16.1.9 Documentation of Statistical Methods

The following Statistical Analysis Plan is included in this section:

Part A:

Statistical Analysis Plan LYT-100-2020-02 Version 4.0 dated 13 May 2022

Part B:

Statistical Analysis Plan LYT-100-2020-02 Version 1.0 dated 15 August 2022

PureTech LYT 100, Inc.

Protocol No: LYT-100-2020-02

CP Project ID: PTH20312

A Phase 2 Randomized, Double-blind, Placebo-controlled Trial and Open Label Extension to Evaluate the Safety and Efficacy of Deupirfenidone (LYT-100) in Post-acute COVID-19 Respiratory Disease

Statistical Analysis Plan

Version: 4.0 (Final)

Date: 13MAY2022

Based on Protocol Version V8.2, 17Mar2022 (US Sites Only) and

Protocol Version V8.0, 26Jan2022 (All Sites except US)

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1 Introduction

Study Description

This study is being conducted in two parts, A and B. Part A is a phase 2 multi-center randomized, double-blind, parallel arm, placebo-controlled study being conducted to evaluate the safety and efficacy of LYT-100 compared to placebo in post-acute adult patients with COVID-19 respiratory disease who were treated with supplemental oxygen (including MV, ECMO or any other means of oxygen administration) in the hospital for at least 1 day and have required only low flow nasal oxygen or no oxygen supplementation for at least 72 hours prior to screening. The second part of the study, Part B, is an open-label extension (OLE) in which eligible patients who completed Part A will be enrolled and treated with open-label LYT-100 for an additional 91 days.

- Patients who received LYT-100 during Part A will continue to receive LYT-100 (this group will be referred to as **LYT-100 to LYT-100**)
- Patients who were randomized to placebo during Part A will switch to LYT-100 (this group referred to as **Placebo to LYT-100**).

The study will be performed in approximately 35 clinical sites in Europe, the US, Asia and South America.

Clinical Outcome Assessment (COA) Development Sub-study (SCOA)

This protocol includes a COA Development Sub-study (SCOA) with a limited number of patients). The purpose of the Sub-study is to develop a Daily COVID Symptoms Questionnaire for use in post-acute COVID-19 clinical trials. Preliminary evidence of content validity and other measurement properties based on qualitative and quantitative research methods will be generated. Anchor scales will also be developed to inform estimates of clinically meaningful within-patient change in all COA study endpoint measures utilized in Parts A and B. Specifically, following completion of enrolment into Part A (which has been completed as of January 21, 2022 and includes a total of N=177 patients), additional enrolment (at U.S. centers and potentially other countries where local amendments are adopted) will be performed for this Sub-study only, until an additional approximately 20 patients have been randomized. The eligibility, randomization, procedures, and treatment of patients enrolled in the SCOA will be identical to that of Part A. In addition, patients will be asked to participate in a 1-on-1 audio-recorded video conference interview for qualitative research to generate content validity evidence for the Daily COVID Symptom Questionnaire. The methods of analysis of the data for the Sub-study will be addressed in a separate Supplemental Analysis Plan. A separate report will be generated for the Sub-study.

- Note that of the N=177 patients in Part A, n=10 patients participated in the collection of the Daily Covid Symptom Questionnaire to generate content validity evidence. Thus, these n=10 subjects will be included in both the Part A analysis and the Sub-study analysis.
- Sub-study patients enrolled after completion of the Part A enrolment will NOT be included in the primary analyses of Part A outcomes.

1.1 Timing and Sequence of Statistical Analyses

The primary efficacy and safety analysis for this study will be performed after the Part A patients have completed and the database (based on their data) has been processed and 'locked'. It is expected that this will occur in Q2 2022.

- Data for the COA Development Substudy will remain fully blinded during the analysis of Part A.

The COA Development Substudy analysis will be performed after the Substudy patients have completed and the database (based on THEIR data) has been processed and locked. It is expected that this is expected to occur in early Q4 2022.

- A supplemental analysis on the efficacy and safety of the entire study population (including both the Part A patients AND the SCOA patients) may also be performed at this time.

1.2 Preface

The objective of this document is to detail the statistical methodology to be used for the final statistical analysis for Part A of study LYT-100-2020-02. The statistical methodology of Part B and of the substudy will be provided in a separate document.

The statistical analysis plan is based on the following information and documents:

- LYT-100-2020-02 Protocol 8.0/ Date: 26Jan2022 (All sites except US country)
- LYT-100-2020-02-US Protocol 8.2/ Date: 17Mar2022 (US sites only)
- LYT-100-2020-02 Subject Case Report Forms V14.0/ Date: 26APR2022

2 Modification History

2.1 Changes to the study protocol

The Per-Protocol (PP) population was defined as “all randomized subjects who completed 91 days of treatment, with at least 80% compliance and have at least one post-baseline 6MWT outcome” and changed to “all randomized subjects who (1) completed 91 days of treatment, (2) at least 80% compliance, (3)have at least one post-baseline 6MWT outcome, and (4) have no major protocol deviations that could affect interpretability of the efficacy outcomes” in order to exclude the subjects who have major protocol deviations that will affect the efficacy outcomes.

2.2 Changes to previous SAP versions

The following changes were made compared to the first version of the statistical analysis plan (SAP):

Version	Date	Author	Significant Changes from Previous Authorized Version
Final v 2.0	07Dec2021	Irma Chang	Changes per protocol v6.0, protocol v7.0, FDA comment and new released FDA Guidance “Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products”
Final v 2.0	02Feb2022	Derrick Gallagher	Changes per protocol v8.0, dyspnoea-12 was moved to the key secondary objective and Modified Borg Dyspnoea Scale was moved to the other secondary objectives
Final v 3.0	28Apr2022	Derrick Gallagher	Changes to baseline definition for mBDS, dyspnoea-12 analyses to include the physical and affective domains, as well as final specification of the MMRM models,

	revised definitions of study medication compliance, and other minor adjustments as identified during blinded table and listing analysis 'dry runs' prior to database lock.
Final v 4.0	Update to day 91 analysis visit window.

3 Study Design

Indication	Post-acute Coronavirus Disease 2019 (COVID-19) Respiratory Disease
Design	Randomized, Double-blind, Placebo-controlled study
Phase	Phase 2
Primary Objective	To evaluate the effect of LYT-100 on the change in distance walked on the six-minute walk test (6MWT) performed in line the American Thoracic Society/European Respiratory Society Guidelines.
Secondary Objective	• Key Secondary Objective: To evaluate the effect of 91 days of treatment with LYT-100 compared to placebo on the Dyspnoea-12 • Other Secondary Objectives: To evaluate the effect of 91 days of treatment with LYT-100 compared to placebo on: 1. Saint George Respiratory Questionnaire-I (SGRQ-I) 2. Modified Borg Dyspnoea Scale (mBDS). 3. The World Health Organization (WHO) Ordinal Scale for Clinical Improvement 4. Quality of Life (QoL) assessment as collected using the 36-item QoL questionnaire version 2 (SF-36 v2), including 8 domains and 2 component scores 5. Number of lung segments involved using computed tomography (CT) Scan and semi-Quantitative Lung Fibrosis (QLF) assessment 6. Inflammatory, fibrosis and other biomarkers 7. Pulmonary exacerbations, severe and non-severe 8. All-cause rehospitalizations 9. Severity of lung lobe(s) involvement, using CT Scan 10. Pulse oximetry 11. Chest Xray 12. Length of hospital stay 13. All-cause mortality 14. Use of supplemental oxygen from baseline to end of treatment.

	15. COVID-19 Symptoms Assessments • Safety Objectives: To evaluate the safety and tolerability of LYT-100 up to 91 days of treatment and 14-day follow-up post-study drug treatment. • Pharmacokinetic (PK) Objectives: To evaluate the plasma concentration versus (vs.) time data via population PK analysis of LYT-100, and its metabolite(s). **Study Objectives SCOA** The objective of the Sub-study is to conduct qualitative and quantitative research to provide evidence of content validity for the Daily COVID Symptom Questionnaire and to evaluate its longitudinal measurement properties. The Dyspnoea-12 and modified Borg patient-reported COAs plus COA-specific anchor items will be cognitively debriefed for content validity. Anchor based methods will be used to generate initial estimates of within-patient meaningful change. During the SCOA , patients will remain blinded to treatment.
Endpoints	Day 91 (the end of double-blind treatment) will be the primary timepoint from which efficacy conclusions will be drawn, with supportive outcomes at earlier time points assessed to better understand the time profile of any treatment effects. • Primary Efficacy Endpoint: Changes from baseline in the 6MWT distance. • Key Secondary Efficacy Endpoint: Changes from baseline in the Dyspnoea-12. Note that the two subscales for the Dysp-12 will be included as other secondary objectives. • Other Secondary Efficacy Endpoints: To evaluate the effect of 91 days of treatment with LYT-100 compared to placebo on: 1. SGRQ-I 2. mBDS 3. The WHO Ordinal Scale for Clinical Improvement 4. QoL assessment as collected using the SF-36 v2, including 8 domains and 2 component scores 5. Number of lung segments involved using CT Scan and semi-QLF assessment 6. Inflammatory, fibrosis and other biomarkers 7. Pulmonary exacerbations, severe and non-severe

	8. Severity of lung lobe(s) involvement, using CT Scan 9. Pulse oximetry 10. Chest X-ray 11. Length of hospital stay 12. All-cause mortality 13. Other clinical outcomes – Percentage of subjects who experience rehospitalization for any cause, while on treatment – Use of supplemental oxygen from Baseline to end of treatment. – COVID-19 Symptoms Assessments • Safety Endpoints: Safety endpoints include adverse events (AEs), concomitant medications, vital signs, physical examination, electrocardiogram (ECG), laboratory data and biomarkers. • Exploratory analysis: Correlation of changes in biomarkers with clinical endpoints (e.g., 6MWT, mBDS) will be assessed where relevant. • Pharmacokinetic Objectives: Change from baseline in plasma concentration. Population PK analysis will be performed.
Treatments	LYT-100 or Placebo
Number of subjects	**Part A:** Approximately 168 patients with post-acute, documented COVID-19 were planned to be randomized to receive LYT-100 or placebo in a ratio of 1:1, respectively, in Part A. All eligible patients who complete Part A may elect to continue in Part B, the open label extension. A total of N=177 were randomized, in total, as of January 21, 2022. Note that of the N=177 patients in Part A, n=10 patients participated in the collection of the Daily Covid Symptom Questionnaire to generate content validity evidence. Thus, these n=10 subjects will be included in both the Part A analysis and the Sub-study analysis. **SCOA** Enrollment (at U.S. centers and potentially other countries where local amendments are adopted) will remain open until an additional approximately 20 subjects are randomized as part of the SCOA .
Data Safety Monitoring Board	An independent, unblinded DSMB will assist with oversight of subject safety during this study. The DSMB will meet approximately monthly

	during the study (as per the DSMB Charter) to review unblinded safety and efficacy data (where warranted per the DSMB Charter) of all subjects.
Planned enrolment	Approximately 35 study centers in Europe, United States, Asia and South America.

3.1 Sample size estimation

The sample size was based on the 6MWT.

The target sample size is based on the hypothesis that LYT-100 versus the placebo control group will significantly improve the "90-day time-distance profile" as measured via changes from baseline in the 6MWT distance walked as collected at multiple on-treatment time points. Because this study is being performed in subjects with active COVID-19, there may be limitations at investigational centers to facilitate collection of some data points. Thus, this study assumes that missing data may occur due to COVID-19 (e.g., subjects may be unable to travel due to COVID restrictions) and thus may lead to missing data. The study has been powered accordingly. Further, there is little data available regarding certain aspects of the distribution of 6MWT outcomes in the COVID-19 population, and thus the assumptions below are intended as best-estimates for purposes of sample size calculation.

- Specifically, group sample sizes of 84 per arm (total = 168) achieve 85% power to detect a difference of 30 meters in the change from baseline in the 6MWT, using a mixed model for repeated measures (MMRM) with at least 2 time points, an autoregressive covariance structure, an assumed standard deviation (SD) of 75 meters, estimated correlation between observations on the same subject of 0.50, and an alpha of 5%. (Note, the primary method of analysis will initially assume an unstructured covariance structure, with the best structure then identified for future study designs and sample size determinations, as appropriate).
- The sample size above assumes the difference of 30 meters change from baseline is observed at each time point measured, which may or may not necessarily reflect the actual time course of treatment benefit (response profile over time) in the target population. Due to the unknown time-distance response profile, and as there is no single time point of primary interest (rather, it is the full 90-day time-distance profile that is of primary interest), the treatment benefit at each measured time point will also be tested independently. The power at each individual time point, assuming group sample sizes of 84 per arm and the same assumptions as above, is over 70%, using the same MMRM as for the overall (90-day) treatment effect. No adjustments for multiplicity are planned; rather, a combination of the overall 6MWT response and the response at each individual time point will inform the basis for conclusions regarding LYT-100 treatment benefit over placebo.

An additional approximately 20 patients will be randomized accordingly as part of the SCOA, using the same general statistical methods as for Part A patients as well as the qualitative and quantitative assessments. Note that of the N=177 patients in Part A, n=10 patients participated in the collection of the Daily Covid Symptom Questionnaire to generate content validity evidence. Thus, these n=10 subjects will be included in both the Part A analysis and the Sub-study analysis.

3.2 Randomization, blinding and unblinding procedures

Subjects will be randomized into the study once they have completed screening pre-dosing assessments and have satisfied all eligibility criteria.

Subjects will be randomized in a 1:1 ratio to receive LYT-100 study drug or placebo, stratified by 6MWT baseline and the following risk factors.

