form and email to PPD , also within 24 hours of becoming aware of the event. The reported information submitted as a paper SAE must be entered into the EDC system once it becomes operational. Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.	
Updated reporting of adverse events and moved to Section 11.2.5 ~~11.2.4~~ 11.2.5 Reporting Adverse Events ~~All SAEs and pregnancies must be reported to Apellis Pharmaceuticals, Inc, via eCRF immediately, whether or not the event is deemed treatment-related. If the electronic data capturing system is not operational, the site must complete the appropriate paper SAE form and email it to the number/address listed on the SAE form immediately on becoming aware of the event. The reported information submitted as a paper SAE must be entered into the electronic data capturing system once it becomes operational.~~ ~~The collection of clinical information will begin after the subject's written consent to participate in the study has been obtained. Adverse events will be collected after signing the ICF through completion of the last study visit. Any events that occur prior to dosing will be categorized as pretreatment events; events occurring after dosing will be recorded as TEAEs (the start date of dosing and therefore the categorization of the event will be dependent on randomization assignment). Adverse events may be either spontaneously reported or elicited during questioning and examination of a subject.~~ ~~All identified AEs, including clinically significant laboratory findings, must be recorded and described on the appropriate AE page of the eCRF. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. Adverse events will be coded in accordance with the *Medical Dictionary for Regulatory Activities* (MedDRA).~~ ~~Subjects experiencing AEs that cause interruption or discontinuation of study drug or experiencing AEs that are present at the exit visit should receive follow-up as appropriate. SAEs should be followed up until resolution. If possible, the outcome of any AE that caused permanent discontinuation or was present at the end of the study should be reported, particularly if the AE was considered by the investigator to be related to the study drug~~ The sponsor has the responsibility to inform concerned health authorities, ethics committees, and investigators about suspected unexpected serious adverse reactions in line with GCP guidance and applicable regulatory requirements. If required, specific SAEs should be reported to the concerned ethics committees in compliance with local requirements. ~~Apellis Pharmaceuticals, Inc, and/or its designee are responsible for reporting SAEs to all applicable regulatory agencies and the central ethics committees within the required timelines.~~	Section 11.2.5

~~Investigators are responsible for submitting required safety information to their local institutional review board (IRB) or independent ethics committee (IEC) as per local regulations. This information includes but is not limited to any safety alert letters received from Apellis Pharmaceuticals, Inc, and any SAEs occurring at their investigative sites.~~	
Revised Pregnancy section and moved to Section 11.2.6 ~~11.2.5~~ 11.2.6 Pregnancy ~~Should a pregnancy occur, it must be reported and recorded on the Apellis Pharmaceuticals, Inc, pregnancy form. Although pregnancy is not considered an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication, the outcome of a pregnancy may be an SAE if there is a spontaneous abortion, congenital anomaly, or other adverse fetal outcome.~~ ~~The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.~~ ~~All reports of congenital abnormalities, birth defects, or other adverse fetal outcomes are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All SAEs are to be reported to Apellis Pharmaceuticals, Inc, on the SAE form.~~ ~~If a female subject/partner of a male subject becomes pregnant during the study, the investigator should report the pregnancy to the safety monitor within 1 calendar day of being notified. The subject or partner should be followed by the investigator until completion of the pregnancy. At the completion of the pregnancy, the investigator will document and report the outcome. If the outcome of the pregnancy meets the criteria for classification as an SAE (ie, postpartum complication, stillbirth, neonatal death, spontaneous abortion, or congenital anomaly) the investigator should follow the procedures described in Section for reporting~~ Although pregnancy is not an AE, all pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring with a female subject or the female partner of a male subject must be followed to conclusion to determine their outcome and are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Apellis Safety within 24 hours of the investigator's awareness using the paper Pregnancy Report Form. The Pregnancy Report Form shall be signed and dated by the investigator and submitted via email to PPD . The investigator must follow the subject until completion of the pregnancy and must report the outcome of the pregnancy (eg, delivery, termination, etc) and neonatal status up to 12 months post delivery. An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. In the event of an abnormal outcome, an SAE Report Form will be required.	Section 11.2.6
Updated Section 11.3, Overdose 11.3 Drug Abuse, Misuse, Overdose, and Medication Error Occurrences of events of drug abuse, drug misuse, drug overdose, and medication error must be reported to Apellis Safety.	Section 11.3

