A RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED PHASE I STUDY TO EVALUATE THE SAFETY AND EFFICACY OF AMPION IN PATIENTS WITH PROLONGED RESPIRATORY SYMPTOMS DUE TO COVID-19 (LONG-COVID)

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: AP-018

NCT04880161

14 FEBRUARY 2022

STATISTICAL ANALYSIS PLAN

Protocol AP-18

A Randomized, Double-Blinded, Placebo-Controlled Phase I Study to Evaluate the Safety and Efficacy of Ampion in Patients with Prolonged Respiratory Symptoms due to COVID-19 (Long-COVID)

Drug Development Phase:	Phase 1
Investigational Product:	Ampion
Indication:	Prolonged Respiratory Symptoms due to COVID-19 (Long-COVID)
Sponsor:	Ampio Pharmaceuticals, Inc. 373 Inverness Parkway Englewood, CO 80112
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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWT	Six-minute walk test
AE	Adverse event
ARDS	Acute respiratory distress syndrome
BP	Blood pressure
CDC	Centers for Disease Control and Prevention
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 19
CRO	Contract research organization
DSMB	Data and safety monitoring board
EC	Ethics committee
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic data capture
HSA	Human serum albumin
ICH	International conference on harmonization
IRB	Investigational review board
ITT	Intent to treat
IV	Intravenous
mBDS	Modified Borg Dyspnoea Scale
PASC	Post Acute Sequelae SARS-CoV-2
SAE	Serious adverse event
SOP	Standard operating procedure
Sp02	Blood oxygen saturation
TNFα	Tumor necrosis factor alpha
WHO	World Health Organization

2 INTRODUCTION

This statistical analysis plan (SAP) outlines the proposed statistical methods to be implemented during the review of data to ensure that it confirms with categories determined by the CRF or the anticipated ranges for continuous variables and analysis of data collected within the scope of Clinical Protocol AP-018, "A Randomized, Double-Blinded, Placebo-Controlled Phase I Study to Evaluate the Safety and Efficacy of Ampion in Patients with Prolonged Respiratory Symptoms due to COVID-19 (Long-COVID)".

It is not intended that each table, listing, or graph will be included in the clinical study report (CSR). It is also possible that additional analyses will be conducted after review of the data. Any analyses or summaries not specified in the SAP, but performed after review of the data, will be identified in the CSR as post hoc.

There will be an unblinded team responsible for obtaining the required material for the analysis from the study's unblinded data manager (DM) for the clinical trial. The unblinded team will present the results of the interim analysis at D28 to the sponsor in a blinded fashion.

2.1 PURPOSE OF THE ANALYSES

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in the pandemic spread of coronavirus disease 2019 (COVID-19), which has a high rate of infection, has a high rate of hospitalization, and has overwhelmed healthcare systems. Increasing numbers of people with COVID-19 are experiencing the lingering effects of COVID-19 and continue to have prolonged respiratory complications months after the onset of the disease, also known as Post-Acute Sequelae of SARS-CoV-2 (PASC), long-COVID, and/or long-hauler patients.

The SARS-CoV-2 virus is transmitted through the respiratory system, which can cause a severe dysregulation of the immune response and damage in the lungs. Chronic, prolonged inflammation of the lungs maybe responsible for a myriad of continuing respiratory signs and symptoms post-infection, including cough, shortness of breath, chest discomfort, low exercise tolerance and low blood oxygen saturation.

Ampion is the low molecular weight filtrate of human serum albumin with the in vitro ability to modulate inflammatory cytokine levels. Ampion has the potential to improve clinical outcomes for long-COVID patients.

This study aims to evaluate the safety of Ampion and the clinical outcomes in patients with long-COVID. This is the first study for at-home use of Ampion inhaled treatment for long-COVID patients and will be used to inform decisions for the clinical development of Ampion.

2.2 STUDY OBJECTIVES

2.2.1 Primary Objective

The primary trial objective is to evaluate the safety and tolerability of inhaled Ampion versus placebo control in adult participants with prolonged respiratory complications after COVID-19 infection.