Table 1. Randomization Stratification Levels

6MWT 10 to <100 m		**6MWT 100 to 200 m**		**6MWT >200 m**	
Prior Mechanical Ventilation/Prior ECMO Status		**Prior Mechanical Ventilation/Prior ECMO Status**		**Prior Mechanical Ventilation/Prior ECMO Status**	
Yes	No	Yes	No	Yes	No
Age ≥ 65		Age ≥ 65		Age ≥ 65	
Yes	No	Yes	No	Yes	No

ECMO: Extracorporeal membrane oxygenation

Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific participant, the Investigator may unblind a patient's treatment assignment.

In the event that the Investigator considers an AE to be of such severity as to require specific knowledge of the identity and dose of the relevant product, the Investigator must contact the Medical Monitor and Sponsor. The Investigator may break the study code for that participant only using the Medidata Randomization and Trial Supply Management (RTSM) system. A record, including date, time, name and signature of the person breaking the blind and justification for premature unblinding of the investigational product (e.g., accidental unblinding, unblinding due to serious AE [SAE]), must be documented in the participant's medical records. The study monitor should be promptly informed of premature unblinding.

All unblinding events must be reported to the Sponsor, Medical Monitor and Sponsor Representative promptly.

4 Analysis Sets

4.1 Enrolled Population (ENR)

The Enrolled Population is defined as all subjects who sign the inform consent.

4.2 Safety Population (SAF)

The Safety Population is defined as all subjects who received at least one dose of study treatment. All safety endpoints will be assessed using this population. Subjects will be analyzed according to the treatment they actually receive, regardless of which treatment they were randomized to.

4.3 Intent to Treat (ITT) population

The Intent to Treat (ITT) population is defined as all randomized subjects. All efficacy endpoints will be assessed using this population, with primary conclusions regarding study drug effect be based on the ITT population outcomes. Subjects will be analyzed according to the treatment group they were randomized to, regardless of which treatment they actually receive.

4.4 Full Analysis (FAS) population

The Full Analysis (FAS) population is defined as all randomized subjects who received at least one dose of study treatment and had at least one post-baseline assessment for the 6MWT. All efficacy endpoints will be assessed using this population. Subjects will be analyzed according to the treatment group they were randomized to, regardless of which treatment they actually receive.

4.5 Per-Protocol (PP) population

The Per-Protocol (PP) population is defined as all randomized subjects who (1) completed 91 days of treatment, (2) have at least 80% compliance, (3)have at least one post-baseline 6MWT outcome, and (4) have no major protocol deviations that could affect interpretability of the efficacy outcomes. Subjects who died or discontinued due to treatment-emergent AE (TEAE) will be included in this population.

4.6 Pharmacokinetic (PK) Population

The PK Population is defined as all subjects who receive study treatment and provide at least one plasma concentration measure. This population will be determined by the study PK.

4.7 Clinical Outcome Assessment (COA) Development Sub-study (SCOA) Population

The SCOA population is defined as any randomized subjects who have participated in the COVID symptoms diary data collection and have at least one post-baseline COVID symptom diary. This population includes subjects who have also participated in the qualitative research interviews.

If not otherwise stated in the respective section, the statistical analyses will be performed for the following analysis sets:

Table 2. Analysis Sets for Statistical Analyses

Analyses	ENR	ITT	FAS	PP	SAF	PK	SCOAS
Disposition	V						
Subject accounting		V					
Demographics and background characteristics		V	V	V	V		
Exposure and compliance		V			V		
Previous and concomitant therapies					V		
Efficacy: Primary		V	V	V			
Efficacy: Secondary		V	V	V			

Analyses	ENR	ITT	FAS	PP	SAF	PK	SCOAS
Safety					V		
Pharmacokinetics						V	
Psychometric Analysis							V

5 General Statistical Methods and Definitions

5.1 General statistical methods

The statistical analyses will be presented by treatment group for the different analysis sets as defined in Section 4. Summary tables will usually be structured with a column for each treatment in to order of “Placebo”, “LYT-100”, and (where appropriate) “All Subjects”.

In general, continuous variables will be summarized using descriptive statistics, i.e., generally displaying number of subjects in the respective analysis population, number of subjects with data, number of subjects with missing values, mean, SD, minimum, lower quartile, median, upper quartile, and maximum.

Categorical and ordinal variables will be summarized by using frequency counts and percentages. In addition, the number of subjects with missing values will be displayed.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Means, medians and quartiles will be presented by 1 additional decimal place and SD will be presented by 2 additional decimal places than the standard presentation level of the respective subject data. Minimum and maximum values will be presented using the same number of decimal places as the subject data. Percentages will be presented to 1 decimal place if not otherwise stated.

If the number of subjects in a category is 0, then percentage will not be displayed, and only a count of 0 will be shown.

All p-values will be two-sided and reported to 3 decimal places (e.g., 0.XXX). Values < 0.001 will be reported as < 0.001.

All data collected as part of the study will be reported in data listings, sorted by Site, Subject, and visit/study day.

5.2 Covariates and Strata

In MMRM analysis, the baseline value of the endpoint and study center will be considered as covariates for efficacy endpoints.

5.2.1 Multicenter Studies

This study will be conducted by multiple investigators at various centres (Approximately 35 study centers in Europe, United States, Asia, and South America). Data from individual centers may be combined prior into ‘pooled centers’ for use in the analysis as a covariate. This pooling would be

performed via regions (United States, East Europe, West Europe, and others) and by actual number of subjects enrolled, where applicable.

5.2.2 Output Presentations

Appendix II details the conventions for presentation of data in outputs.

The table, figure, and listing (TFL) shells provided with this SAP describe the presentations for this study and therefore the format and content of the summary TFLs to be provided by Clinipace Biostatistics.

5.3 Subgroups

The following subgroup analysis will be performed by presenting the results for the primary efficacy analysis and key secondary endpoint separately for each subgroup where applicable.

- 6MWT (10 to <100 m vs. 100 to 200 m vs. >200 m)
- Prior mechanical ventilation/prior ECMO Status (Yes vs. No)
- Age (<65 vs ≥ 65 years old)
- Hospitalization status at baseline (Yes vs. No)
- Initial CT score (≤ median vs. > median)
- Sex (Female vs. Male)
- Baseline Body Mass Index (BMI) (<30 kg/m^2 vs. ≥ 30 kg/m^2)
- Ethnicity (Hispanic or Latino vs. others)
- COVID-19 Vaccine Status (yes vs. no, as assessed from the "Prior/Concomitant Medications" page). This will include subjects who had the vaccination either before study entry or during the study.
- Race group (Race includes American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and other, but the subgroups will be determined depending on the actual data.)
- Geographic region (US, East Europe, West Europe and Other [rest of world]).

5.4 Missing data

This study is being performed in subjects with active COVID-19 diagnosis. There may be restrictions beyond the subject's control that may limit the collection of study visit assessments. Except for subject withdrawal of consent, which may result in missing data, all subjects will be followed for all scheduled assessments and their observed data used for analysis. Thus, it is expected that this study will have very little missing data and that imputation may only be necessary in a small number of instances. There will be no imputation for missing safety data, other than dates as indicated in Appendix III. Missing data will be left as 'missing' for all data except:

- The 6MWT distance
- Dyspnoea-12
- SGRQ-I
- mBDS

- SF-36.

Note, the WHO Ordinal scale will have no imputation as the scale, by definition, considers hospitalization and death.

Attempts should be made to collect assessments at the hospital, rehabilitation, out-patient clinic and/or subject's home, whenever possible. Missing data for endpoints due to this circumstance may occur. Missing data due to COVID-19 restrictions will be clearly documented in the database as COVID-19-related protocol deviations. The effects of missing data from COVID-19-related deviations will be explored as best as is possible. It is expected that within-center restrictions would be applied to all subjects within each center and thus these missing data would have similar incidence between the treatment groups. Exploration of the patterns of missing data, reasons for missing data, and any imputations of missing data will be described in the respective section of the SAP prior to unblinding.

A listing of the number of subjects with each unique missing pattern for each endpoint during the study period will be presented.

Table 3. Example of How Patterns of Missingness will be Displayed (separate table for each endpoint)

Pattern	Treatment Group	Number of Subjects (%)		Day			
			Baseline	14	28	56	91
1	Placebo	XX (XX.X)	X	X	X	X	X
	LYT-100	XX (XX.X)	X	X	X	X	X
2	Placebo	XX (XX.X)	X	X	X	X	.
	LYT-100	XX (XX.X)	X	X	X	X	.
3	Placebo	XX (XX.X)	X	X	X	.	.
	LYT-100	XX (XX.X)	X	X	X	.	.
4	Placebo	XX (XX.X)	X	X	.	.	.
	LYT-100	XX (XX.X)	X	X	.	.	.
…	…	…	…	…	…	…	…

For subjects with arbitrary missing data patterns (missing at random [MAR]), here meant to represent 6MWT, Dysp-12 and other scores that are missing for reasons other than the subject discontinuing (and specifically, 'intermediate time points', e.g., a subject has valid non-missing Day 28 values, but no Day 14 values, the Day 14 value is considered MAR), a Markov chain Monte Carlo (MCMC) method (Schafer 1997[8]) that assumes multivariate normality to impute all such MAR missing values will be used to create preliminary imputed (resulting) data sets that have strictly monotone missing patterns. A monotone missing pattern implies that all observations after a certain time point are missing, but that there are no intermediate missing values. This pattern occurs when missing values are usually caused by subject discontinuation.

After this first step, any subjects who have monotone missing values will then be divided into two groups. Using the 6MWT as an example:

- For subjects who discontinued prematurely but NOT due to an AE or death, or subjects who did not perform 6MWT but not due to hospitalization, a second imputation using regression-based method for continuous variables will then be run to complete the imputed data sets by imputing the remaining monotone missing 6MWT/mBDS scores assuming MAR. This PROC MI will include, in the imputation dataset, all subjects who

complete the study, as well as any subjects who discontinued for reasons other than AE or death. Note that because the monotone missing data pattern will already have been performed (in the prior imputation step), all subjects who 'complete' will have non-missing data.

- For subjects with monotone missing data as a result of discontinuation due to AE or subjects who did not perform 6MWT due to hospitalization, they will be considered as missing not at random (MNAR). The same pattern-mixture approach will be taken for the imputation (as for the monotone MAR data). However, the difference will be that, while a similar regression-based method for continuous variables will be applied after the MCMC step, a scaled (constant) adjustment to the imputed values will be made such that the outcomes that are imputed are distributionally 'worse' than those imputed for the monotone MAR data. This scaled adjustment will decrease each imputed value (from the regression) for these MNAR data by a constant of 25% of the baseline ITT population mean for the endpoint, e.g., if the regression provides an imputed 6MWT value of 300 for a given missing 6MWT for a subject, and the baseline average 6MWT is 250 meters for the ITT population, MNAR imputed value will be reduced by 250*0.25=62.5 meters, i.e., 300 – 62.5 = 237.5 for that subject at that time point. Further, if (as an example), the baseline mean mBDS value is 4, the scaled 25% adjustment (for patients missing mBDS values because of discontinuing due to TEAE) would be '1' unit on the mBDS scale. This will, in effect, guarantee that the overall distribution of missing values for discontinuations due to AE or to death or hospitalization is WORSE than those for other reasons. Again, the PROC MI will include in the imputation dataset all completed subjects along with subjects who discontinued due to an AE or death or hospitalization. The statistical analysis system (SAS) software will be used to perform this imputation.
- For subjects with monotone missing data as a result of discontinuation due to death, the worst possible score for the clinical outcome assessment will be assigned to the missing data. For the 6MWT distance, the missing data will be imputed a 0 (zero). For the mBDS, the missing data will be assigned as 10 (maximal).

Because the imputation of missing data is a key aspect to the analysis of these endpoints, explicit details regarding this imputation are provided via ***sample*** SAS code that is intended to demonstrate the application of these strategies. Variable definitions are (again, using the 6MWT as an example, but similar code would be used for the other endpoints):

- TRT=treatment group (2 or 1)
- 6MWT_1 is the first time point for the 6MWTd
- 6MWT_2 is the second time point for the 6MWTd
- 6MWT_last is the last time point for the 6MWTd. Additional 6MWT (between 6MWT_1 and 6MWT_last) would be included in this model according to the time points for collection.
- COMPLFL – Completers flag (this refers to subjects that have non-missing values for timepoints baseline, day 14, day 28, day 56, and day 91)
- DCREAS – Reason for Discontinuation from study

- percent is 25% of the baseline mean value (e.g., for 6MWT) for the overall ITT population.

The first step will be to impute partially to obtain a monotone missing data pattern.

```
Proc mi data=DATAIN out=DATAIN_MONO nimpute=100 seed=123 min=XX max=XX;
by TRT;
var 6MWT_1 6MWT_2 …. 6MWT_last;
mcmc chain=multiple impute=monotone;
run;
```

The second step will be to impute the remaining (monotone) missing data that is MAR for each of the 100 imputed datasets from the first step.

```
Proc mi data=DATAIN_MONO out=DATAIN_REG seed=465 nimpute=1 min=XX max=XX;
by _Imputation_ TRT;
where COMPLFL='Y' or DCREAS not in ('Adverse Event','Death') or FTREASND not in
('Hospitalization');
var 6MWT_1 6MWT_2 …. 6MWT_last;
monotone regression;
run;
```

In the case of MNAR missing data due to an AE or hospitalization, the following step will be used:

```
proc mi data=DATAIN_MONO out=DATAIN_REG seed=465 nimpute=1 min=XX max=XX;
by _Imputation_ TRT;
where COMPLFL='N' and (DCREAS in ('Adverse Event') or FTREASND in
('Hospitalization'));
var 6MWT_1 6MWT_2 …. 6MWT_last
monotone regression (6MWT_1 6MWT_2 …. 6MWT_last);
mnar adjust (6MWT_2 / shift=&Percent)
     adjust (6MWT_3 / shift=&Percent)
     adjust (6MWT_4 / shift=&Percent)
     adjust (6MWT_... / shift=&Percent)
     adjust (6MWT_last / shift=&Percent);
run;
```

In the case of MNAR missing data due to death, the worst possible score for the clinical outcome assessment will be assigned to the missing data as the following step:

```
Data DATAIN_DTH;
Set DATAIN_MONO;
where COMPLFL='N' and DCREAS in ('Death');
if 6MWT_1 = . then 6MWT_1 = 0;
if 6MWT_2 = . then 6MWT_2 = 0;
…
if 6MWT_last = . then 6MWT_last = 0;
run;
```

A total of 100 imputed datasets will be created using these imputed data and analyzed according to the primary method of statistical analysis. These datasets will be saved (reserved) and used to analyze the 6MWT and mBDS to ensure internal consistency between variables.

