A Phase 2 Multiple Dose Study to Evaluate the Efficacy and Safety of PUL-042 Inhalation Solution in Reducing the Severity of COVID-19 in Adults Positive for SARS-CoV-2 Infection

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STATISTICAL ANALYSIS PLAN

Version 1.0

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Version 1.0

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Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse event
ATC	Anatomical, Therapeutic, and Chemical
BMI	Body mass index
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
COVID-19	Coronavirus Disease 2019 caused by the SARS-CoV-2 virus
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FEV1	forced expiratory volume in 1 second
ICU	Intensive care unit
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
ODN	ODN M362
Pam2	Pam2CSK4
PT	Preferred term
PUL-042	drug product consisting of a 4:1 molar ratio of Pam2:ODN; Inhalation Solution
SAE	Serious adverse event
SAF	Safety
SAP	Statistical analysis plan
SARS-CoV-2	Coronavirus causing COVID-19
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the Protocol # PUL-042-502 Version 1.70, dated 29 January 2021, and titled "A Phase 2 Multiple Dose Study to Evaluate the Efficacy and Safety of PUL-042 Inhalation Solution in Reducing the Severity of COVID-19 in Adults Positive for SARS-CoV-2 Infection." See the study protocol for full details.

This document details the statistical methods planned to perform the analysis for the Data Safety Monitoring Board (DSMB), as well as the final analysis of the study.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To determine the efficacy of PUL-042 Inhalation Solution in decreasing the severity of Coronavirus Disease 2019 caused by the SARS-CoV-2 virus (COVID-19) in subjects: 1) who have documented SARS-CoV-2 infection, and 2) if receiving oxygen, should have pulse oximetry ≥ 93% on 3 liters per minute of oxygen or less delivered by nasal prongs (Ordinal Scale for Clinical Improvement 4 or less) at the time of enrollment.

2.1.2 Secondary Objectives

- To determine the difference in the proportion of COVID-19 patients with clinically meaningful worsening of COVID-19 within 14 days from the start of experimental therapy, as indicated by an increase of at least 2 points on the Ordinal Scale for Clinical Improvement.
- To assess the progression of COVID-19 severity during the study as measured by the Ordinal Scale for Clinical Improvement
- To assess the progression of COVID-19 severity during the study as measured by the SARS-CoV-2 Symptom Score.
- To determine SARS-CoV-2 positivity 28 days from the start of experimental therapy
- To determine mortality rate at 28 days after the start of PUL-042 therapy
- To assess the requirement for intensive care unit (ICU) admission within 28 days from the start of experimental therapy
- To assess the requirement for mechanical ventilation within 28 days from the start of experimental therapy
- To determine the tolerability of PUL-042 Inhalation Solution in this population

2.2 Endpoints

2.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study will be the difference in the proportion of patients with clinically meaningful worsening of COVID-19 within 28 days from the start of experimental

therapy, as indicated by an increase of at least 2 points on the Ordinal Scale for Clinical Improvement.

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- The difference in the proportion of patients with clinically meaningful worsening of COVID-19 within 14 days from the start of experimental therapy, as indicated by an increase of at least 2 points on the Ordinal Scale for Clinical Improvement.
- Ordinal Scale for Clinical Improvement during the study to determine time course of severity and resolution of disease
- SARS-Cov-2 Symptom Score during the study to determine the time course of disease symptoms and resolution of symptoms
- SARS-Cov-2 test result at Day 29
- All-cause mortality rate through Day 29
- Proportion of subjects requiring ICU admission from Day 1 to Day 29
- Number of ICU Days from Day 1 to Day 29
- Proportion of subjects requiring mechanical ventilation from Day 1 to Day 29
- Number of days on mechanical ventilation from Day 1 to Day 29

2.2.3 Safety and Tolerability Endpoints

- Change in forced expiratory volume in 1 second (FEV1) from Pre-dose to Post-dose
- Treatment-emergent serious adverse events (SAEs) through Day 29
- Treatment-emergent adverse events (TEAEs) and severity through Day 29
- Vital signs from Pre-dose to Post-dose

3. INVESTIGATIONAL PLAN

3.1 Study Design

This will be a double-blind trial. A total of approximately 100 subjects randomized 1:1 (PUL-042 Inhalation Solution: placebo) will be enrolled in the trial.