2.2.2 Secondary Objective

The exploratory trial objectives evaluate the efficacy of inhaled Ampion versus placebo control in improving the clinical course and outcomes of participants with prolonged respiratory complications after a COVID-19 infection.

2.3 ENDPOINTS

2.3.1 Primary

Adverse events (AEs) will be evaluated from baseline through Day 60. The primary endpoint is incidence and severity of adverse events (AEs) and serious adverse events (SAEs) from baseline to Day 28 and Day 60.

2.3.2 Exploratory

Exploratory efficacy endpoints assess the effect of inhaled Ampion compared to placebo on the clinical outcomes for participants with prolonged respiratory complications after a COVID-19 infection as follows:

Objective	Endpoint
Assess the effect of Ampion compared to placebo on symptom improvement	• Change in FDA Assessment of 14 Common COVID-19-Related Symptoms questionnaire from baseline to Day 7; Day 28; Day 60 • Change in Borg Dyspnoea Scale (mBDS) from baseline to Day 7; Day 28; Day 60 • Change in all-cause mortality
Assess the effect of Ampion compared to placebo on pulmonary function	• Change in blood oxygen saturation from baseline to Day 7; Day 28; Day 60 • Change in six-minute walk test (6MWT) score from baseline to Day 7; Day 28; Day 60
Assess the effect of Ampion compared to placebo on global impression	• Change in Quality-of-Life Assessment using SF-36 from baseline to Day 7; Day 28; Day 60

	• Change in Fatigue questionnaire from baseline to Day 7; Day 28; Day 60 • Change in Sleep Disturbance questionnaire from baseline to Day 7; Day 28; Day 60
Assess the effect of Ampion compared to placebo on radiographic findings	• Change in chest imaging on ground-glass opacity, local patchy shadowing, bilateral patchy shadowing, and/or interictal abnormalities from baseline to Day 60

3 STUDY METHODS

3.1 STUDY DESIGN

This is a randomized, double-blinded, placebo-controlled Phase I trial to evaluate the safety and efficacy of a 5-day Ampion inhalation treatment in participants with prolonged respiratory complications after a COVID-19 infection.

Participants with COVID-19 infection will be screened for eligibility and consented. Participants (n=30) will be randomized in one of two groups, active (n=15) or placebo control (n=15) and randomized 1:1 following an equal allocation. The treatment arm will receive Ampion inhalation treatment, and the control arms will receive saline inhalation treatment. Participants will be followed for 60 days.

3.2 RANDOMIZATION AND BLINDING

The treatment in this study will be blinded to the subjects, investigators, any individual conducting the study (e.g., nursing and pharmacy staff) and clinical study personnel. Participants will be assigned to treatment by a randomization schedule developed and maintained by an independent statistician.

Participants are randomized 1:1 to active treatment or placebo control, following an equal allocation to treatment arms as follows:

Treatment Arm	**Investigational Treatment**
Active	Ampion Inhalation for 5-days
Control	Placebo Inhalation for 5-days

Given the changing nature of the pandemic, periodic adjustments to the allocation ratio may be made in an effort to achieve equal allocation across the treatment arms at the end of the enrollment.

Study drug and placebo will be provided as blinded investigational product (IP) with appropriate labeling to link to the randomization code. Where required, safety personnel and/or investigator may be unblinded to a particular subject's treatment assignment to meet reporting requirements to Regulators.

A data management plan and statistical analysis plan will be approved by the sponsor prior to unblinding study data.

4 SAMPLE SIZE

This is a Phase I study and is not intended to be powered for the primary endpoint. This trial is designed to enroll up to 30 subjects, randomized to active treatment or placebo control, following an equal allocation to treatment arms (n=15 subjects per arm).

5 STUDY ENDPOINTS AND ANALYSES

5.1 PRIMARY ENDPOINT

The primary endpoint is incidence and severity of adverse events (AEs) and serious adverse events (SAEs) from baseline to Day 28.