The multiple imputation steps will be performed based on the protocol-scheduled 6MWT and mBDS assessment time points (e.g., Baseline, Day 14, Day 28, etc.). After the imputation step is completed, early termination (ET) assessment time data will be merged back into each of the 100 datasets so that the ET assessment times can be included in the calculation of the outcomes.

For the imputed values to make sense clinically (and to be plausible given the range of potential values for each endpoint), a floor and ceiling for imputed values will be set, as follows:

6MWT: 10 and 800

mBDS: 0 and 10 (to match the actual potential range of values for the scale).

SGRQ-I: The SGRQ-I has 3 domains, so a floor/ceiling is set for each domain individually:

- Symptoms 0 to 490.3
- Activity 0 to 744.5
- Impacts 0 to 1483.5

The Total is the sum of the individual domains, and thus would not be imputed but rather calculated as the sum of the 3 imputed domains.

The values for the domains and total scores would then be normalized as per the scoring instructions (See Appendix IV) to a range from 0 to 100%.

Dyspnoea-12:

- Overall Score 0 to 36
- Physical Score 0 to 21
- Affective Score 0 to 15

SF-36

- Physical Functioning (PF): 10 to 30
- Role-Physical (RP): 4 to 20
- Bodily Pain (BP): 2 to 11
- General Health (GH): 5 to 25
- Vitality (VT): 4 to 20
- Social Functioning (SF): 2 to 10

- Role-Emotional (RE): 3 to 15
- Mental Health (MH): 5 to 25
- Self-Evaluated Transition (SET): 1 to 5

SF-36 Physical and Mental components will be derived from these imputed scores accordingly.

5.5 Observation and analysis times

5.5.1 Study Days

Reference start date is defined as the day of first dose of study drug and study day relative to the reference start date will appear in every listing where an assessment date or event date appears.

Study day will be calculated from the reference start date and will be used to show start/stop day of the assessments and events relative to the first administration of study treatment.

- If the date of the event is on or after the reference date, then:
  Study day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  Study day = (date of event – reference date).

Thus, the date of first dose study drug is defined as Study Day 1, with the day prior defined as Study Day -1.

In case of that event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix III, Partial Date Conventions.

5.5.2 Definition of baseline values

For the 6MWT, two tests are intended to be conducted between Day 1 and Day -1, and the longest distance will be recorded as the baseline (ie, used in the statistical analysis as the baseline value for all descriptive and inferential assessments). For purposes of determining the pre-treatment longest 6MWT distance, any 6MWT performed on Study Day 1 or prior can be used in the determination of the 'baseline' value.

For all other endpoints and other analyses, the baseline value is defined to be the last non-missing value collected on or before Study Day 1 (defined in EDC) and before the first treatment administration except for mBDS and height/weight.

For mBDS baseline is defined as the last non-missing value before Study Day 1 (ie either baseline or if baseline is missing then screening as defined in the EDC).

For height and weight, the baseline value used for analysis will be the value assigned in the EDC as baseline regardless of the timing even after first study dose.

5.5.3 Study periods or stages

This study includes screening, study treatment, and post-treatment periods.

- Over five days, subjects will be screened and complete baseline assessments. Randomization (Day 1) occurs on the day following the Baseline Visit/assessment.

- All subjects will be treated up to 91 consecutive days during the study treatment period. Study assessments are at Days 14, 28, 56 and Day 91 ± 3 days.
- A follow-up post-treatment completion visit will occur within 14 days of last day of study treatment ± 3 days.

5.5.4 Definition of analysis timepoints or time windows

The following table outlines the analysis visits that data will be mapped to for analysis of efficacy, safety and PK data collected during the study, except that the 6MWT baseline visit will be determined by the longest distance of the two tests conducted between Day 1 and Day -1. If after mapping, multiple data points share the same analysis visit, the data point closest to the expected study visit will be used; if the two tests are the same number of days from the target day for the visit, the earliest of the two will be used.

Table 4. Analysis Visit Window

Study Visit	Target Day*	Study Day Interval*	Analysis Visit
Baseline (pre-treatment) This window is intended to capture any data collected prior to first dose of study medication.	-1	-10 to 1	Baseline
Day 1	Day 1	1	Day 1
Day 14	Day 14	4 to 20	Day 14
Day 28	Day 28	21 to 42	Day 28
Day 56	Day 56	43 to 73	Day 56
Day 91 (Last Day of Double-Blind Treatment)	Day 91	74 to 98	Day 91
Post-Treatment Safety Follow-up Visit/Day 105	Day 105	99 to 111	Day 105

*Relative to the first day of study drug taken. Study Day 1 is the day of first dose of study medication, while Study Day -1 is the day immediately prior.
Note that the Day 105 post-treatment safety follow-up visit would only occur if a patient does not continue into the open-label extension (Part B).
Note: Due to the Covid pandemic, some centers had scheduling changes to accommodate local regulations as the local situation evolved. In particular, Philippines center 601 and Argentina center 802 had Day 91 visits that occurred beyond the window in this table (ie, the window is 74 to 98, but these patients had actual Study Days out to as far as 107). Because these visits were intended to be targeted for the last double-blind study visit per the protocol, these visits have been windowed into the Day 91 analysis wind accordingly. Therefore, for any site, if the EDC lists the visit as Day 91, but the visit is out of the 74 to 98 window, those visits up through day 107 were set the analysis visit to day 91.

5.6 Multiple Comparison/Multiplicity

The significance level of all tests will be a 2-tailed alpha level of 0.05. There is one key secondary efficacy endpoint. Endpoints will be tested at the nominal alpha level of 0.05 with no adjustment for multiplicity. Due to the serious nature of the COVID-19 crisis and the unknowns associated with outcomes, this protocol will not include adjustments for multiple testing but rather will assess each endpoint independently, with study conclusions based on a preponderance of evidence. In this context, stringent type 1 error control (e.g., in the form of a testing hierarchy) as expected for a confirmatory trial is not required. However, highlight of the primary and key secondary endpoints in a hierarchical sense will aid in interpretation of the results (in the context of potential treatment benefit based on these two pre-defined endpoints).

6 Subject Accounting and Disposition

6.1 Subject accounting

The number and relative frequencies of subjects in each analysis set as defined in section 4 Analysis Sets will be performed by ITT and presented overall and by treatment groups. Number and percentage of subjects randomized will also be summarized by country.

6.2 Disposition and withdrawals

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion. The subject disposition outcomes will be tabulated including the number and percent of subjects who are randomized, who receive treatment, who complete the treatment, and who complete the post-treatment follow-up. In addition, reasons for treatment discontinuation and study withdrawal will be presented. The summary will be performed by ENR.

6.3 Important protocol deviations

Protocol deviations will be presented in a listing including severity, protocol deviation type, and the action taken, if any. The protocol deviation which impacts subject safety, International Council for Harmonisation-Good Clinical Practice (ICH-GCP) compliance, or efficacy endpoints could be marked as important protocol deviation per study team's approval prior to database lock during the blinded data review meeting. The decision whether a protocol deviation is important or not will be made on a case-by-case basis.

Only those important deviations that may affect interpretation of study outcomes will be used to exclude patients from the PP Population. For instance, if the informed consent form (ICF) is signed after some screening study procedures are performed, this may (or may not) be a important protocol deviation. If it is assigned as a important protocol deviation, this would not, however, affect the interpretability of the efficacy outcomes and thus would not result in exclusion of the patient from the PP population.

The possible reasons of major protocol deviations are listed but not limited to the following:

- Failure to obtain informed consent
- Deviation of inclusion/exclusion criteria
- SAE(/pregnancy) reporting requirement not followed
- Any known study medication administration error
- Any study-specific related procedure done before the signature of the informed consent
- Non-compliance with study drug. A participant is defined as non-compliant if the participant took < 80% of the study drug
- Intake of prohibited medication
- Source document/data missing

Important protocol deviations will be summarized by treatment group based on ITT population. All subjects with protocol deviations including those specified above will be listed.

7 Demographics and Background Characteristics

7.1 Demographics

Analysis of demographics data will be performed for the ITT, FAS, PP, and SAF populations. Demographics and baseline characteristics will be summarized using appropriate descriptive statistics.

Demographics will be summarized by overall subjects and treatment group, with corresponding listing as follows:

- Age (years)
- Age Group (< 65, ≥ 65 years old)
- Sex (Female, Male)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, and Unknown)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple and Other)
- Weight (kg) at baseline
- Height (cm) at baseline
- BMI (kg/m^2) at baseline
- Days since Initial Confirmed Positive COVID-19 Diagnosis (days), derived from the date of first dose of study drug minus the date of initial confirmed positive COVID-19 diagnosis.
- Days since discharge from hospital (days), derived from the date of first dose of study drug minus the date of discharge for the qualifying hospitalization from electronic case report form (eCRF) form “Qualifying Hospitalization Discharge Date”.
- Time (days) from date of initial hospitalization to date of randomization.

Baseline characteristics will be summarized as follows:

- 6MWT distance (m), for each of the first and the second attempts 6MWT distance (m) for the attempt used as ‘baseline’ for purposes of analysis
- The number (%) of subjects where the first and where the second attempt was used as baseline for purposes of analysis
- 6MWT distance status at baseline (10 to <100 m, 100 to 200 m, > 200m)
- mBDS at baseline
- Prior Mechanical Ventilation/Prior ECMO Status (Yes, No)
- Charlson Comorbidity Index (CCI) at baseline

Qualifying respiratory support for COVDI-19 at baseline (MV, ECMO, NIV, HFNO, other high flow oxygen, low flow oxygen)CCI will be calculated using the following table and add all items of the comorbidity score. The score ranges from 0 to 33. A higher score indicates worse health condition.

Table 5. Charlson Comorbidity Index

Disease	Points
Myocardial Infarction	1
Congestive Heart Failure	1
Peripheral Vascular disease	1
Cerebrovascular disease	1
Dementia	1
COPD	1
Connective Tissue disease	1
Peptic Ulcer disease	1
Diabetes Mellitus	1 point if uncomplicated 2 points if end-organ damage
Moderate to severe CKD	2
Hemiplegia	2
Leukaemia	2
Malignant Lymphoma	2
Solid Tumour	2 points 6 points if metastatic
Liver disease	1 point if mild 3 points if moderate to severe
AIDS	6 points

7.2 Medical history

Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA® version 23.0 [or later]) and will be classified as follows:

- Previous medical history: medical conditions that stopped prior to start of treatment
- Ongoing (concomitant) medical conditions: medical conditions still present after start of treatment. Medical conditions with onset or end-date on the date of the first dose of study drug will be considered concomitant.

Frequency and percentage of medical history and concomitant medical conditions will be summarized by system organ class (SOC) and preferred term (PT) by SAF. The number (%) of subjects reporting each condition will be presented by overall and treatment group. If subjects have more than one disease within an SOC or PT they will be counted only once for the respective SOC or PT.

8 Exposure and Compliance

8.1 Extent of Exposure

Duration of study drug exposure, defined as the number of days between the date of first dose following randomization and the date of the last dose, will be summarized using descriptive statistics by treatment group and overall.

Duration (days) will be calculated as date of last dose – date of first dose + 1.

If the date of first intake of study medication is missing, it will be assumed to be identical to the date of randomization.

Descriptive statistics for the treatment duration will be presented using ITT and SAF Populations.

8.2 Compliance

Compliance will be based on the protocol-defined planned 91 days of study drug dosing. The total amount (in mg) of study drug will be determined for each patient, and then compared to the total EXPECTED amount (135,000 mg) of study drug that would be given if a patient completed exactly 91 days of treatment (as per protocol).

The expected amount of study drug is derived based on both the titration period (first 3 days) and then the remaining full-dosage days, as follows:

- Days 1 through 3 (3 days): 1000 mg/day x 3 days = 3000 mg during titration period
- Days 4 through 91 (88 days): 1500 mg/day x 88 days = 132,000 mg.
- TOTAL: 135,000 mg expected.

The actual mg taken by each patient will be calculated using the start and stop dates for each dose level, multiplied by the dosage given from the study drug adjustment eCRF page dataset. As an example, the following patient titrated to full dose, had a dose interruption for 13 days, and then restarted study drug but at half the prescribed dosage for the remainder of study participation.

- Start Day 1 and Stop Day 3 (total daily dose 1000mg): Total mg given=3,000
- Start Day 4 and Stop Day 26 (total daily dose 1500mg): Total mg given=33,000
- Start Day 27 and Stop Day 40 (total daily dose 0mg, dose interrupted): Total mg given=0
- Start Day 27 and Stop Day 40 (total daily dose 750mg, reduced dose): Total mg given=37,500
- Total mg given to subject=73,500

Compliance (expressed as a percent) would then be calculated as:

$$\frac{\text{Total mg given}}{\text{Total mg expected}} = \frac{73{,}500}{135{,}000} = \mathbf{54.4\%}$$

The second example below is a patient who had the Day 91 study visit a full 10 days after the target study day (Day 91) and yet who continued taking double-blind study medication.