Doses will be administered via nebulization with a PARI Sprint nebulizer. All subjects will receive 3 doses of PUL-042 Inhalation Solution or placebo over 1 week (Days 1, 3, and 6).

Subjects will participate for approximately 28 days. See Appendix A for the Schedule of Events.

An overview of the study design is presented below:

3.2 Treatment

3.2.1 Randomization Scheme and Treatment Arm Assignment

Subjects will be randomly assigned to receive PUL-042 Inhalation Solution or placebo in a 1:1 ratio. A central randomization system, the Medication Assignment Center (MAC; CTI Clinical Trial and Consulting Services), will be used for this study.

3.2.2 Blinding

The sponsor, subjects, Principal Investigator (PI), and site study staff (except for the unblinded study drug personnel) will not know the treatment (PUL-042 vs. placebo) a subject receives. The CRO staff dealing with blinded site study staff and the study statistician will also be blinded. The statistician who generates the production randomization code, MAC Operators who perform the randomization and the unblinded study team will be unblinded to the treatment a subject receives.

All doses of study drug (i.e., both Active and Placebo) will be prepared at the site, so the site Pharmacists will also be unblinded.

3.2.3 Dosing Schedule

The dose level of PUL-042 Inhalation Solution in this study will be 20.3 µg Pam2 : 29.8 µg ODN/mL (50 µg PUL-042. A total of up to 3 doses will be administered over a 1-week period for a total dose of 60.9 µg Pam2 : 89.4 µg ODN.

Doses of PUL-042 or placebo will be prepared by an unblinded pharmacist and administered to the subject within 4 hours of preparation.

Doses will be administered via nebulization to deliver 4 mL using a PARI Sprint nebulizer equipped with a filter valve to prevent aerosol generation. The nebulizer will be operated until all drug is delivered.

3.2.4 Subject Compliance

Any material deviation from study procedures (identified by site personnel or monitor) will be documented. Major subject-level deviations will be captured on the protocol deviation form. A list of protocol deviations will be compiled and reviewed by the PI and Sponsor to identify major and minor deviations periodically using the criteria specified in the Protocol, Section 14.5.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Unless otherwise specified, continuous variables will be summarized using descriptive statistics

(n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage of subjects within each category.

Summary results will be provided for each treatment group. All tabulations will be based on pooled data across centers.

Unscheduled visits will be excluded from the summaries but will be included in the data listings.

All statistical tests will be two-sided and tested at the 5% level of significance.

Analyses will be performed using SAS for Windows statistical software, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

CTI will perform all efficacy and safety analyses described in this SAP.

Subject data will be listed, sorted by treatment group and subject number. When applicable, listings will be additionally sorted by visit and assessment date/time.

4.1 Data Quality Assurance

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to CTI Biostatistics for final analysis.

Data may be pulled by CTI Biostatistics for DSMB analysis at a time when source verification and query resolution is ongoing.

All SAS programs used to create analysis data sets, tables, and listings are double programmed. The SAS outputs will be compared and the programs will be updated until the outputs match.

4.2 Analysis Sets

The following two analysis sets will be defined for this study:

Intent to Treat (ITT) Set

The ITT set is defined as all randomized subjects who receive at least one dose of experimental treatment (i.e., PUL-042 or Placebo). The primary analysis of all efficacy endpoints will be carried out using the ITT set based on the randomized treatment.

Safety (SAF) Set

The SAF set is also defined as all randomized subjects who receive at least one dose of experimental treatment (i.e., PUL-042 or Placebo), but subjects are categorized based on the treatment actually received rather than as randomized. All safety and tolerability analyses will be carried out using the SAF set. If, as expected, the Safety analysis set is redundant (i.e., is identical to the ITT analysis set), the ITT set will be used for the assessments of safety and tolerability.

4.3 Assessment Windows

Data will be summarized by nominal study visit recorded in the database.

4.4 Handling of Dropouts or Missing Data

Except for the time to event endpoints (Table 1), partial end dates of prior and concomitant medications (Section 5.6), and partial onset dates of AEs (Section 7.2.1), all other missing data

will be treated as missing and no method for imputation is planned.