The hypotheses to be tested are:

$H_0: \pi_A = \pi_S$ versus $H_A: \pi_A \neq \pi_S$

Where π_A and π_S represent the adverse event rates for Ampion and placebo during the first 28 days after randomization.

The difference between Ampion and Placebo will be tested using the appropriate chi-square test or Fisher's exact test utilizing PROC FREQ with the EXACT option, if necessary.

5.2 EXPLORATORY (EFFICACY) ENDPOINTS

There are several exploratory endpoints. In order to preserve the alpha level these will be tested hierarchically in the order presented here. Each endpoint along with the analysis method and SAS procedure to analyze the data is presented.

5.2.1 Assess the effect of Ampion compared to placebo on symptom improvement

- Change in FDA Assessment of 14 Common COVID-19-Related Symptoms questionnaire from baseline to Day 7; Day 28; Day 60

  The hypotheses to be tested are:

  $H_0: \mu_A = \mu_S$ versus $H_A: \mu_A \neq \mu_S$

Where μ_A and μ_S represent the score shift through day 7, 28, and 60 for Ampion and Placebo after randomization. The difference between Ampion and Placebo with respect to the percent change from baseline at day 7, 28, and 60 will be tested utilizing a Wilcoxon rank-sum test via PROC NPAR1WAY. To assess any potential time trends an exploratory repeated measures analysis of variance will be performed with terms for treatment, time and the interaction between the two. This will be done utilizing PROC GLM with the REPEATED option.

- Change in Borg Dyspnoea Scale (mBDS) from baseline to Day 7; Day 28; Day 60

  The hypotheses to be tested are:

  H_0: $\mu_A = \mu_S$ versus H_A: $\mu_A \neq \mu_S$

  Where μ_A and μ_S represent the scale shift through day 7, 28, and 60 for Ampion and Placebo after randomization. The difference between Ampion and Placebo with respect to the percent change from baseline at day 7, 28, and 60 will be tested utilizing a Wilcoxon rank-sum test via PROC NPAR1WAY. To assess any potential time trends an exploratory repeated measures analysis of variance will be performed with terms for treatment, time and the interaction between the two. This will be done utilizing PROC GLM with the REPEATED option.

- Change in all-cause mortality

  The hypotheses to be tested are:

  H_0: $\pi_A = \pi_S$ versus H_A: $\pi_A \neq \pi_S$

  Where π_A and π_S represent the all-cause mortality rates for Ampion and Placebo during the first 60 days after randomization.

  The difference between Ampion and Placebo will be tested using the appropriate chi-square test or Fisher's exact test utilizing PROC FREQ with the EXACT option, if necessary

5.2.2 Assess the effect of Ampion compared to placebo on pulmonary function

- Change in blood oxygen saturation from baseline to Day 7; Day 28; Day 60

  The hypotheses to be tested are:

  H_0: $\mu_A = \mu_S$ versus H_A: $\mu_A \neq \mu_S$

  Where μ_A and μ_S represent the percentage shift through day 7, 28, and 60 for Ampion and Placebo after randomization. The difference between Ampion and Placebo with respect to the percent change from baseline at day 7, 28, and 60 will be tested utilizing

a Wilcoxon rank-sum test via PROC NPAR1WAY. To assess any potential time trends an exploratory repeated measures analysis of variance will be performed with terms for treatment, time and the interaction between the two. This will be done utilizing PROC GLM with the REPEATED option.

- Change in six-minute walk test (6MWT) score from baseline to Day 7; Day 28; Day 60

  The hypotheses to be tested are:

  H_0: $\mu_A = \mu_S$ versus H_A: $\mu_A \neq \mu_S$

  Where μ_A and μ_S represent the percentage shift through day 7, 28, and 60 for Ampion and Placebo after randomization. The difference between Ampion and Placebo with respect to the percent change from baseline at day 7, 28, and 60 will be tested utilizing a Wilcoxon rank-sum test via PROC NPAR1WAY. To assess any potential time trends an exploratory repeated measures analysis of variance will be performed with terms for treatment, time and the interaction between the two. This will be done utilizing PROC GLM with the REPEATED option.