- Start Day 1 and Stop Day 3 (total daily dose 1000mg): Total mg given=3,000

- Start Day 4 and Stop Day 101 (total daily dose 1500mg): Total mg given=145,500
- Total mg given to subject=148,500

Compliance (expressed as a percent) would then be calculated as:

$$\frac{\text{Total mg given}}{\text{Total mg expected}} = \frac{148{,}500}{135{,}000} = \textbf{110.0\%}$$

9 Previous and Concomitant Medications and Therapies

Prior and concomitant medications are coded according to the World Health Organization drug dictionary (WHODrug Global B3 September 2020 or later) and stored with anatomical therapeutic class (ATC) codes and generic names.

Prior medication is defined as any medication other than the study drug within 30 days prior to the first study drug administration. Medications used over the course of the study will be classified to prior or concomitant based on the imputations specified in Appendix III: Partial Date Conventions. Summary tables by treatment groups and overall for prior and concomitant medication will be provided detailing the number and percentage of subjects by ATC Level 1 and preferred name using the WHO Drug Dictionary by SAF.

A table of new-onset medications will also be provided, including only those medications with a start date on or after the date of the first dose of study medication.

Concomitant procedures will be provided in listing. In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

10 Efficacy

Analyses regarding the primary and key secondary efficacy endpoints will be based on the analysis of Day 91 (end of double-blind treatment), with supporting data from earlier time points included to describe the time-profile of any treatment benefits.

For each of the following endpoints, a line plot of the LSMean (+/- Standard Error [SE-) changes over time (by treatment group) from MMRM models will be provided for the ITT, FAS and PP populations:

- 6MWT
- mBDS
- SRGQ-I
- Dyspneoa 12
- WHO Ordinal
- SF-36 Mental and Physical Components
- SF-36 Domains (eight)

Note that since the imputation of missing values is based on a multiple imputation strategy (i.e., not a single-imputation method such as last observation carried forward [LOCF]), these plots will be presented both with the imputed values as obtained from PROC MIANALYZE (using the combined

inferential statistics and least square means [LSMeans] et al from the 100 imputed datasets) and without imputated values, i.e., based on observed values.

10.1 Primary efficacy analysis

10.1.1 6-minute Walk Test distance (6MWT)

The primary efficacy endpoint is the change from baseline to Day 91 of the 6MWT distance. Analysis of the 6MWT will be performed at each protocol-scheduled time point, i.e., baseline, Day 14, 28, 56, and 91.

Two 6MWT will be performed on Days -1 and/or 1, at baseline, and with the longest distance will be recorded for the baseline measure. These tests can take place on Days -1 and/or Day 1, prior to dosing.

The 6MWT measures the distance a subject can quickly walk on a flat, hard surface in a period of 6 minutes. It evaluates the global and integrated response of all the systems involved during exercise.

Subjects who are unable to complete (or walk) due to disease severity will be assigned a distance of 0 (zero). However, some subjects may not be able to complete the 6MWT due to restrictions on their movement at the investigational center (due to the COVID-19 diagnosis), and thus would have their distance imputed according to the missing data imputation strategy.

Change from baseline in 6MWT will be summarized as descriptive statistics by treatment and visit. 6MWT will be analyzed using MMRM, assuming a Gaussian distribution, an unstructured covariance matrix, the Between-Within denominator degrees of freedom approximation and the Huber-White robust sandwich estimation for standard errors. Fixed effects will include treatment, visit, the treatment by visit interaction, the baseline value of the endpoint, study center, prior mechanical ventilation/prior ECMO Status (Yes vs. No), age group (< 65 vs. >= 65), and duration of Covid diagnosis to first dose of study drugas covariates. Visits will include Day 14, 28, 56, and Day 91. Where applicable, the study center will be pooled into regions (United States, East Europe, West Europe, and others). The covariate of study center will then be replaced by region. However, if there is a convergence problem with the unstructured covariance matrix, then alternative covariance structures will be first order autoregressive structure (AR [1]). If the model does not converge using AR(1) then alternative covariance structure will be compound symmetry. Missing data will be imputed as by multiple imputation as indicated in the Section 5.4. By-visit pairwise comparisons will be assessed. Least square means and their SEs, LSmeans for treatment difference along with their 95% confidence interval (CI) of will be reported.

The 100 resulting treatment effect parameters and SEs from these MMRMs will be presented individually and then combined, using the PROC MIANALYZE procedure, to provide a distribution of parameters (and SEs) upon which the primary hypothesis of treatment effect will be determined. SAS code similar to this example will be used, where ‘estimate’ reflects the outcomes (e.g., LSmean differences) from each MMRM:

```
proc mianalyze data=diffs alpha=0.05;
  by treat;
  modeleffects estimate;
  stderr stderr;
run;
```

The results of the analyses will be presented in summary tables with standard summary statistics as well as LSmeans, active vs. placebo LS mean differences (treated group – Placebo), SEs, CIs, and paired-comparison p-values. The mean 6MWT values and SE of the mean (SEM) for each treatment group will also be presented graphically. This analysis will be referred to as the multiple imputation (MI) analysis.

The box plot and line plot of LSMeans (+/- SE) over time will be graphically displayed by treatment group to allow for visual comparison of the 6MWT distance profiles.

Primary conclusion regarding efficacy of these endpoints will be based on the ITT, with sensitivity support based on the FAS and PP populations. Note that the subgroup analyses (e.g., by baseline 6MWT, mechanical ventilation use, etc.) of this endpoint will use the same imputed datasets as for the full ITT assessment.

To perform MMRM, SAS programming will be used as follows, with code similar to the following sample used (where DIAGDUR is the time from initial Covid-19 positive test to the date of first dose of double-blind medication):

```
proc mixed data= dataset empirical;
    class trt visit subjid center pves agegr1;
    model chg=trt avisit trt*avisit base center pves agegr1 DIAGDUR/htype=3
    ddfm=BETWITHIN ;
    repeated time/type=un sub= subjid;
    lsmeans time*treatment/cl pdiff alpha=0.5 slice=time;
    ods output lsmeans = lsmeans diffs=diffs tests3=tests3 slices=slices
run;
```

10.2 Key Secondary efficacy analyses

Dyspnoea-12 is an instrument used to assess the dyspnea severity ”these days” reflecting breathlessness experienced in daily life. Dyspnoea-12 consist of 12 descriptor items ranging from none (0), mild (1), moderate (2) or severe (3).

An overall score (range 0-36) of breathlessness severity that encompasses seven ***physical*** items (Items 1-7, range 0-21) and five ***affective*** items (Items 8-12, range 0-15) is provided. The total score ranges from 0 to 36 whereby the higher score correlates with greater severity. The instrument with data from more than three items missing will not be used. The method for scoring the Dyspnoea-12 with up to three missing items is detailed in the table below (Yorke *et al*., 2010[7]).

Table 6. Missing Items Handling of Dyspnoea-12 for Overall Score

Number of items missing	Calculation to account for missing items	Dyspnoea-12 score calculation
1	36 ÷ 33 =1.09	1.1 × total Dyspnoea-12 score
2	36 ÷ 30 =1.2	1.2 × total Dyspnoea-12 score
3	36 ÷ 27 =1.3	1.3 × total Dyspnoea-12 score

The scoring approach defined in Table 6 above will only be performed for the overall score. A scoring adjustment for the domains of physical and affective will not be performed.

Dyspnoea-12 will be assessed at Day -1, 14, 28, 56, and Day 91. Changes from baseline in the total Dyspnoea-12 will be analyzed using MMRM method as primary efficacy endpoint by treatment group and visit. The visits will include Day 14, 28, 56, and Day 91. The MMRM model fixed effects will include treatment, visit, the treatment by visit interaction, the baseline value of the endpoint, study center, 6MWT group at baseline (10 to <100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO Status (Yes vs. No), duration of Covid diagnosis to first dose of study drug, and age group (< 65 vs. >= 65) as covariates.

The analysis will be performed separately by the following: overall score (questions 1-12), physical subgroup score (questions 1-7), and affective subgroup score (questions 8-12).

10.2.1 Sensitivity and Robustness Analyses

A sensitivity analysis of the primary and key secondary endpoints will be performed using the same MMRM method on the basis of missing at random assumptions. Missing data will be regarded as missing except for death. If a subject dies, the worst possible scores will be assigned to each clinical outcome assessment. If 6MWT distance is missing due to death, the data will be imputed as 0 (zero). If Dyspnoea-12 is missing due to death, the data will be imputed as 36.

In addition, a sensitivity analysis of the primary and key secondary endpoints will be performed using a nonparametric Wilcoxon rank sum test to test the LYT-100 vs. placebo comparison at each time point.

Because of the evolving understanding of Covid continues to inform, post-hoc exploratory analyses will be performed. These may include rerunning of the same primary efficacy statistical model with additional covariates (eg, index duration of hospitalization, use of corticosteroids). Examination of the pre-treatment disease characteristics between the treatment arms will be performed and, for any clinically relevant differences in those distributions between the treatment arms, inclusion of those parameters as covariates may be performed.

10.3 Other secondary efficacy analyses

Missing data imputation will only be considered for the other secondary efficacy analysis when there is a significant amount of missing data, e.g., from excess mortality or withdrawal numbers.

10.3.1 St. George's Respiratory Questionnaire-I

The SGRQ-I, assessed at Day -1, 28, 56 and Day 91, is an idiopathic pulmonary fibrosis disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in subjects with interstitial lung disease. There are 34 self-completed items with the following 3 domain component scores calculated.

- Symptoms - this component has to do with the effect of respiratory symptoms, their frequency and severity
- Activity – has to do with activities that cause or are limited by breathlessness
- Impacts - covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease.

A total score is also calculated which summarizes the impact of the disease on overall health status. Scores are expressed as a percentage of overall impairment where 100 represents worst possible health status and 0 indicates best possible health status. The scoring method is detailed in Appendix IV.

Changes from baseline in the total score and component scores of the SGRQ-I will be analyzed using the same MMRM method as primary efficacy endpoint by treatment group and visit. The visits will include Days 28, 56 and 91.

Proportion of subjects experiencing a decrease by at least 4 units (vs. less than 4 units) from baseline in the total score will be tabulated by treatment group as responder analysis. The number and percentage of responder/non-responder subjects will be tabulated by treatment group and visit and analyzed by Cochran-Mantel-Haenszel (CMH) test, stratified by center, 6MWT group at baseline (10 to <100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO Status (Yes vs. No), duration of Covid diagnosis to first dose of study drug, and age group (< 65 vs. >= 65), where applicable.

A cumulative distribution plot of the changes from baseline in the SGRQ-I total score will be generated to demonstrate the differences between the treatment groups for each change from baseline value observed.

10.3.2 Modified Borg (Dyspnoea) Scale

The mBDS will be assessed at Screening, Day -1, 1, 14, 28, 56, and Day 91. The mBDS from eCRF form 'Modified Borg (Dyspnoea) Scale (mBDS)' will be adopted as a secondary efficacy endpoint. Change from baseline in mBDS will be summarized as descriptive statistics by overall subjects and treatment and visit. It will further be analyzed using the similar MMRM method as primary efficacy endpoint (including the same populations and methods for missing data) where fixed effects will include treatment, visit, the treatment by visit interaction, the baseline value of the endpoint, study center, 6MWT group at baseline (10 to <100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO Status (Yes vs. No), duration of Covid diagnosis to first dose of study drug, and age group (< 65 vs. >= 65) as covariates. Visits will include baseline, Day 14, 28, 56, and Day 91. The LSMeans (+/- SE) line plot over time will be graphically displayed by treatment group to allow for visual comparison of the mBDS profile. For this endpoint baseline is defined as the last assessment prior to the day 1 assessment. The baseline assessment and day 1 assessment can be on the same day, however, the day 1 assessment is intended to be conducted after the first treatment administration.

10.3.3 WHO Ordinal Scale for Clinical Improvement

The WHO Ordinal Scale for Clinical Improvement will be assessed at Day -1, 14, 28, 56 and Day 91. This assessment is a nine-category ordinal scale with the following categories:

0 - Uninfected (No clinical or virologic evidence of infection)

1 - Ambulatory (No limitation of activities)

2 - Ambulatory (Limitation of activities)

3 - Hospitalized Mild Disease (Hospitalized, no oxygen therapy)

4 - Hospitalized Mild Disease (Oxygen by mask or nasal prongs)

5 - Hospitalized Severe Disease (Non-invasive ventilation or high-flow oxygen)

6 - Hospitalized Severe Disease (Intubation and mechanical ventilation)

7 - Hospitalized Severe Disease (Mechanical ventilation plus additional organ support (i.e., extracorporeal life support [ECLS], continuous renal replacement therapy [CRRT], vasopressors)

8 - Dead (Death).

The WHO Ordinal Scale for Clinical Improvement will be assessed for responder analysis. Responders will be analyzed by using two definitions according to the level of improvement.

- Improvement by at least 1 point from baseline
- Improvement by at least 2 points from baseline.

Number and percentage of responder/non-responder subjects will be tabulated by treatment group and visit and analyzed by CMH test with modified ridit scores to assess the row mean scores between the treatment groups (referred to as a CMH-RMS), stratified by center, 6MWT group at baseline (10 to <100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO Status (Yes vs. No), age group (< 65 vs. >= 65), where applicable. Bar charts of the distribution of WHO Ordinal Scale outcomes will be provided for each visit to allow for visual inspection of any treatment differences.

The sample SAS codes are provided as following. Variable definitions are:

- TRT=treatment group (2 or 1)
- RESP is the responder (Yes or No)
- SITEID is the center
- MWTGR is the 6MWT group at baseline (10 to <100 m, 100 to 200 m, >200 m).
- AGEGR is the baseline age group (< 65 vs. >= 65)
- MVECGR is the prior mechanical ventilation/prior ECMO Status (Yes vs. No)

```
proc freq data=indata;
    tables SITEID*mwtgr*agegr*mvecgr* TRT*RESP/ chisq relrisk cmh2 scores =
modridit;
    output out=cmh2 cmh2;
run;
```

WHO outcomes will also be assessed on a continuum using similar MMRM as for the primary efficacy endpoint. The visits will include baseline, Day 14, 28, 56 and Day 91.