Missing data on the time to event endpoints will have events coded as right censored per the following table:

Table 1 Missing Data Coding for Time to Event Data Analyses

Endpoint	Right Censoring
Time to clinical improvement on Ordinal Scale	Subject who did not meet the criteria for clinical improvement on Ordinal Scale or died at any time during follow-up will be right censored as of the date of last non-missing assessment of Ordinal Scale on or prior to Day 29.
Time to resolution of disease	Subject who did not meet the criteria for the resolution of disease or died at any time during follow-up will be right censored as of the date of last non-missing assessment of Ordinal Scale on or prior to Day 29.
Time to resolution of symptoms	Subject who did not meet the criteria for the resolution of symptoms or died at any time during follow-up will be right censored as of the date of last non-missing assessment of symptoms on or prior to Day 29.
Time to clinical improvement on symptoms	Subject who did not meet the criteria for clinical improvement on symptoms or died at any time during follow-up will be right censored as of the date of last non-missing assessment of symptoms on or prior to Day 29.
Subject Survival	Subjects who are still alive as of the last known follow-up will be right censored as of the date of last subject contact when the subject was known to be alive.

4.5 Multiple Comparisons

Because of the exploratory nature of this study, there will be no adjustment for multiple comparisons.

4.6 Data Derivations and Transformations

The following derivations will be used in this study:

Study Day (Note: There is no day 0 in this study):

- Date of assessment – date of 1st Study Drug administration + 1 for assessments done on or after date of 1st Study Drug administration
- Date of assessment – date of 1st Study Drug administration for assessments done before date of 1st Study Drug administration

Baseline Observation: the last non-missing value prior to 1st Study Drug administration.

Duration:

- Duration in days = end date – start date + 1

- Duration in minutes = end time in minutes – start time in minutes

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A table of frequency counts and percentages of all subjects who are randomized, and in each analysis set will be provided. Subject disposition including study completion status and reasons for early termination will be tabulated by treatment group and overall. A by subject listing will be provided.

5.2 Protocol Deviations

Distribution of the types of protocol deviations and the number of subjects that deviate from the protocol will be tabulated for the treatment groups in the ITT set. Protocol deviations will also be tabulated by severity (e.g., minor or major) if appropriate. A listing of all protocol deviations will be provided.

5.3 Demographic Characteristics

Descriptive statistics will be used to summarize the demographic characteristics (age, gender, race, ethnicity, height, weight, and Body Mass Index [BMI]) for the ITT set. A by subject listing will be provided.

5.4 Baseline Characteristics

Baseline characteristics of ITT subjects including confirmation of SARS-CoV-2 infection, pulse oximetry if available, and spirometry results at Screening will be listed and tabulated.

5.5 Medical History

All medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percent of subjects with each medical condition and surgical procedure will be presented for each SOC and PT for the ITT set.

5.6 Concomitant Medications and Procedures

All concomitant medications collected will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percent of ITT subjects using concomitant medications will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) level 2 and by preferred name. If the ATC level 2 is missing, the higher ATC level term will be used in the medication summary table and data listing.

A listing of all medications will be provided. The listing will include flags for prior medications.

Prior medications are defined as medications that ended prior to the date of first Study Drug administration. Concomitant medications are defined as medications that started at any time but ended on or after the date of first Study Drug administration, including those that are ongoing at study completion. In the case of a partial end date/time, in order to determine whether a medication is prior or concomitant, the following conservative imputation rule will be used: the unknown

portions of a medication end date will be imputed to the latest possible. The imputed medication end date will then be compared with the date of first Study Drug administration to determine if the medication is prior or concomitant.

Note the imputed end date will only be used to determine whether a medication is prior or concomitant. The actual date reported on the electronic case report forms (eCRFs) will be presented in the listing.

Concomitant procedures will be collected via free text in the eCRF. These data will be presented in a listing.

6. EFFICACY ANALYSES

All efficacy analyses will be carried out using the ITT set. Data on all efficacy endpoints will be listed and tabulated as appropriate.