5.2.3 Assess the effect of Ampion compared to placebo on global impression

- Change in Quality-of-Life Assessment using SF-36 from baseline to Day 7; Day 28; Day 60

- Change in Fatigue questionnaire from baseline to Day 7; Day 28; Day 60

- Change in Sleep Disturbance questionnaire from baseline to Day 7; Day 28; Day 60

  The hypotheses to be tested for all three assessments are:

  H_0: $\mu_A = \mu_S$ versus H_A: $\mu_A \neq \mu_S$

  Where μ_A and μ_S represent the percentage shift through day 7, 28, and 60 for Ampion and Placebo after randomization. The difference between Ampion and Placebo with respect to the percent change from baseline at day 7, 28, and 60 will be tested utilizing a Wilcoxon rank-sum test via PROC NPAR1WAY. To assess any potential time trends an exploratory repeated measures analysis of variance will be performed with terms for treatment, time and the interaction between the two. This will be done utilizing PROC GLM with the REPEATED option.

5.2.4 Assess the effect of Ampion compared to placebo on radiographic findings

- Change in chest imaging on ground-glass opacity, local patchy shadowing, bilateral patchy shadowing, and/or interictal abnormalities from baseline to Day 60. These changes will be assessed qualitatively with descriptive information presented.

6 GENERAL CONSIDERATIONS

6.1 TIMING OF ANALYSES

An interim analysis for safety and efficacy endpoints will be performed once all subjects have completed their Day 28 assessments. The final analysis will be performed after all subjects have completed the study.

6.2 ANALYSIS POPULATIONS

6.2.1 Safety Analysis Population

The safety analysis population is defined as all patients who are randomized and receive any study medication. Participants will be analyzed as treated.

6.2.2 Intent-to-treat Population

The intent-to-treat (ITT) analysis population is defined as all randomized patients. All efficacy analyses will be performed in the ITT population. Patients will be analyzed as randomized.

6.3 MISSING DATA

All data collected under this study protocol will be included in the assessment of patient safety. Missing or incomplete AE data will assume greatest relationship to study drug and/or severity.

6.4 INTERIM ANALYSES AND DATA MONITORING

The interim analysis will involve unblinded data. Only a small, sequestered team will have access to the unblinded data and results. The data will not be transferred, or results viewed by any person involved in the day-to-day conduct of the clinical trial, including, but not limited to the blinded sponsor staff, Medical Monitor, and/or blinded CRO staff. These individuals will remain blinded to the results.

The unblinded team will be responsible for obtaining the required material for the analysis from the study's unblinded data manager (DM) for the clinical trial. The unblinded team will present the results of the interim analysis to the sponsor in a blinded fashion.

All individuals on the sequestered team who are unblinded will be documented and archived by the sponsor

A Data Safety Monitoring Board (DSMB) will be established to review the safety, as the study progresses, of IV Ampion. The DSMB will be primarily responsible for reviewing any serious Adverse Event (SAE) and other clinically important safety findings (e.g., discontinuations due to AEs) that may occur during the study. The study may be stopped upon recommendation by the DSMB.

7 SUMMARY OF STUDY DATA

Data will be summarized by each treatment arm and by pooled Control and Ampion arms. Descriptive statistics on continuous variables will include mean, standard deviation, median, 25^{th,} and 75th percentiles, and range. Change from baseline will include a 95% confidence interval. Categorical variables will be summarized using frequency counts and percentages. Data listings of individual subject's data will be provided.