10.3.4 Quality of Life Assessment Using the SF-36 (v2)

The SF-36 v2 is a self-administered questionnaire containing 36 items that measures health on functional status, well-being, and overall evaluation of health in 8 domains and assessed at Day -1, 28, 56, and Day 91.

Except for the one single-item of SET (item 2), the scores of the other thirty-five items are summated into eight multi-item scales, including PF, limitations due to physical health problems (RP, BP, GH, VT, and SF), limitations due to emotional health problems (RE and MH). The eight multi-item scales are aggregated into physical component summary (PCS) and mental component summary (MCS). The scoring of two summary components and eight scales will be performed by QualityMetric Health Outcomes™ Scoring Software based on norms with a mean of 50 and a standard deviation of 10. According to the scoring algorithm, there is no total score of SF-36. For all scales and summary components, higher scores demonstrate better quality of life. The Study Data Tabulation Model (SDTM) datasets will be imported in the software and an aggregated data report will be provided.

Table 7. Scales of SF-36 v2

Scale	Item	Lowest and highest possible raw scores	Possible raw score range
Physical Functioning (PF)	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	10-30	20
Role-Physical (RP)	4a, 4b, 4c, 4d	4-20	16
Bodily Pain (BP)	7,8	2-11	9
General Health (GH)	1, 11a, 11b, 11c, 11d	5-25	20
Vitality (VT)	9a, 9e, 9g, 9i	4-20	16
Social Functioning (SF)	6, 10	2-10	8
Role-Emotional (RE)	5a, 5b, 5c	3-15	12
Mental Health (MH)	9b, 9c, 9d, 9f, 9h	5-25	20
Self-Evaluated Transition (SET)	2	1-5	4
Physical Component Summary (PCS)	PF, RP, BP, GH	21-86	65

Scale	Item	Lowest and highest possible raw scores	Possible raw score range
Mental Component Summary (MCS)	VT, SF, RE, MH	14-70	56
For all scales and summary components, higher scores demonstrate better QoL.			

Changes in the standardized component scores and domain scores will be respectively calculated and analyzed using the same MMRM method as primary efficacy endpoint and summarized by treatment group and visit. The visits will include Day 28, 56, and 91.

10.3.5 Number of Lung Segments Involved Using CT Scan and Semi-QLF Assessment

Chest CT Scan will be assessed at Day -1 and 91 and it will be performed according to the CT Scan manual.

CT scans will be analyzed with semi-QLF and computer-Aided Diagnosis (CAD) QLF Scores (Kim et al, 2010[9]). Table 8 shows how each of the five lobes will be scored; the total score for each of the five findings per lobe (range 0-5), each finding across the five lobes (range 0-25) and total score for the whole lung for all findings together (0-100) will be derived accordingly.

Changes from baseline to Day 91 in CT Scan with QLF scores will be tabulated by treatment group, using MMRM method.

Table 8. Lung Lobe Involvement Scores

Lung lobe involvement – for each of the five lung lobes (Right upper, Right middle, Right lower, Left Upper, Left lower), and lingula	Score
Ground glass opacity (GGO) Score	
No alveolar disease	0
Ground glass opacity involving < 5% of the lobe	1
GGO involving 5-25% of the lobe	2
GGO involving 25-49% of the lobe	3
GGO involving 50-75% of the lobe	4
GGO involving >75% of the lobe	5
Fibrosis Score	
No interstitial disease	0
Interlobular septal thickening; no discrete honeycombing	1
Honeycombing (+/- septal thickening) involving up to 25% of the lobe	2
Honeycombing (+/- septal thickening) involving 25-49% of the lobe	3
Honeycombing (+/- septal thickening) involving 50-75% of the lobe	4
Honeycombing (+/- septal thickening) involving > 75% of the lobe	5
Consolidation Score	
No Consolidation	0
Consolidation involving <5% of the lobe	1
Consolidation involving 5-25% of the lobe	2
Consolidation involving 25-49% of the lobe	3

Lung lobe involvement – for each of the five lung lobes (Right upper, Right middle, Right lower, Left Upper, Left lower), and lingula	**Score**
Consolidation involving 50-75% of the lobe	4
Consolidation involving >75% of the lobe	5
Reticulation/bronchiectasis Score:	
No reticulation	0
Reticulation involving < 5% of the lobe	1
Reticulation involving 5-25% of the lobe	2
Reticulation involving 25-49% of the lobe	3
Reticulation involving 49-75% of the lobe	4
Reticulation involving >75% of the lobe	5

A responder analyses will be performed, in which the proportion of subjects showing ground glass opacities, fibrosis, consolidation, reticulation/bronchiectasis by determining at least a 2-point score improvement for each abnormality across the five lobes (range 0-25) will be derived. The number and percentage of responder/non-responder subjects will be tabulated by treatment group and visit and analyzed using the CMH test, stratified by center, 6MWT group at baseline (10 to <100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO Status (Yes vs. No) and age group (< 65 vs. ≥ 65), where applicable.

10.3.6 Severity of Lung Lobe(s) Involvement, Using CT Scan

For each of the five lobes, an assessment of lung lobe involvement using CT Scan will be assessed using the scale as shown in Table 9 Summary of these characteristics will be tabulated by lung lobes and visits. In addition, shifts in ground-glass opacity, consolidation, reticular pattern, mixed pattern, honeycomb pattern and crazy paving over the course of treatment will be provided by lung lobes as well.

Table 9. Chest CT Scan Number of Involved Segments

Per lobe, for each of the five lung lobes (Right upper, Right middle, Right lower, Left Upper, Left lower), and lingula	
Ground-Glass Opacity	• Central • Peripheral • Diffuse • Absent • Not Evaluable
Consolidation	• Central • Peripheral • Diffuse • Absent • Not Evaluable
Reticular Pattern	• Central • Peripheral • Diffuse • Absent • Not Evaluable

Per lobe, for each of the five lung lobes (Right upper, Right middle, Right lower, Left Upper, Left lower), and lingula	
Mixed Pattern	• Central • Peripheral • Diffuse • Absent • Not Evaluable
Honeycomb Pattern	• Central • Peripheral • Diffuse • Absent • Not Evaluable
Crazy Paving	• Central • Peripheral • Diffuse • Absent • Not Evaluable
Septal Thickening	• Right • Left • Bilateral • Absent • Not Evaluable
Pleural Thickening	• Right • Left • Bilateral • Absent • Not Evaluable NE
Per Lung	
Pleural Effusion	• Right • Left • Bilateral • Absent • Not Evaluable
Pleural Effusion Impact	• Yes • No • Not Evaluable
Lymphadenopathy	• Present • Absent • Not Evaluable

10.3.7 Inflammatory, Fibrosis and Other Biomarkers

Biomarkers, including C-reactive protein (CRP), lymphocyte count, D-dimer, cardiac troponin, ferritin, lactate dehydrogenase (LDH), IL-6, TGF-β1, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), platelet derived growth factor-β (PDGF-β), granulocyte colony stimulating factor (GCSF), and vascular endothelial growth factor (VEGF) will be assessed at Days -1, 14, 28, 56, and 91. Changes

from baseline of the biomarkers will be summarized by treatment group and visit, and analyzed using the same MMRM method as primary efficacy endpoint. Visits will include Day 14, 28, 56 and Day 91.

10.3.8 Pulmonary Exacerbations, Severe and Non-severe

The number and percentage of subjects with the following clinical outcomes will be tabulated separately by treatment groups, and group differences will be compared using the CMH, stratified by center, 6MWT group at baseline (10 to <100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO Status (Yes vs. No) and age group (< 65 vs.≥65), where applicable.

- The percentage of subjects who develop severe pulmonary exacerbations
- The percentage of subjects who develop non-severe pulmonary exacerbations

Time to first severe exacerbations will be derived by taking the date of first severe exacerbation minus the date of first study drug taken and adding one. Subjects who die or withdraw from the study without any severe exacerbation will be censored on the date of death/withdrawal. Subjects will be censored on the visit date of Day 91 if none of severe exacerbation occurred at this time point. The time-to-first severe exacerbation will be graphically displayed using a Kaplan-Meier plot and analyzed by log-rank test.

If there are multiple severe exacerbations observed for some subjects, the total number of episodes of severe pulmonary exacerbations during the treatment period will be summarized and the difference between treatment groups will be performed using a CMH-RMS test.

10.3.9 Pulse Oximetry (SpO2)

Pulse-Oximetry (SpO2) will be assessed at Screening, Days -1, 1, 14, 28, 56, 91, and 105. Changes from baseline in SpO2 will be summarized by treatment group and visit and analyzed using the same MMRM method as primary efficacy endpoint. Visits will include Days 14, 28, 56, 91 and 105.

10.3.10 Chest X-Ray

Chest X-Ray will be assessed at Screening and Day 91. The proportion of subjects with “Normal” and “Abnormal” chest X-ray will be tabulated by treatment group and visit. CMH test, stratified by center, 6MWT group at baseline (10 to <100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO Status (Yes vs. No) and age group (< 65 vs. >= 65) will be adopted to analyze the treatment difference for the normality, where applicable. Shift in assessment of chest X-Ray from baseline to Day 91 will be tabulated by treatment group, using frequency tabulations. Subjects with pre-existing chest pathology pre-COVID-19 should be considered 'normal' for those pre-existing items/findings.

10.3.11 Time to Discharge from Original Hospitalization

Time to discharge from original hospitalization will be derived by taking the date of discharge minus the date of randomization and adding one day for the original hospitalization. Subjects who die or withdraw from the study while in original hospitalization will be censored on the date of death/withdrawal. Subjects will be censored on the visit date of Day 105 if they are still hospitalized at this time point.

Total duration of hospitalization during the study will be summed up for the days of hospitalization from the date of randomization to last date of the study (Day 105/End of Study [EoS]) including the duration of original hospital stay and the duration of rehospitalizations from any cause by EoS. The duration of original hospital stay will be calculated as date of discharge or EoS whichever occurs earlier minus the date of randomization and plus. The duration of rehospitalization will be calculated as discharge date minus admission date of rehospitalization and plus one.

The length of hospitalization prior to enrolment will be calculated for the original hospitalization from the date of admission to date of enrolment, i.e., Study Day 1.

The Kaplan-Meier method and log-rank test will be performed to estimate the time to discharge from original hospitalization. The time and 95% CI for the 25th, 50th, 75th percentile of events time will be presented by treatment groups. In addition, a stratified log-rank test with 6MWT at baseline (10 to 100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO status (Yes/No) and age group (>= 65 years/<65 years) as strata will be provided. The Kaplan-Meier survival curve will also be graphically displayed by treatment groups.

Total duration of hospitalization and length of hospitalization prior to enrolment will be analyzed by Analysis of Covariance (ANCOVA) with treatment group, study center, 6MWT group at baseline (10 to <100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO Status (Yes vs. No) and age group (< 65 vs. >= 65) as factors and baseline value of the endpoint as covariates.

In addition, a correlational analysis will also be undertaken to identify patient factors e.g., age, gender, BMI, and potential biomarkers that are associated with successful resolution of all signs and symptoms of the disease. A univariate and multivariate Cox proportional hazards model with the abovementioned factors as covariates will be used to estimate the hazard ratio and compare treatment groups, respectively.

10.3.12 All-cause Mortality

Time to all-cause mortality will be assessed if data permit. It is defined as date of death from any cause minus date of randomization plus 1 day. If death is not observed, the subject will be censored at date of last known survival date.

The Kaplan-Meier method and log-rank test will be performed to estimate the all-cause mortality (if sufficient mortality data exist to allow for meaningful comparisons) as well as length of hospital stay from admission and from first dose of study drug (in days). The time and 95% CI for the 25th, 50th, 75th percentile of events time will be presented by treatment groups. In addition, a stratified log-rank test with 6MWT at baseline (10 to 100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO status (Yes/No) and age group (>= 65 years/<65 years) as strata will be provided. The Kaplan-Meier survival curve will also be graphically displayed by treatment groups.

The number of subjects dying (all-cause mortality) through Day 91 will be tabulated. All efforts will be made to follow up with subjects who discontinue the study for their survival status through Day 91. Therefore, the survival status will not be imputed. The difference in proportions of death will be compared by CMH test, stratified by center, 6MWT group at baseline (10 to <100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO Status (Yes vs. No) and age group (< 65 vs. ≥ 65), where applicable.

In addition, a correlational analysis will also be undertaken to identify patient factors e.g., age, gender, BMI, and potential biomarkers that are associated with overall survival. A univariate and

multivariate Cox proportional hazards model with the abovementioned factors as covariates will be used to estimate the hazard ratio and compare treatment groups, respectively.

10.3.13 Other clinical outcomes

Other clinical outcomes will be assessed as follows:

- Percentage of subjects who experience rehospitalization for any cause, while on treatment
- Use of supplemental oxygen from baseline to end of treatment.

The number and percentage of subjects with each of the above clinical outcomes will be tabulated by treatment groups and group difference will be compared using the CMH test, stratified by center, 6MWT group at baseline (10 to <100 m, 100 to 200 m, >200 m), prior mechanical ventilation/prior ECMO Status (Yes vs. No) and age group (< 65 vs. ≥ 65), where applicable.

The number of rehospitalizations during the 91-day treatment period will be analyzed with CMH-RMS which uses modified ridit score. If the subjects do not experience any rehospitalization, the value will be '0'.

10.4 SCOA Mixed Methods Analysis of COVID-19 Symptoms Assessments

The COVID symptoms assessments include daily COVID Symptoms Scale, Weekly Patient Global Item of Severity (PGIS) and Patient Global Item of Change (PGIC). The detailed analysis method will be documented in a separate addendum to this SAP.