6.1 Primary Efficacy Endpoint and Analysis

The primary efficacy variable is the clinically meaningful worsening of COVID-19 within 28 days from the start of experimental therapy.

The Ordinal Scale for Clinical Improvement is a 9-point scale that measures disease severity. For this study, an increase of 2 or more points is considered meaningful worsening of disease (Table 2). This endpoint considers changes in disease severity that are observed at any time over the course of this study.

The Ordinal Scale for Clinical Improvement to be used in this study is derived from a draft scale proposed by the World Health Organization[1] for clinical improvement as presented below:

Table 2 Ordinal Scale for Clinical Improvement (Derived from draft WHO scale)[1]

Descriptor	Score
No clinical or virological evidence of infection	0
Infected but no limitation of activities	1
Limitation of activities	2
Hospitalized not requiring oxygen therapy (SpO2 > 93% on room air)	3
Oxygen by mask or nasal prongs	4
Non-invasive ventilation or high-flow oxygen	5
Intubation and mechanical ventilation	6
Ventilation + additional organ support- pressors, RRT, ECMO	7
Death	8

The null hypothesis is that there is no difference in proportions of subjects with clinically meaningful worsening of COVID-19 through Day 29 between randomized treatment groups; H_0: $\pi_t - \pi_c = 0$. The alternative hypothesis is that the proportions of subjects with clinically meaningful worsening of COVID-19 through Day 29 are different between the treatment groups; H_1: $\pi_t - \pi_c \neq 0$.

Subjects who had an increase of 2 or more points in Ordinal Scale from the baseline will be treated as meeting the criteria for clinically meaningful worsening of COVID-19. The proportion of subjects who met the criteria within each treatment group will be presented along with a two-sided exact (Clopper-Pearson) 95% confidence interval (CI).

The observed difference in the proportion of subjects meeting the criteria between treatment groups along with the exact unconditional 95% CI for risk difference will be calculated. The null hypothesis will be tested using Fisher's exact method and the p-value will be reported.

6.2 Secondary Efficacy Endpoints and Analyses

Clinically meaningful worsening of COVID-19 through Day 15

The analysis of the proportion of subjects who met the criteria of an increase of at least 2 points on the Ordinal Scale for Clinical Improvement through Day 15 within each treatment group will be performed using the method described above in Section 6.1.

Ordinal Scale for Clinical Improvement

Clinical improvement is defined as a reduction of at least 1 point on the Ordinal Scale. The time to the first occurrence of clinical improvement will be estimated using the KM method. The KM estimates along with 95% CI, and survival curves will be provided. Based on the KM estimates, the probabilities of experiencing clinical improvement and associated 95% CIs on Days 15 and 29 will be reported; in addition, the 25%, 50% (median), and 75% percentiles of the time to clinical improvement with associated 95% CIs will be provided, as data permit. The survival rates between treatment groups will be compared using Log-rank test. The p-value from Log-rank test will be presented.

In addition, the time to the first occurrence of resolution of COVID-19 defined as an Ordinal Scale of 0 will also be evaluated, using the KM method described above for the analysis of time to clinical improvement.

The progression of COVID-19 severity as measured by the Ordinal Scales through Day 29 will be evaluated by graphical illustrations using stacked bar chart for each treatment group. The X axis representing time points and Y axis representing the cumulative number of subjects for each Ordinal Scale. Each bar is divided into a number of sub-bars stacked end to end corresponding to different Ordinal Scales.

The changes in Ordinal Scales through Day 29 will be examined using box and whisker plots for each treatment group. The X axis representing the post-baseline time points and the Y axis representing the change from baseline in Ordinal Scales at each post-baseline visit.

The absolute value and change from baseline in the Ordinal scale from Day 1 through Day 29 will be summarized by treatment group and visit using descriptive statistics.

Symptom Score

The symptoms due to SARS-CoV-2 infection will be assessed and the symptom scores (Cough (0-3), Shortness of breath or difficulty breathing (0-3), Muscle aches or fatigue (0-3), Fever (0-4)) will be recorded in the eCRF.