Abuse of a medicinal product: Persistent or sporadic, intentional excessive use of medicinal products, which is accompanied by harmful physical or psychological effects. Misuse: Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration and/or the indication(s) or not within the legal status of its supply. Overdose: Administration of a quantity of study drug given per administration or per day, which is above the assigned dose. Medication Error: An error made in prescribing, dispensing, administration and/or use of the study drug. Medication errors are reportable to the sponsor as defined below: • The dispensing, administration, and/or use of the unassigned study drug. • The administration and/or use of an expired study drug. All AEs or SAEs associated with drug abuse, drug misuse, drug overdose, or medication error must be reported as appropriate.~~To date, neither nonclinical nor clinical studies of APL-9 have identified safety risks specifically associated with an APL-9 overdose. In case of suspected overdose please contact the sponsor immediately.~~	
Revised section heading 11.4 and updated text 11.4 Viral RNA/Viral Antigen Assessment Presence of SARS-CoV-2 viral RNA or viral antigen will be detected in respiratory specimens (collected using nasopharyngeal or oropharyngeal swabs) with a qualitative nucleic acid amplification test (such as RT-PCR) or 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 for active infection and cannot be used for study eligibility screening or for subsequent SARS-CoV-2 assessments.	Section 11.4
Revised Section 11.5, Pharmacokinetics The exposure of subjects to APL-9 will be evaluated in serum from blood collected in a serum separator tube. Two serum aliquots of at least 0.5 mL will be stored at –70 °C and shipped on dry ice. ~~Blood will be collected on Day 1, once prior to administration of the APL-9 bolus, once as soon as possible following the bolus (5-10 minutes), and before the continuous infusion commences. Blood will also be collected at 2 hours after the initial bolus administration.~~Blood will be collected 3 times on Day 1: (1) once prior to administration of the APL-9 bolus, (2) once as soon as possible following the bolus (within 5-10 minutes) prior to the continuous infusion, and (3) once at 2 hours after the beginning of the continuous infusion. Blood will then be collected once daily between 1-2 hours after the first dose, on Days 3, 5, 7, 11 (if treatment is ongoing), and 15 (if treatment is ongoing) and at the end-of-treatment visit (if the patient is discharged on a day not indicated for a clinical laboratory test~~PK~~ sample).	Section 11.5
Revised Section 11.6, Pharmacodynamics The pharmacodynamic parameters evaluated in this study~~are~~ related to complement activation ~~markers~~ (are levels of C3, C3a, Bb, C4, C4a, C5a, and TCC) and a hemolytic assay measuring the function of the alternative complement pathway (AH50). The pharmacodynamic parameters evaluated in this study related to	Section 11.6

~~thrombotic microangiopathy~~ coagulopathy are reticulocyte count, presence of schistocytes, levels of D-dimer, ferritin, lactate dehydrogenase, haptoglobin, fibrinogen, CCI [redacted]. The pharmacodynamic parameters evaluated in this study related to inflammation are levels of C-reactive protein, tumor necrosis factor α, IL-1β, and IL-6. The complement activation markers and inflammatory cytokines will be analyzed in plasma from blood collected in K2 EDTA (dipotassium ethylenediaminetetraacetic acid) tubes with the exception of C-reactive protein, which is measured from serum. The AH50 hemolytic assay will be measured in serum from blood collected in red plain top (no gel) tubes. ~~The thrombotic microangiopathy~~ coagulopathy markers will be analyzed in plasma collected in sodium citrate tubes or serum. These blood samples will be collected at the same time as the pharmacokinetic samples described in Section 11.5~~. Blood will be collected on the first day, once prior to administration of the APL-9 bolus, once as soon as possible following the bolus (5 to 10 minutes), and before the continuous infusion commences. Blood will also be collected at 2 hours after the initial bolus administration. Blood will be collected then once daily, between 1-2 hours after first dose on Days 3, 5, 7, 11 (if treatment is ongoing), 15 (if treatment is ongoing), and the end-of-treatment visit (if the patient discharges on a day not indicated for a PK/PD sample).~~ Blood will be collected 3 times on Day 1: (1) once prior to administration of the APL-9 bolus, (2) once as soon as possible following the bolus (within 5-10 minutes) prior to the continuous infusion, and (3) once at 2 hours after the beginning of the continuous infusion. If the patient discharges on a day not indicated for a clinical laboratory test sample, blood will be collected between 1-2 hours after first dose of the end-of-treatment (EOT) visit.	
Revised Section 12.3.3 Analysis of Time-to-Event Data Event rates (eg, mortality through the safety ~~Day 30~~ follow-up assessment) will be estimated along with the corresponding 2-sided 95% CI (or 2-sided 90% CI if appropriate).	Section 12.3.3
Updated schedule of reviews by the independent data monitoring committee for Part 2: In Part 2, ~~DMC review will occur after first 10 subjects reach the approved treatment duration (or resolution of ARDS) and after the first 30 subjects reach the approved treatment duration (or resolution of ARDS).~~ two reviews will be required: 1. After the 10th subject reaches the approved treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge 2. After the 30th subject reaches the approved treatment duration, discontinuation of respiratory support (oxygen supplementation or mechanical ventilation), or hospital discharge	Section 12.7