7.1 SUBJECT DISPOSITION

The number of subjects who are randomized, receive study drug, and complete the study will be summarized. The number of subjects included in the safety and ITT analysis sets will be included in the table. Attendance at each assessment (see Schedule of Assessments), including missed visits, discontinuations, lost to follow-up, and percentage accountability will be summarized. A list of subjects who withdraw early will be provided. It will include the reason and timing of the withdrawal. Similarly, the reason any subject is excluded from an analysis set will also be provided.

7.2 PROTOCOL DEVIATIONS

Significant known protocol deviations will be noted for individual subjects; a summary table may also be provided.

7.3 DEMOGRAPHIC AND BASELINE VARIABLES

Age, gender, race, height and weight, and comorbidities will be summarized by treatment arm for all subjects receiving study drug, using descriptive statistics.

Comparability of demographic and baseline characteristics will be evaluated between the Placebo and Ampion arms. Comparisons will use a two-sample t-test/Wilcoxon rank-sum test for continuous variables or a chi-square test (or Fisher's exact test if any expected value is less than 5) for categorical variables.

The following demographic and baseline characteristics will be evaluated:

1) Age (calculated as [date of study entry-date of birth]/365.25)
2) Gender
3) Race
4) Height
5) Weight

7.4 MEDICAL HISTORY AND PHYSICAL EXAM

The number and percent of participants with past and current medical disorders at the time of randomization will be presented overall and by treatment group for the ITT analysis population.

The following variables will be included:

1) Medical history term

8 SAFETY EVALUATION

The safety analyses of exposure, AEs, concomitant medications, and vital signs will include descriptive statistics and will be summarized separately by treatment arm and overall. Summaries of AEs will be generated by type (AE or SAE), body system and preferred term, severity, and relationship to study product.

8.1 EXPOSURE

Total exposure to the test product or placebo will be calculated by treatment arm. Descriptive statistics will be presented.

8.2 ADVERSE EVENTS

Adverse events (AEs) will be evaluated from baseline through Day 60. The primary endpoint is incidence and severity of adverse events (AEs) and serious adverse events (SAEs) from baseline to Day 28. The primary endpoint analysis is presented in Section 5.1.

There will be no statistical tests for incidence and severity of AEs. AEs will be tabulated using descriptive statistics and shift tables of lab tests will be presented for safety assessment.

All reported AEs, will be listed, documenting the course, outcome, severity, and causality to study drug. Verbatim terms on CRFs will be mapped to preferred terms and related system organ class using the Medical Dictionary for Regulatory Activities (MedDRA).

8.3 CONCOMITANT MEDICATIONS

The number and percent of subjects receiving concomitant medications or therapies prior to and during the study and at the final visit will be tabulated and presented overall and by treatment group for the ITT analysis population.

Concomitant medications/treatments will be summarized using descriptive statistics and will be presented by type of drug (WHO DRUG classification) overall and by treatment group for the safety and ITT analysis populations. There should be no significant differences in the use of concomitant treatments between groups. Differences will be assessed using a chi-square or Fisher's exact test.

8.4 VITAL SIGNS

Vital signs will be listed for each subject. These will include temperature, respiration, pulse, and blood pressure. Summaries over time and changes from baseline will be provided.

9 TECHNICAL DETAILS

All analyses will be conducted using SAS Version 9.4. MedDRA Version 24.0 will be used to code adverse events and medical history conditions.

10 CHANGES IN CONDUCT OF STUDY OR TO PLANNED ANALYSES FROM PROTOCOL

Deviations from the statistical analyses outlined in this plan will be indicated; any further modifications would be noted in the final statistical analyses.