The respiratory symptom score will be calculated by summing the symptom scores from Cough and Shortness of breath or difficulty breathing. The scores from each symptom together with calculated respiratory symptom scores will be summarized by presenting the number and percentage of subjects for each category by visit and treatment group.

The time to the first occurrence of resolution of symptoms defined as the time from the first symptom score of >=1 to a symptom score of 0 will be estimated using the KM method. If a subject had a symptom score of 0 from Baseline through Day 29, then that subject will be excluded from the analysis.

> *Time to Resolution of Symptoms (days) = (Date of the first symptom score of 0 since the initial score of >=1) - (Date of the initial symptom score of >=1 at or after Baseline) + 1*

For each individual symptom and the respiratory symptoms (cough, shortness of breath and difficulty breathing), the KM estimates along with 95% CI, and survival curves will be provided. Based on the KM estimates, the probabilities of experiencing the resolution and associated 95% CIs on Days 15 and 29 will be reported; in addition, the 25%, 50% (median), and 75% percentiles of the time to resolution with associated 95% CIs will be provided, as data permit. The survival rates between treatment groups will be compared using Log-rank test. The p-value from Log-rank test will be presented.

In addition, the time to the first occurrence of improvement of symptoms defined as the time from the initial symptom score of >=1 to a reduction of ≥1 point on initial symptom score will also be evaluated for each individual symptom and the respiratory symptoms (cough, shortness of breath and difficulty breathing), using the KM method described above for the analysis of time to resolution of symptoms.

If a subject had a symptom score of 0 from Baseline through Day 29, then that subject will be excluded from the analysis.

> *Time to Improvement of Symptoms (days) = (Date of the first reduction of >=1 point on initial symptom score of >=1) - (Date of the initial symptom score of >=1 at or after Baseline) + 1*

A radar plot will be created by presenting each symptom score at each time point by treatment group.

SARS-CoV-2 Test

The SARS-CoV-2 tests will be performed at the end of the study or early discontinuation visit.

If the test result for a subject is missing at the end of the study or early discontinuation visit, then the subject will be excluded from the analysis. The proportion of subjects with positive test results within each treatment group will be presented along with a two-sided exact (Clopper-Pearson) 95% CI.

The observed difference in the proportion of subjects with positive test results between treatment groups along with the exact unconditional 95% CI for risk difference will be calculated. The null hypothesis of no difference in proportions of subjects with positive test results between treatment groups will be tested using Fisher's exact method and the p-value will be reported.

Mortality Rate through Day 29

Subject status (Alive/Death) will be recorded in the database. If the vital status of the subject is missing at the end of the study, then the subject will be excluded from the binomial analysis for the mortality rate. The subject will be included in the Kaplan-Meier (KM) analysis with right censoring at the date the subject was last known to be alive.

The mortality rate (proportion of subjects who die) through Day 29 within each treatment group will be analyzed and compared using the method as describe in Section 6.1.

If deemed appropriate, an alternative analysis will be performed in which the survival rates will be estimated using the KM method. The KM estimates along with 95% CIs and survival curves will be provided. Based on the KM estimates, the survival probabilities and associated 95% CIs on Days 15 and 29 will be reported; in addition, the 25%, 50% (median), and 75% percentiles of the survival time with associated 95% CIs will be provided, as data permit. The survival rates between treatment groups will be compared using Logrank test and the p-value from Logrank test will be presented.

Subjects requiring ICU admission

Subject data pertaining to ICU admission will be recorded in the database.

The proportion of subjects who are admitted to the ICU from Day 1 to Day 29 within each treatment group will be presented along with a two-sided exact (Clopper-Pearson) 95% confidence interval (CI).

The observed difference in the proportion of subjects requiring ICU admission between treatment groups along with the exact unconditional 95% CI for risk difference will be calculated. The null hypothesis will be tested using Fisher's exact method and the p-value will be reported.

Subjects who have died without ICU admission during the study will be counted as requiring ICU admission for the analysis.

Number of ICU Days

The number of ICU days from Day 1 to Day 29 will be calculated based on the ICU admission and discharge dates recorded in the eCRF. The calculated number of ICU days will be compared between treatment groups using 2-sided Student's t-test. The 95% CI and p-value will be presented.