10.4.1 Qualitative Participants Interviews

Up to approximately fifty (50) adults from the United States will be targeted to participate in the qualitative interviews. The interviews will occur either during screening or after completion of 91-days of blinded treatment (to be completed around days 91-105). Early termination patients may also be interviewed at the sponsor's discretion. All interviews will be conducted based on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force recommendations. The interviews will be based on an interview guide with open-ended questions that will be used to encourage spontaneous responses and good qualitative data. The analysis method of the interviews results is provided in the following sections.

10.4.2 Qualitative Analyses

The qualitative analysis strategy is to use qualitative analysis software (Atlas.ti) to code each interview transcript to identify and categorize patient responses to systematically identify symptom concepts of interest within the transcripts. A code book will be developed that will be used to organize and catogorize the concepts of interest from the interviews. The code book will include descriptions and examples for each code to ensure consistency across coders. Each transcript will be coded by one coder, and then reviewed by a second coder. Inconsistencies will be reviewed and adjudicated by a third coder, if necessary. Revisions to the code book may be made during the course of the interviews and coding process to ensure that codes are clearly defined and consistently applied.

The frequency of the concepts identified will be summarized and representative quotes from participants will also be included to provide supportive information about how participants refer to symptoms. The coded data will be taken from those statements that are spontaneously generated in open ended concept elicitation questioning during the interview to ensure that the codes represent the terminology used by patients. Interviews will continue until saturation is reached, i.e., the chronological point when no new relevant or important codes are generated with additional interviews. Saturation grids will be developed to present these data. After saturation is demonstrated, the interviews will shorten the concept elicitation portion of the interviews and expand the cognitive debriefing focus.

The cognitive debriefing portion of interviews will generate evidence of comprehension, clarity, relevance, and appropriateness of the item stems, response options, and recall period and to confirm that no additional relevant and important symptoms are experienced by patients with Long COVID. The cognitive debriefing of the Dyspnoea-12 and 6MWT-related PRO items will be analyzed in the same way. Any problems related to any of the item content will be reported.

10.4.3 Quantitative Analyses

10.4.4 Content Confirmation: Item Analysis

The quantitative analysis strategy will include the following item level analyses to support final Daily COVID Symptom Questionnaire content to flag areas where content modification may be considered. The SCOA population flag will be used to select subjects for this initial psychometric analysis.

Quality of Completion

The quality of completion for the COVID Symptom Questionnaire items will be described at Baseline The following descriptive statistics will be presented:

- Frequency (count) and percentage of patients with a missing response by item
- Frequency (count) and percentage of patients with no missing item data by day

Items that have substantial missing data (≥ 20%) will be flagged for hypothesis generation regarding possible explanation(s) ([10]Cappelleri 2013).

Internal Consistency Reliability

Internal consistency refers to the extent to which individual items are consistent with each other and reflect a single underlying construct. Cronbach's alpha statistic ([11]Cronbach 1951) will be used to assess reliability (ie, homogeneity of item scores) for the COVID symptom questionnaire ([12]Nunnally 1978). An overall alpha value will be calculated for each domain along with item-level alpha values showing the change in alpha following the exclusion of each item in turn. An alpha value of 0.80 is provided as a guideline for determining that a total score is internally consistent, although values of ≥ 0.70 are also acceptable ([13]Nunnally 1994b, [14]Nunnally 1994b). Alpha scores more than 0.90 may

indicate an overly homogenous measure where items are redundant due to excessive similarity or a domain that contains too many items. Further, item-level alpha values that are substantially higher than the overall alpha level will be investigated to determine the saliency of the item to the overall domain.

Internal consistency reliability will be presented using the SCOA population at Baseline and day 91.

Exploratory Item Fit Analysis: Rasch Measurement Theory (RMT)

The Rasch measurement theory (RMT) response scale model (RSM) will be performed to investigate item properties in relation to their underlying construct for the initial item set generated from the qualitative patient in queary and will be used to support the interpretation of the qualitative concept elicitation. No items will be flagged for deletion in this initial analysis; they will be reviewed against the qualitative and item descriptive analyses described above to support the final conceptual framework.

RMT is a modern psychometric method designed to determine how well the items within a domain (factor) measure people (patients) along the latent continuum. The Rasch model simultaneously measures a person's latent factor score (known as a *person measure*) and item difficulty (known as an *item measure*) with the same "ruler." The common ruler is measured with logits (natural log of the odds; note, a z-score = logit / 1.7) rather than the scale labels used for the items. The advantage of working in logits, rather than raw scores (eg, total or mean scores) is that all measures are linear, thereby permitting comparisons and arithmetic operations. This is particularly important because a S-shaped curve (ie, the logistic ogive) depicts the relationship between nonlinear raw scores and linear Rasch measures. Consequently, persons and items near the extreme points of the response scale are measured with a great deal of error when a linear model is assumed to exist ([15]Bond 2013).

Person measures are analogous to composite (domain) scores and are estimated from a logistic function of the total score across all the items in a domain. Similarly, item measures are an expression of how likely an average patient is to endorse an item using the response categories. An Andrich threshold demarks the middle point (probabilistically speaking) between adjacent response categories. In other words, it is the point at which there is a 50% chance a person will select one of the two adjacent categories. For example, if the first Andrich threshold (demarking the threshold between 0="never" and 1="rarely") is set at -1 logits, then a person with a person measure of -1 would have a 50% chance of endorsing either response category whereas a person with a score < -1 would be more likely to endorse the first category (0) and a person with a score > -1 would be more likely to endorse the second category (1). The implication of this is that an item with *k*-point response options provides as much information as (*k*-1) dichotomous items.

Item difficulty (measure) is calculated as the point at which the category probability curve for the lowest response category crosses the one for the highest response category (ie, the point at which they are equiprobable). This measure is then added to the Andrich thresholds to identify the locations along the continuum at which the item provides optimal information for persons located nearby. That is, the item-Andrich thresholds are analogous to the marks on a ruler which allow for the measurement "distances" (ie, linear differences in severity between persons). Hence, often only

a handful of targeted items (ie, uniformly spread-out item difficulties that cover the distribution of person measures) and a 4- or 5-point response scale are needed to distinguish between a wide spectrum of person severities.

Final Scoring Algorithm

After these quantitative analyses are reviewed, decisions concerning the final content to inform the conceptual framework and scoring algorithm for the Daily COVID Symptom Questionnaire will be made in conjunction with a review of the qualitative data.

Upon finalization of the scoring algorithm, a detailed psychometric analysis plan will be presented separately describing the score-based psychometric procedures to be conducted using data from the FAS and SCOA population, merged to examine construct validity, known-groups validity, ability to detect change, and derivation of within-subject meaningful change thresholds.

SCOA Endpoints Considered in the Psychometric and Efficacy Analyses

- The same endpoints as for Part A will be collected. In addition, the following will be collected:
- Daily COVID Symptoms Questionnaire
- Patient Global Item of Severity (PGIS) -Symptoms
- Patient Global Item of Change (PGIC) - Symptoms
- Patient Global Item of Severity (PGIS) - Breathing Trouble
- Patient Global Item of Change (PGIC) - Breathing Trouble
- Patient Global Item of Severity (PGIS) - Leg Fatigue
- Patient Global Item of Change (PGIC) - Leg Fatigue
- Patient Global Item of Severity (PGIS) - Shortness of Breath
- Patient Global Item of Change (PGIC) - Shortness of Breath

11 Safety

Safety endpoints will be based on outcomes from the SAF Population.

11.1 Adverse events

An AE is defined as any event, side-effect, or other untoward medical occurrence that occurs in conjunction with the use of a medicinal product in humans, whether considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavourable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product.

Treatment emergent AEs (TEAEs) are defined as an AE that occurs or worsened on or after the first dose of study drug and will be evaluated from the first administration of study drug until the EoS visit. AEs which occurred (start) prior to the first dose of study medication will be classified as pre-treatment AEs. The classification of TEAEs of the imputations for partial dates is specified in Appendix III: Partial Date Conventions.

All AEs will be coded using the MedDRA Version 23.0 (or later); this version has the most up-to-date COVID-19 coding terms. The analysis will focus on the TEAEs.

Number and percent of subjects with TEAEs and number of events will be given by SOC and by PT within each SOC by treatment group and overall, for the following:

- All TEAEs with 95% CI about the point estimate based on the Clopper Pearson method
- All TEAEs and all TEAEs judged by the investigator to be at least possibly related
- All TEAEs by severity (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5)
- All TEAE related to study drug (i.e. considered as possible and probable)
- Drug-related TEAEs with severity of Grade 3 or higher
- Serious TEAEs and Serious TEAE related to study drug (i.e., considered as possible and probable)
- TEAEs leading to study drug dose reduction
- TEAEs leading to study drug discontinuation and also those related to study drug (i.e., considered as possible and probable)
- TEAEs leading to death
- Pre-treatment AE

Unless otherwise specified, at each level of summarization a subject will be counted once if they reported one or more events at that level of summarization. If more than one occurrence of an event is reported, the event of the worst severity or the worst-case relationship assessment will be summarized.

Subject listings will be provided for TEAEs, treatment related TEAEs, SAEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death. The listings will also include subjects enrolled but not randomized. If AEs are reported prior to study drug, they will be listed in a SEPARATE data listing from the TEAEs.

Based on the established safety profile of pirfenidone and the nonclinical and clinical development programs for LYT-100 the following AEs are considered of special interest (AESI). AESIs will be evaluated and discussed in the clinical study report with special consideration as prospectively defined events. These AESIs, which will be identified from a pre-unblinding medical review of all TEAEs, will be binned according to MedDRA SOC and tabulated, generally as follows (exact details to be determined prior to unblinded):

1) General disorders and administrative site conditions: anorexia, decreased appetite, fatigue
2) Cardiac disorders: e.g., primarily arrhythmias, syncope
3) GI disorders: diarrhea, nausea, vomiting
4) Investigations, e.g., hepatic laboratory abnormalities: increase in transaminases
5) Skin and subcutaneous tissue disorders, e.g., photosensitivity reaction, rash

Exploratory analysis of TEAEs may be considered to best assess the safety/tolerability profile of LYT-100 in this Covid population.

The cumulative incidence rate of serious TEAEs, TEAEs leading to study drug discontinuation, and AESIs will be derived from the cumulative number of subjects with the specific AEs divided by number of subjects in the treatment group on Days 14, 28, 56, 91, and 105. The comparison of cumulative incidence between treatment groups will be measured by risk difference along with the associated 95% CI.

11.2 Deaths

Deaths will be presented as listings using the "Death Details" form of eCRF. Additional analysis of death is planned as part of the efficacy assessments.

11.3 Laboratory Evaluations

11.3.1 Changes from Baseline and Shift Tables

Laboratory tests will include hematology, biochemistry, coagulation and urinalysis and will be performed at the time points specified in the study schedules (Screening, Days -1, 14, 56, 91, and 105).

- Hematology test: Hemoglobin (HGB), hematocrit (HCT), erythrocytes (RBC), platelets (PLAT), leukocytes with differential (including eosinophils [ESN], neutrophils [NEUT], basophils [BASO], lymphocytes [LYM] - collected with biomarkers) and reticulocytes (RETI)
- Biochemistry tests: CRP- collected with biomarkers, urea (U), creatinine (CREAT), total bilirubin (BILI) and direct bilirubin (BILIDIR), blood urea nitrogen (BUN), albumin (ALB), globulin (GLOBUL), alkaline phosphatase (ALP), creatine phosphokinase (CPK), troponin 1 (TROP1- collected with biomarkers), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma- glutamyl transpeptidase (GGT), glucose (GLU), sodium (NA), potassium (K), calcium (CA), chloride (CL), phosphate (PHOS), bicarbonate (BICARB), lactate dehydrogenase (LDH- collected with biomarkers and at screening), ferritin (collected with biomarkers and at screening).
- Coagulation test: international normalized ratio (INR), Prothrombin time, activated partial thromboplastin time (aPTT), d-dimer (collected with biomarkers)
- Dipstick Urinalysis test: pH (PH), specific gravity (SPGRAV), creatinine (CREATININE), protein (PROT), glucose (GLUC), ketones (KETONES), BILI, occult blood (OCCBLD), nitrite (NITRITE), urobilinogen (UROBIL), leukocytes (WBC)
- Urine Cotinine – collected at Screening, Days 28, and 91.
- Serum pregnancy test.

Observed value and absolute change from baseline to each visit will be summarized by treatment group using descriptive statistics. Quantitative data will be analyzed using summary statistics (number of subjects, number of missing values, mean, SD, median, quartiles, minimum and maximum) of observed value and actual changes from baseline to each visit. Qualitative data will be displayed by number and percentages of subjects for each level.

Based on normal range and clinical significance for each laboratory parameters, the values of each laboratory parameter at each time point will be categorized into three levels: normal, abnormal without clinical significance, and abnormal with clinical significance. Shift tables for laboratory assessment results (Normal, Abnormal Not Clinically Significant [NCS], Abnormal Clinically Significant

[CS]) from baseline to each visit will be summarized by treatment group, using frequency tabulations.

Boxplots by treatment group with outliers identified will be graphically displayed for all laboratory tests.

Abnormal urinalysis results, if applicable, will be listed only.

11.3.2 Potentially Clinically Significant Laboratory Ranges

The number and percentage of subjects with potentially clinically significant (PCS) values during the treatment phase will be summarized. A focus will be on new-onset serum chemistry and hematology PCS values, i.e., subjects with pre-existing PCS values at pre-treatment will not be considered to have new-onset values on-treatment. The criteria used to identify PCS laboratory values are listed in Table 10.