11 REFERENCES

12 LISTING OF TABLES, LISTINGS, AND FIGURES

12.1 TABLES

10.1 Accountability

10.1.1	Accountability (Analysis population: All Enrolled)
10.1.2	Analysis Populations (Analysis population: All Enrolled)
10.1.3	Subject Disposition (All Screened)
10.1.4	Major Protocol Deviations (Analysis population: All Enrolled)
10.1.5	Demographics and Baseline Characteristics (Analysis population: ITT)

10.2 Efficacy (Analysis population: ITT)

10.2.1	Summary of Change in FDA Assessment of 14 Common COVID-19-Related Symptoms
10.2.2	Summary of Change in Borg Dyspnoea Scale
10.2.3	Summary of Change in All-Cause Mortality
10.2.4	Summary of Change in Blood Oxygen Saturation
10.2.5	Summary of Change in Six-Minute Walk Test
10.2.6	Summary of Change in SF-36 Quality of Life Assessment
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10.3 Safety

10.3.1	Exposure to Study Treatment
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10.3.3	Incidence and Severity of Serious Treatment-Emergent (TEAE) Events from Baseline to Day 28
10.3.4	Overall Summary of Treatment-Emergent Adverse (TEAE) Events
10.3.5	Incidence of TEAEs by System Organ Class and Preferred Term
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10.3.11.1	Concomitant Medication Use by ATC Level 1
10.3.11.2	Concomitant Medications Preferred Term in Descending Order of Use
10.3.11.3	Medication Started on Study Preferred Term in Descending Order of Use

12.2 LISTINGS

12.3 LISTINGS

Adverse Events

Subject Accountability

1. Randomization List (including, subject ID, randomization number, randomized treatment and treatment administered, and date of treatment)
2. Inclusion and Exclusion Criteria
3. Protocol Deviations
4. Subjects Withdrawing from the Study Prematurely (date and reason)
5. Analysis Populations with Reason for Exclusion (if populations differ)

Demographics and Baseline Characteristics

6. Demographics and Baseline Characteristics

   [age, sex, race, ethnicity, weight, height, BMI]
7. Medical History
8. Baseline Medication Use

Efficacy

9. FDA Assessment of 14 Common COVID-19-Related Symptoms
10. Borg Dyspnoea Scale
11. Deaths
12. Blood-Oxygen Saturation (SpO2)
13. Six-Minute Walk Test

14. SF-36 Quality of Life Assessment
15. Fatigue Questionnaire
16. Sleep Disturbance Questionnaire
17. Chest Imaging

Safety

18. Exposure to Study Treatment
19. All Adverse Events [with indication of TEAE]
20. Concomitant Medications
21. Vital Signs Data [with flagging of values outside of normal range]
22. ECG Data

12.4 FIGURES (TBD)

13 HANDLING OF MISSING OR INCOMPLETE DATES FOR ADVERSE EVENTS AND CONCOMITANT MEDICATIONS

13.1 IMPUTATION RULES FOR PARTIAL OR MISSING STOP DATES

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or concomitant medication stopped and the stop date will be imputed, if partial.

		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		Missing
Start Date		**<1st Dose**	**≥1st Dose**	**<1st Dose yyyymm**	**≥1st Dose yyyymm**	**<1st Dose yyyy**	**≥1st Dose yyyy**	
Partial: yyyymm	**=1st Dose yyyymm**	2	1	2	1	N/A	1	1
	≠ 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	**=1st Dose yyyy**	3	1	3	1	N/A	1	1
	≠ 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

14 SCHEDULE OF EVENTS

	Screen	Treatment					Post-Treatment Follow-Up		
Study Day	**-3 to 1**	**1[2]**	**2**	**3[2]**	**4**	**5[2]**	**7**	**28**	**60**
Visit Window (± days)	**--**	**--**	**--**	**--**	**--**	**--**	**3**	**3**	**3**
COVID-19 tests	X								
Informed consent	X								
Medical history and pre-existing conditions	X								
Electrocardiogram (ECG)	X								
Pregnancy test	X								
Inclusion/exclusion criteria	X	X							
Demographics	X								
Randomization		X							
Treatment[1,2]		X	X	X	X	X			
Health check		X		X		X			
Blood oxygen saturation		X					X	X	X
Assessment of 14 Common COVID-19-Related symptoms questionnaire		X					X	X	X
Borg Dyspnoea Scale (mBDS)		X					X	X	X
Walk test		X					X	X	X
Chest x-ray imaging		X[3]							X
Concomitant medications[2]		X	X	X	X	X	X	X	X
Quality of Life Assessment (SF-36)		X					X	X	X
PROMIS Fatigue questionnaire		X					X	X	X
PROMIS Sleep Disturbance questionnaire		X					X	X	X
Adverse events[2]		X	X	X	X	X	X	X	X