If the Student's t-test normality assumption is found to be clearly violated, a sensitivity analysis will be performed using a non-parametric Wilcoxon rank-sum test. The p-value from the test will be presented.

Subjects who died will be assigned as hospitalized in the ICU for the number of days remaining from the day of death to Day 29 for the analysis. Subjects who are alive and never admitted into the ICU will be included in the analysis with a value of zero ICU days.

Subjects who were at ICU at study completion will be assigned an ICU end date equal to the date of completion for the purpose of deriving number of ICU days.

Subjects requiring mechanical ventilation

Subject data pertaining to mechanical ventilation use will be recorded in the database.

The proportion of subjects who were on mechanical ventilation from Day 1 to Day 29 within each treatment group will be analyzed and compared using the method described above for the analysis of subjects requiring ICU admission.

Subjects who have died without mechanical ventilation during the study will be counted as requiring mechanical ventilation for the analysis.

Number of days on mechanical ventilation

The number of days on mechanical ventilation from Day 1 through Day 29 will be calculated based on the start/stop dates of mechanical ventilation recorded in the eCRF. Number of days on mechanical ventilation will be compared between treatment groups using 2-sided Student's t-test. The 95% CI and p-value will be presented.

If the Student's t-test normality assumption is found to be clearly violated, a sensitivity analysis will be performed using a non-parametric Wilcoxon rank-sum test. The p-value from the test will be presented.

Subjects who died will be assigned as being on mechanical ventilation for the number of days remaining to Day 29 for the analysis. Subjects who had mechanical ventilation ongoing at study completion will be assigned a mechanical ventilation end date equal to the date of completion for the purpose of deriving duration of mechanical ventilation. Subjects who are alive and never placed on mechanical ventilation will be included in the analysis with a value of zero days on mechanical ventilation.

6.3 Subgroup and Sensitivity Analyses

Exploratory subgroup analyses of the primary efficacy endpoint by baseline characteristics, e.g. age group and gender, will be performed using the analysis method described in Section 6.1, if appropriate.

If an ITT subject did not have an onset of COVID-19 signs and symptoms within 7 days prior to Screening, a sensitivity analysis of the primary efficacy endpoint will be carried out using the analysis method described in Section 6.1.

Additional analyses may be performed to gain a better understanding but would not replace analyses planned for primary and secondary efficacy endpoints.

7. SAFETY AND TOLERABILITY ANALYSIS

Safety and tolerability assessments will include adverse events (AEs), vital signs, and pulmonary function tests. If there is a difference between the ITT set and SAF set, then all safety summaries (or analyses if applicable) will be conducted using the SAF set. Otherwise, the ITT set will be used. No formal hypothesis testing will be performed to compare differences between treatment groups.

7.1 Extent of Exposure and Compliance

The number of doses received will be summarized by treatment group. The duration of study drug administration in minutes, the reason for study drug discontinuation, and whether 100% of study drug (4 mL) was delivered will be summarized for each dose by treatment group.

7.2 Adverse Events

The AE reporting period for this study is continuous and begins at the time of randomization to study treatment and ends on Day 29. All AEs (both serious and nonserious) must be followed until resolution or until a stable clinical endpoint is reached. All measures required for AE management and the ultimate outcome of the AE must be recorded in the source documentation and in the eCRF.

AEs will be classified by SOC and PT using the most recent version of MedDRA.

7.2.1 Treatment-emergent Adverse Events

Treatment-emergent AEs are defined as those that begin or worsen after the start of study drug administration.

For adverse events with incomplete start dates, the same imputation algorithm for partial date information as described in Section 5.6 will be used for the determination of an AE being treatment emergent or not. Briefly, the unknown portions of an AE onset date will be imputed to the latest possible before being compared to the date of first study drug administration.

7.2.2 Adverse Event Severity

The severity (i.e., grade) of an AE will be assessed by the Investigator according to the definitions in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. If the AE is not specifically listed in the reference above, the following grades should be used:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
- Grade 3 Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

7.2.3 Adverse Event Relationship to Study Drug

The Investigator must record his/her opinion concerning the relationship of the AE to study therapy (Unrelated, Unlikely, Possibly, Probably, Definitely) on the AE eCRF. See study protocol, Section 12.5 for details.