Table 10. List of Potentially Clinically Significant Ranges for Clinical Laboratory Parameters

Variable Name	Reference Range	Units	PCS Criteria	
			Low	High
Hematology				
White Blood Cells	4.0 - 11.0	K/uL	≤2.5	≥16
Neutrophils Absolute	45 - 79	%	≤ 15	80
Lymphocytes	20 - 50	%	NA	≥75
Monocytes	1 - 9	%	NA	≥20
Eosinophils	0 - 4	%	NA	≥10
Basophils	0 - 2	%	NA	≥10
Red Blood Cells	4.30 - 5.80	M/uL	≤3	≥6.5
Hematocrit	38.0 - 53.0	%	≤32	≥58
Hemoglobin	13.5 - 17.5	g/dL	≤9.5	≥20
Platelet	150 - 450	K/uL	≤75	≥700
Serum Chemistry				
Globulin	2.0 - 4.8	g/dL	≤1.0	≥6.0
Albumin	4.03 - 5.51	g/dL	≤2.0	NA
Creatinine	0.63 - 1.20	mg/dL	NA	≥2
BUN	8.2 - 23.8	mg/dL	NA	≥35
Uric Acid	3.8 - 7.7	mg/dL	NA	≥9.0
Bilirubin total	0.24 - 1.49	mg/dL	NA	≥2.5
Bilirubin direct	0.00 - 0.30	mg/dL	NA	≥0.6
Alkaline phosphatase	36.1 - 124.2	IU/L	NA	≥390

Variable Name	Reference Range	Units	PCS Criteria	
			Low	High
AST/SGOT	12.4 - 33.0	IU/L	NA	≥3x
ALT/SGPT	6.7 - 33.4	IU/L	NA	≥3x
CPK	<195	U/L	NA	≥700
Glucose fasting	60 - 99	mg/dL	≤40	≥250
Calcium	8.5 - 10.3	mg/dL	≤8.0	≥12
Phosphorous	2.1 - 4.6	mg/dL	≤1.7	NA
Sodium	138 - 144	mmol/L	≤126	≥150
Potassium	3.8 - 4.9	mmol/L	≤3	≥6
Chloride	98 - 108	mmol/L	≤90	≥120
Bicarbonate	20 - 32	mmol/L	≤18	≥38
LDH	<250	IU/L	NA	≥500
CRP	0.0 - 10.0	mg/L	NA	≥3x

11.4 Vital signs

Vital signs (temperature, blood pressure, heart rate, and respiratory rate) including SpO_2 will be measured at every study visit (Screening, Days -1, 1, 14, 28, 56, 91, and 105). Height will be measured at Day -1, while weight and BMI will be measured at Days -1, 14, 28, 56, 91, and 105. Observed value and absolute change from baseline to each visit will be summarized using descriptive statistics by treatment group.

11.5 Electrocardiogram

ECG values will be assessed at Screening, and Days 14, 91, and 105. This will be done both for actual observed ECG values and for changes from baseline. ECG results will be classified as normal and abnormal and summarized. Shift table from baseline to each post-baseline visits will be summarized by treatment group using frequency tabulations. ECG results for QTcF will also be classified as <450 msec, 450-500 msec or >500 msec. A shift table of QTcF classification from baseline will also be provided.

QTcF and QTcB will be programmatically derived from QT interval and RR interval. The formulas are provided as below.

- $QTcB\ (\text{msec}) = \frac{QT\ (ms)}{\sqrt{RR\ (ms)/1000}}$
- $QTcF\ (\text{msec}) = \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$

12 Population Pharmacokinetics

A population PK analysis describing the exposure-response characteristics will be performed. As this study includes sparse sampling, PK data from prior clinical trials may be used to develop the PopPK model accordingly. A separate PopPK analysis plan will be written to describe these methods.

13 Exploratory analysis

Correlation of changes in biomarkers with clinical endpoints (e.g., 6MWT, Dyspnoea-12) will be assessed where relevant in an exploratory fashion.

The correlation of changes in each biomarker with change from baseline of 6MWT and Dyspnoea-12 will be assessed using Pearson correlation coefficient by treatment groups and visits.

14 Interim Analyses

No interim analysis is planned.

15 Statistical Analyses for Data Safety Monitoring Board

A DSMB will assist with oversight of subject safety during this study. DSMB meetings will occur on a monthly basis (approximately), starting one month after the enrollment of the first subject.

The DSMB will provide ongoing unblinded safety and efficacy data review and make recommendations to the Sponsor regarding continuing, modifying, or even to end the study if it believes the safety information indicates such a decision. The Sponsor will remain blinded to the treatment codes.

A detailed charter has been written for the DSMB and should be referred to for details. Data to be reviewed during DSMB meetings are summarized in the charter, but in brief shall include:

1. Listing of all SAEs, sorted by SOC, regardless of causality
2. Summaries of non-serious AEs, sorted by SOC
3. Listing of withdrawals, sorted by reason
4. Summary statistics for laboratory data, physical exams, vital signs, and ECGs
5. Summaries of enrollment, eligibility violations and baseline characteristics
6. Summary statistics for primary and secondary endpoints to include: 6MWT; the mBDS; SGRQ-I; number of lung segments involved using CT scan and QLF assessment; development of pulmonary exacerbations, i.e., severe respiratory failure requiring MV, ECMO, NIV and/or HFNO; severity of lung lobe(s) involvement, using CT scan; pulse oximetry; chest x-ray; rehospitalizations and lengths of hospital stays; all-cause mortality; use of supplemental oxygen over time.

The DSMB also can request additional information they deem important to their safety and efficacy review.

16 Software

If not stated otherwise, the data will be analysed using SAS Version 9.4 or higher in a secure and validated environment.

17 Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALB	Albumin
ALP	Alkaline Phosphatase

ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
APTT	Activated partial thromboplastin time
AR	Autoregressive
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BASO	Basophils
BICARB	Bicarbonate
BILI	Total Bilirubin
BILIDIR	Direct Bilirubin
BMI	Body Mass Index
BP	Bodily pain
BUN	Blood urea nitrogen
CA	Calcium
CAD	Computer-Aided Diagnosis
CCI	Charlson Comorbidity Index
CI	Confidence interval
CL	Chloride
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus 2019
CoV	Coronavirus
CPK	Creatine phosphokinase
CREAT	Creatinine
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
CS	Clinically significant
CT	Computed tomography
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case Report Form
ECLS	Extracorporeal life support
ENR	Enrolled population
EoS	End of study
ESN	Eosinophils
FAS	Full analysis population
GCSF	Granulocyte colony stimulating factor
GCP	Good Clinical Practice
GH	General health
GGO	Ground glass opacity
GGT	Gamma- glutamyl transpeptidase
GLOBUL	Globulin
GLU	Glucose
HCT	Haematocrit
HFNO	High flow nasal oxygen
HGB	Haemoglobin
ICH	International Council for Harmonisation
IL-6	Interleukin 6

IL-1β	Interleukin-1β
INR	International normalised ratio
ITT	Intent-to-treat
K	Potassium
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LSMeans	Least square means
LYM	Lymphocytes
MAR	Missing at random
MedDRA®	Medical Dictionary for Regulatory Activities
mBDS	Modified Borg dyspnoea scale
MCS	Mental component summary
MCMC	Markov chain Monte Carlo
MH	Mental health
MMRM	Mixed model for repeated measures
MRAR	Missing not at random
MV	Mechanical ventilation
NA	Sodium
NCS	Not clinically significant
NEUT	Neutrophils
NIV	Noninvasive ventilation
OCCBLD	Occult Blood
PCS	Physical component summary
PDGF-β	Platelet derived growth factor-β
PF	Physical functioning
PGIS	Patient Global Item of Severity
PGIC	Patient Global Item of Change
PHOS	Phosphate
PK	Pharmacokinetic population
PLAT	Platelets
PopPK	Population Pharmacokinetics
PP	Per protocol population
PROT	Protein
PT	Preferred term
RP	Role-physical
RT-PCR	Reverse transcription polymerase chain reaction
QLF	Quantitative Lung Fibrosis
QoL	Quality of life
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cells
RE	Role-emotional
RETI	Reticulocytes
RMS	Row mean score
SAE	Serious Adverse Event
SAF	Safety analysis population
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome

SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SET	Self-evaluated transition
SF	Social functioning
SGRQ	Saint George Respiratory Questionnaire
SOC	System organ class
SpO2	Oxygen Saturation
SPGRAV	Specific Gravity
TEAE	Treatment-emergent adverse event
TFL	Table, figure and listing
TGF-β1	Transforming Growth Factor Beta 1
TNF-α	Tumor Necrosis Factor - alpha
TROP1	Troponin 1
U	Urea
UROBIL	Urobilinogen
US	United States
VEGF	Vascular endothelial growth factor
Vs.	Versus
VT	Vitality
WBC	Leukocytes (white blood cells)
WHO	World Health Organization
6MWT	Six-minute walk test

18 References

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19 Appendices

Appendix I: Schedule of Assessments for Part A

Appendix II: Programming Conventions for Outputs

Appendix III: Partial Date Conventions

Appendix IV: Scoring Algorithm for SGRQ-I

Appendix I. Schedule of Assessments for Part A

From Protocol V8.0/Date: 26JAN2022 (All Sites except US)

	Screening	Baseline*	Study Treatment						Post-treatment
	Day	Day	Day	Target Days ± 3 day window					
Study Day	**-10**	**-1**	**1**	**14**	**28**	**56**	**91**	**Early Term[14]**	**Day 105: End of Study**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7A**	**ET**	**8A**
Informed consent[1]	X								
RT-PCR diagnostic test / SARS-CoV-2 RNA (+ result may predate screening)	X								
Eligibility [2]	X		X						
Demographics	X								
Pertinent Medical History	X								
Physical Exam [3]	X	X		X			X	X	X
Weight/Body Mass Index; Height at Day -1		X		X	X	X	X	X	X
Vital signs (BP, HR), Respiratory Rate, SpO_2, Contactless, Tympanic or oral Temperature[4]	X	X	X (post-treatment)	X	X	X	X	X	X
Standard 12-lead ECG[4]	X			X			X	X	X
Charlson Comorbidity Index		X					X		
Chest CT Scan[5]		X					X		

	Screening	Baseline*	Study Treatment						Post-treatment
	Day	Day	Day	Target Days ± 3 day window					
Study Day	**-10**	**-1**	**1**	**14**	**28**	**56**	**91**	**Early Term[14]**	**Day 105: End of Study**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7A**	**ET**	**8A**
Chest X-ray[5]	X						X	X	X
Training for 6-Minute Walk Test (end of visit) [6]	X								
6-minute Walk Test (end of visit) [7]		X	X	X	X	X	X	X	
Modified Borg (Dyspnoea) Scale (start of visit)	X	X	X (post-treatment)	X	X	X	X	X	
Dyspnoea-12 (start of visit)		X		X	X	X	X	X	
St. George's Respiratory Questionnaire (start of visit)		X			X	X	X		
WHO Ordinal Scale for Clinical Improvement		X		X	X	X	X	X	
SF-36 v2 (start of visit)		X			X	X	X	X	
Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status	X	X	X	X	X	X	X	X	X
Hematology	X			X	X	X	X	X	X
Blood chemistry and Coagulation	X			X	X	X	X	X	X
Follicle Stimulating Hormone (post-menopausal females only)	X								
Urinalysis	X			X	X	X	X	X	X

	Screening	Baseline*	Study Treatment						Post-treatment
	Day	Day	Day	Target Days ± 3 day window					
Study Day	-10	-1	1	14	28	56	91	Early Term[14]	Day 105: End of Study
Visit Number	1	2	3	4	5	6	7A	ET	8A
Pregnancy test[8]	X				X	X	X	X	X
Urine Cotinine[9]	X				X		X		
Biomarkers[10]		X		X	X	X	X	X	
Study Drug Accountability[11]			X	X	X	X	X	X	
PK blood samples[12]				X	X	X	X	X	
Adverse Events/Mortality[13]	X	X	X	X	X	X	X	X	X
Prior & Concomitant Meds (30 days prior)	X	X	X	X	X	X	X	X	X

*Baseline may be Day -1 to Day 1 and baseline procedures may be completed over one or two calendar days.

1. Informed consent via written, electronic, or verbal must be documented before any study-specific screening procedures are performed.
2. Eligibility to be confirmed during screening and prior to randomization on Day 1
3. Abbreviated symptom directed physical examination will be performed.
4. For all assessments noted, patients should be resting supine for ≥5 minutes prior to the assessment. ECGs will be performed prior to vital signs and any blood draws. Oral, contactless, or tympanic temperature should be collected using the same method for temperature measurement throughout study. In patients requiring oxygen supplementation, ensure oxygen is administered at the prescribed rate for a minimum of 15 minutes prior to SpO_2 assessment. For ECG,
5. Chest X-ray is required at Screening visit, and a CT scan is required for Baseline. If a CT scan was taken without contrast within 7 days prior to Baseline, and there have been no significant changes in signs and symptoms of respiratory complications in those 7 days, then an additional CT scan does not need to be collected. However, the previous CT scan can be used for baseline ONLY if it was done without contrast.
6. Patients will undergo a training session for the 6 Minute Walk Test at the end of the screening visit.
7. Patients must undergo two 6 Minute Walk Tests at baseline (Day –1 to Day 1) according to the study 6MWT Procedures Manual. Oxygen supplementation is also allowed during the test; however, the subject must use the same device and oxygen flow rate at each 6MWT assessment. Subjects may complete the second 6MWTs on Day -1, provided the tests are separated by at least 30 minutes

(to allow adequate time for the subject to rest between tests), or subjects may return to the site on the subsequent day (Day 1) for the second 6MWT. The longest distance of the two tests will be selected as the baseline assessment.