[1] Day 1, baseline assessments (health check, blood oxygen saturation, assessment of symptoms/questionnaires, mBDS, walk test, and chest x-ray) should occur before the first dose of treatment. These tests and the first dose of treatment will occur at the clinic. Treatment for the remainder of Day 1 and Days 2, 3, 4, 5 will occur at home.
[2] Day 1 post-first dose, Day 3 and Day 5 health check, concomitant medications and adverse event collection will occur via telephone visit.
[3] Baseline chest x-ray may be performed after Screening, up to 3 days prior to Day 1.

15 APPENDIX

15.1 ASSESSMENT OF 14 COMMON COVID-19-RELATED SYMPTOMS QUESTIONNAIRE

Example items *For items 1–10, sample item wording could be: "What was the severity of your **[insert symptom]** at its worst over the last 24 hours?"*	**Example response options and scoring***
1. Stuffy or runny nose	None = 0 Mild = 1 Moderate = 2 Severe = 3
2. Sore throat	
3. Shortness of breath (difficulty breathing)	
4. Cough	
5. Low energy or tiredness	
6. Muscle or body aches	
7. Headache	
8. Chills or shivering	
9. Feeling hot or feverish	
10. Nausea (feeling like you wanted to throw up)	
11. How many times did you **vomit (throw up)** in the last **24 hours**?**	I did not vomit at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3

continued

Table 1, continued

12. How many times did you have **diarrhea (loose or watery stools)** in the last **24 hours**?**	I did not have diarrhea at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3
13. Rate your sense of **smell** in the last **24 hours**	My sense of smell is THE SAME AS usual = 0 My sense of smell is LESS THAN usual = 1 I have NO sense of smell = 2
14. Rate your sense of **taste** in the last **24 hours**	My sense of taste is THE SAME AS usual = 0 My sense of taste is LESS THAN usual = 1 I have NO sense of taste = 2

* Note: Score values are included in the table for ease of reference. FDA cautions against including the score values within the response options presented to trial subjects to avoid confusing subjects.
** The response options shown for items 11 and 12 are intended only for use with a 24-hour recall period.

15.2 BORG DYSPNOEA SCALE

Borg Dyspnoea Scale will be conducted at baseline, Day 7, Day 28, and Day 60. This scale asks you to rate the difficulty of your breathing it starts at number 0 where you are breathing is causing you no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal.

15.3 SIX-MINUTE WALK TEST

The walk test is conducted as follows:

- Flat, straight corridor 30 m (100 feet) in length
- Turnaround points marked with a cone
- Patient should wear comfortable clothes and shoes
- Patient rests in chair for at least 10 minutes prior to test (ie, no warm-up period)
- Heart rate and pulse oxygen saturation (SpO2) should be monitored throughout the test
- If the patient is using supplemental oxygen, record the flow rate and type of device
- Have patient stand and rate baseline dyspnea and overall fatigue using Borg scale*[1]
- Set lap counter to zero and timer to six minutes

 Instruct the patient: Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Pivot briskly around the cone.

 Standardized encouragement statements should be provided at one-minute intervals, such as "You are doing well. You have _ minutes to go" and "Keep up the good work. You have _ minutes to go."

 At the end of the test, mark the spot where the patient stopped on the floor

 If using a pulse oximeter, measure the pulse rate and SpO2 and record

 After the test record the Borg*[1] dyspnea and fatigue levels

 Ask, "What, if anything, kept you from walking farther?"

 Calculate the distance walked and record

1. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982; 14:377.

2. American Thoracic Society. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166:111.

3. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014; 44:1428.