7.2.4 Serious Adverse Events

An AE or suspected adverse reaction is considered “serious” if in the view of either the investigator

or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption to conduct normal life functions
- A congenital anomaly/birth defect
- Intervention to prevent any one of the other outcomes listed above (based on medical judgment)

7.2.5 Adverse Event Summaries

All AEs (serious and non-serious) occurring after randomization and before the end of study, regardless of relationship to study drug, will be included and classified by SOC and PT using MedDRA.

For TEAEs, the following will be summarized and presented:

i. An overall summary of TEAEs, which includes:
   a. the number and percentage of subjects experiencing a TEAE
   b. the number and percentage of subjects experiencing a TEAE by strongest relationship to study drug
   c. the number and percentage of subjects experiencing a TEAE by greatest severity
   d. the number and percentage of subjects experiencing a treatment-emergent SAE
   e. the number and percentage of subjects experiencing a TEAE leading to death
   f. the number and percentage of subjects experiencing a TEAE leading to study withdrawal

ii. the number and percentage of subjects experiencing a TEAE by SOC and PT.

iii. the number and percentage of subjects experiencing a potentially related TEAE by SOC and PT, where a potentially related TEAE is defined as any TEAE with a causal relationship to study drug assessed as 'Possibly Related', 'Probably Related', or 'Definitely Related'.

iv. the number and percentage of subjects experiencing a TEAE by SOC, PT and the strongest relationship to study drug

v. the number and percentage of subjects experiencing a TEAE by SOC, PT and the greatest severity

vi. the number and percentage of subjects experiencing a treatment-emergent SAE by SOC and PT

vii. the number and percentage of patients experiencing a TEAE leading to death by SOC and PT

viii. the number and percentage of subjects experiencing a TEAE leading to study withdrawal by SOC and PT

In the overall summary of TEAEs table (i), besides tabulating the number and percentage of subjects, the total number of TEAE episodes will also be provided. If a subject has repeated episodes of a particular TEAE, all episodes will be counted in the summary table.

In the remaining summary tables, the incidence of TEAEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects. Thus, the incidence of TEAEs is shown in terms of the total number of subjects and not in terms of the total number of episodes. If a subject has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to study drug, will be counted in the summary tables.

A subject with more than one type of TEAE in a particular SOC or PT will be counted only once in the total of subjects experiencing TEAEs in that particular SOC or PT.

All occurrences of all AEs and SAEs will be listed for each subject, grouped by treatment group. The listing will contain the following information: treatment group, verbatim term, SOC, PT, severity and grade (1-Mild, 2-Moderate, 3-Severe, 4-Life threatening, 5-Death), relationship to study drug, date and day of onset, date and day of resolution or death, action taken with regard to study drug, the outcome, whether the event was an SAE, whether it led to study withdrawal, and whether it is a TEAE. Listings will be sorted by treatment group, subject identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

7.3 Pulmonary Function Testing

Spirometry tests including FEV1 (L), % predicted FEV1, FVC (L), % predicted FVC and FEV1/FVC values will be collected at screening and FEV1 (L) will also be recorded at the time points presented in the Appendix A. FEV1 results will be summarized by presenting descriptive statistics of raw data of FEV1 (L) and percent change from each Pre-dose value to Post-dose value on the dosing days.

The proportion of subjects with percent decrease in FEV1 (L) from Pre-dose value to Post-dose value will be presented for each category: >10% and <=12% of reduction; >12% and <=20% of reduction; and >20% of reduction at each measurement time point (Day1, Day 3 and Day 6).

The percent change in FEV1 (L) from Pre-dose value to the protocol defined 30-min Post-dose values will be illustrated in a box/whisker graph on each dosing day by treatment group.

Spirometry results from unscheduled visits will be excluded from table summaries but will be included in the data listing.

7.4 Vital Signs

Descriptive summaries of pre- and post-treatment vital signs including systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature will be prepared for each treatment group by visit.

A listing of all vital sign assessments throughout the study will be provided.

7.5 Other Safety Measures

Pregnancy test results, if applicable, will be presented in a listing.

8. INTERIM ANALYSES

An external DSMB will be used to evaluate safety of the study in an ongoing manner. A full description of the membership, role, and responsibilities of the DSMB is provided in the DSMB charter. As specified in the DSMB charter, the formal review of data will take place at each meeting of the DSMB after 20, 40 and 60 subjects have completed dosing.

As a further effort to ensure the safety of PUL-042, a stopping rule that is based only on mortality will be employed. A recommendation to stop the study would be made only if there is a high probability of excess mortality risk among subjects randomized to PUL-042. The following hierarchical analysis of mortality will be performed after 50% of subjects have been enrolled (25/group) and followed up for 28 days from the start of investigational therapy:

1) Based on blinded data, if no more than 1 death has occurred during the study this analysis will not be conducted due to the lack of evidence of increased mortality risk attributable to PUL-042.

If more than 1 death occurs:

2) The Unblinded statistician will evaluate unblinded mortality data to determine the treatment specific death rate (i.e., $D_{Tx} = Deaths_{Tx} / N_{Tx}$; Tx = Active or Placebo).
3) If the difference, Δ, in treatment-specific death rates (i.e., $\Delta = D_{Active} - D_{Placebo}$) is greater than 7.5%, the DSMB will further review the totality of evidence and render a recommendation to the sponsor regarding study continuation.

Characteristics of this rule are as follows:

Assuming that the true underlying control arm mortality rate is 5% and using a normal approximation when comparing proportions, the probability of stopping is approximately:

- 90% if the true underlying mortality rate attributable to PUL-042 is 25%.
- 62% if the true underlying mortality rate attributable to PUL-042 is 15%.
- only 11% if the true underlying mortality rate attributable to PUL-042 is 5% (equal to the assumed true underlying control arm mortality rate).

9. SAMPLE SIZE AND POWER CALCULATIONS

The trial size of 100 subjects (50 PUL-042 inhalation solution: 50 placebo) was chosen based on clinical considerations. The rates of infection to adequately estimate a sample size for a statistically significant result are unknown.

Enrolled subjects will be randomized with equal probability to receive blinded treatment consisting of either PUL-042 or placebo.

10. REFERENCES

1. World Health Organization. WHO-COVID-19: Treatment Trial Design Master Protocol Synopsis, Draft February 18, 2020

11. APPENDIX

11.1 Appendix A: Schedule of Events

Event	Screening	Dose 1[a,b]	Dose 2, 3[a]	Follow-up	Follow-up/Early Discontinuation from Study	Study End
	V1	V2	V3, 4	V5	V6	V7
	Day -2 to Day 1	Day 1[b]	Days 3, 6	Day 10	Day 15	Day 29
Informed consent	X					
Medical history	X					
Pregnancy test[c]	X				X	X
Physical exam	X	X	X	X	X	
Vital signs[d]	X	X	X	X	X	
Pulse oximetry	X					
Spirometry[e]	X	X	X			
Symptom Score	X	X	X	X	X	X
SARS-CoV-2 test[f]	X				X	X
Ordinal Scale for Clinical Improvement	X	X	X	X	X	X
Study drug administration[g]		X	X			
Adverse events	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Randomization	X					

[a] Vital signs, adverse events, and concomitant medications will be assessed prior to administration of study medication and also at 30 minutes post-dose.

[b] There is no Day 0 in this study

[c] Urine pregnancy test or serum pregnancy test if women are of child-bearing potential. If urine pregnancy test is positive, a serum pregnancy test must be done. Pregnancy test will be repeated at Day 29 or Early Discontinuation

[d] Vital signs will include body temperature, blood pressure measurements, heart rate, and respiratory rate

[e] Spirometry will be done at screening to document eligibility. On days of dosing, spirometry will be done pre-dose and at 30 minutes (±15) minutes post-dose. If the FEV1 is reduced > 10% compared to the pre-dose baseline the FEV1 should be repeated as clinically indicated

[f] SARS-CoV-2 testing will be performed at screening to confirm eligibility if a positive test SARS-CoV-2 has not been documented. SARS-CoV-2 testing will be performed at Early Discontinuation visit

[g] Study drug administration must be done by a health care professional