8. Pregnancy test not required for amenorrhoeic female patients. Where required by local regulations, a serum pregnancy test should be conducted in addition to the urine pregnancy test. (In Romania, a serum pregnancy test is required at screening.) If a urine pregnancy test is positive, a serum pregnancy must also be performed as confirmation.
9. Local urine "dipstick" qualitative tests should be used during initial eligibility assessment, after the informed consent is obtained. The local urine "dipstick" negative result will be documented for determination of eligibility.
10. The time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon). The same general time of day for biomarker sample collection will ensure consistency relative to circadian rhythm intervals that, if not adhered to, may affect interpretation of outcomes.
11. Doses are to be administered with meals and approximately 10 to 12 hours apart. Day 1 is the first day of intake.
12. When pharmacokinetic levels are collected, last dose of study medication administered prior to blood collection, including the date and time will be recorded. A minimum of one (1) on-treatment PK sample will be collected at these designated study visits and grouped into the following timepoint ranges post study med dose administration: Hour 0, Hour 1 to <2, Hour 2 to <4, Hour 4 to <8, Hour 8 to <12. Avoid on-treatment duplications of the same timepoint interval within the same patient.
13. Adverse Events reported prior to first dose of study medication must be denoted as "pre-treatment".
14. Patients are required to complete their End of Study (ONLY if they are not continuing into Part B) within 2 weeks of the last study drug treatment administered to the patient, ± 3 days. All patients will be encouraged to return for all remaining study visits through Day 196 even if not on study medication.

Protocol V8.1/ Date: 26JAN2022 (US Sites Only)

	Screening	Baseline*	Study Treatment						Post-treatment
	Day	Day	Day	Target Days ± 3 day window					
Study Day	**-10**	**-1**	**1**	**14**	**28**	**56**	**91**	**Early Term[15]**	**Day 105: End of Study**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7A**	**ET**	**8A**
Informed consent[1]	X								
RT-PCR diagnostic test / SARS-CoV-2 RNA (+ result may predate screening)	X								
Eligibility [2]	X		X						
Demographics	X								
Pertinent Medical History	X								
Physical Exam [3]	X	X		X			X	X	X
Weight/Body Mass Index; Height at Day -1		X		X	X	X	X	X	X
Vital signs (BP, HR), Respiratory Rate, SpO_2, Contactless, Tympanic or oral Temperature[4]	X	X	X (post-treatment)	X	X	X	X	X	X
Standard 12-lead ECG[4]	X			X			X	X	X
Charlson Comorbidity Index		X					X		
Chest CT Scan[5]		X					X		
Chest X-ray[5]	X						X	X	X

	Screening	Baseline*	Study Treatment						Post-treatment
	Day	Day	Day	Target Days ± 3 day window					
Study Day	**-10**	**-1**	**1**	**14**	**28**	**56**	**91**	**Early Term[15]**	**Day 105: End of Study**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7A**	**ET**	**8A**
Training for 6-Minute Walk Test (end of visit) [6]	X								
6-minute Walk Test (end of visit) [7]		X	X	X	X	X	X	X	
Modified Borg (Dyspnoea) Scale (start of visit)	X	X	X (post-treatment)	X	X	X	X	X	
Dyspnoea-12 (start of visit)		X		X	X	X	X	X	
St. George's Respiratory Questionnaire (start of visit)		X			X	X	X		
WHO Ordinal Scale for Clinical Improvement		X		X	X	X	X	X	
SF-36 v2 (start of visit)		X			X	X	X	X	
COVID Symptom Assessments: Daily COVID Symptoms Diary, Weekly PGIS, and PGIC Scales[8]	X	X	X	X	X	X	X	X	
Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status	X	X	X	X	X	X	X	X	X
Hematology	X			X	X	X	X	X	X
Blood chemistry and Coagulation	X			X	X	X	X	X	X
Follicle Stimulating Hormone (post-menopausal females only)	X								
Urinalysis	X			X	X	X	X	X	X

	Screening	Baseline*	Study Treatment						Post-treatment
	Day	Day	Day	Target Days ± 3 day window					
Study Day	-10	-1	1	14	28	56	91	Early Term[15]	Day 105: End of Study
Visit Number	1	2	3	4	5	6	7A	ET	8A
Pregnancy test[9]	X				X	X	X	X	X
Urine Cotinine[10]	X				X		X		
Biomarkers[11]		X		X	X	X	X	X	
Study Drug Accountability[12]			X	X	X	X	X	X	
PK blood samples[13]				X	X	X	X	X	
Adverse Events/Mortality[14]	X	X	X	X	X	X	X	X	X
Prior & Concomitant Meds (30 days prior)	X	X	X	X	X	X	X	X	X
Participant Interview[16]	X						X	X	

*Baseline may be Day -1 to Day 1 and baseline procedures may be completed over one or two calendar days.

1. Informed consent via written, electronic, or verbal must be documented before any study-specific screening procedures are performed.
2. Eligibility to be confirmed during screening and prior to randomization on Day 1
3. Abbreviated symptom directed physical examination will be performed.
4. For all assessments noted, patients should be resting supine for ≥5 minutes prior to the assessment. ECGs will be performed prior to vital signs and any blood draws. Oral, contactless, or tympanic temperature should be collected using the same method for temperature measurement throughout study. In patients requiring oxygen supplementation, ensure oxygen is administered at the prescribed rate for a minimum of 15 minutes prior to SpO_2 assessment. For ECG,
5. Chest X-ray is required at Screening visit, and a CT scan is required for Baseline. If a CT scan was taken without contrast within 7 days prior to Baseline, and there have been no significant changes in signs and symptoms of respiratory complications in those 7 days, then an additional CT scan does not need to be collected. However, the previous CT scan can be used for baseline ONLY if it was done without contrast.
6. Patients will undergo a training session for the 6 Minute Walk Test at the end of the screening visit.

7. Patients must undergo two 6 Minute Walk Tests at baseline (Day –1 to Day 1) according to the study 6MWT Procedures Manual. Oxygen supplementation is also allowed during the test; however, the subject must use the same device and oxygen flow rate at each 6MWT assessment. Subjects may complete the second 6MWTs on Day -1, provided the tests are separated by at least 30 minutes (to allow adequate time for the subject to rest between tests), or subjects may return to the site on the subsequent day (Day 1) for the second 6MWT. The longest distance of the two tests will be selected as the baseline assessment.
8. A daily COVID Symptoms diary (to be performed by the subject during screening and from Day 1 through Day 91). A Patient Global Item of Severity (PGIS) to be performed at baseline and weekly (on the first day of each week). A Patent Global Item of Change (PGIC) will be done at Day 14, Day 28, Day 56 and Day 91.
9. Pregnancy test not required for amenorrhoeic female patients. Where required by local regulations, a serum pregnancy test should be conducted in addition to the urine pregnancy test. (In Romania, a serum pregnancy test is required at screening.) If a urine pregnancy test is positive, a serum pregnancy must also be performed as confirmation.
10. Local urine "dipstick" qualitative tests should be used during initial eligibility assessment, after the informed consent is obtained. The local urine "dipstick" negative result will be documented for determination of eligibility.
11. The time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon). The same general time of day for biomarker sample collection will ensure consistency relative to circadian rhythm intervals that, if not adhered to, may affect interpretation of outcomes.
12. Doses are to be administered with meals and approximately 10 to 12 hours apart. Day 1 is the first day of intake.
13. When pharmacokinetic levels are collected, last dose of study medication administered prior to blood collection, including the date and time will be recorded. A minimum of one (1) on-treatment PK sample will be collected at these designated study visits and grouped into the following timepoint ranges post study med dose administration: Hour 0, Hour 1 to <2, Hour 2 to <4, Hour 4 to <8, Hour 8 to <12. Avoid on-treatment duplications of the same timepoint interval within the same patient.
14. Adverse Events reported prior to first dose of study medication must be denoted as "pre-treatment".
15. Patients are required to complete their End of Study (ONLY if they are not continuing into Part B) within 2 weeks of the last study drug treatment administered to the patient, ± 3 days. All patients will be encouraged to return for all remaining study visits through Day 196 even if not on study medication.
16. Up to approximately 50 participants will be asked to participate in interviews to discuss their long COVID/post-acute COVID respiratory symptoms either during screening (i.e., to include subjects that are deemed ineligible and not able to participate in the study) or at the end of the treatment period (Around Days 91-105 for those that are deemed eligible and complete study treatment). Early termination patients may also be interviewed at the sponsor's discretion.

Appendix II: Programming Conventions for Outputs

❖ Clinipace Output Conventions

Outputs will be presented according to the Clinipace general guidelines and template for outputs conventions.

❖ General Rules

The following conventions will be applied for reporting descriptive statistics of all continuous data.

Means, medians, Q1, and Q3, will be reported at 1 more significant digit than the precision of the data. Minimum, and Maximum will have the same precision as Raw data (number of digits) for non-derived data (*e.g.,* weight). SD will be presented with one digit more than mean.

Statistics on derived data (*e.g.,* treatment exposure time in days) will be rounded to reasonable number of digits.

Qualitative variables will be summarized by counts and percentages. Unless otherwise stated, the calculation of proportions will be based on the number of available subjects. Therefore, counts of missing observations will not be included in the denominator and not presented as a separate category.

❖ Dates & Times

Depending on data available, dates and times will take the form YYYY-MM-DD and HH:MM.

❖ Spelling Format

English US

❖ Presentation of Treatment Groups

All listings will be ordered by the following (unless otherwise indicated in the template):

- Center-subject ID
- Treatment group
- Date (where applicable)

All tables containing coded terms (concomitant medication, medical history, AE), coded records will be sorted in frequency order.

Appendix III: Partial Date Conventions

Partial dates for Adverse Events and Previous/Concomitant Medications

In cases of incomplete dates (e.g., pertaining to AE and concomitant medication), the missing component(s) will be assumed as the most conservative value(s) possible.

For example, if the start date has a missing day value and year and month are available, the first day of the month but not before first intake of study medication will be imputed for study day computations (i.e., treatment-emergent status, etc.). The start date will be set to the first day of the year but not before first intake of study medication if month and day are missing and year is available.

If day is missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month and year components.

Date imputation will only be used for computational purposes e.g., treatment-emergent status, etc. Actual data values as they appear in the original eCRFs will be shown in the data listings.

Appendix IV: Scoring Algorithm for SGRQ-I

- **ITEM WEIGHTS**

Symptoms Component

There are 6 items which displayed disordered thresholds and required adjacent response categories to be collapsed. The format for the SGRQ-I symptoms component is detailed below.

SGRQ-I Symptoms Component

Part 1 Please describe how often your respiratory problems affect you currently.
Item 1: I cough:
2 = Almost everyday (new weight=80.6)
1 = Only with infections (new weight=40.2)
0 = Not at all (new weight=0)

Item 2: I bring up phlegm:
2 = Almost everyday (new weight=76.8)
1 = Only with infections (new weight=41.4)
0 = Not at all (new weight=0)

Item 3: I have shortness of breath
2 = Almost everyday (new weight=87.2)
1 = Only with infections (new weight=50.3)
0 = Not at all (new weight=0)

Item 4: I have attacks of wheezing
2 = Almost everyday (new weight=86.2)
1 = Only with infections (new weight=51.0)
0 = Not at all (new weight=0)

Item 5: How many times in a typical week do you suffer from respiratory attacks?
1 = more than one (new weight=66.2)
0 = none (new weight=0)

Item 6: In a typical week, how many good days do you have?
2 = every day (new weight=93.3)
1 = a few days (new weight=51.2)
0 = none (new weight=0)

Activities Component
The activities component contains 10 items.

SGRQ-I Activities Component
Part 2 Section 2: Questions about what activities usually make you feel short of breath these days
Item 1: Washing or dressing yourself
1 = true (new weight=82.2)
0 = false (new weight=0)

Item 2: Walking around in the house
1 = true (new weight=80.2)
0 = false (new weight=0)

Item 3: walking outside on level ground
1 = true (new weight=81.4)
0 = false (new weight=0)

Item 4: Walking up a flight of stairs
1 = true (new weight=76.1)
0 = false (new weight=0)

Item 5: Playing sports or other physical activities
1 = true (new weight=72.1)
0 = false (new weight=0)

Part 2 Section 5: These are questions about how your activities might be affected by your respiratory problems
Item 1: Jobs such as household chores take a long time, or I have to stop to rest
1 = true (new weight=70.6)
0 = false (new weight=0)

Item 2: If I walk up one flight of stairs, I have to go slowly or stop
1 = true (new weight=71.6)
0 = false (new weight=0)

Item 3: If I hurry or walk fast, I have to stop or slow down
1 = true (new weight=72.3)
0 = false (new weight=0)

Item 4: My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, bowl or play golf
1 = true (new weight=74.5)
0 = false (new weight=0)

Item 5: My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports

1 = true (new weight=63.5)
0 = false (new weight=0)

Impacts Component

The SGRQ-I includes 18 items to calculate the impacts component.

SGRQ-I Impacts Component

Part 2 Section 1

Item 1: If you ever held a job:

1 = My lung condition interferes or made me stop work (new weight=83.3)
0 = My lung problem does not affect my job (new weight=0)

Part 2 Section 3: Some more questions about your cough and shortness of breath these days

Item 1: Coughing hurts

1 = true (new weight=81.1)
0 = false (new weight=0)

Item 2: Coughing makes me tired

1 = true (new weight=79.1)
0 = false (new weight=0)

Item 3: Short of breath when I talk

1 = true (new weight=84.5)
0 = false (new weight=0)

Item 4: Short of breath when I bend over

1 = true (new weight=76.8)
0 = false (new weight=0)

Item 5: My coughing or breathing disturbs my sleep

1 = true (new weight=87.9)
0 = false (new weight=0)

Item 6: I get exhausted easily

1 = true (new weight=84.0)
0 = false (new weight=0)

Part 2 Section 4: Questions about other effects that your respiratory problems may have on you these days.

Item 1: My cough or breathing is embarrassing in public

1 = true (new weight=74.1)

0 = false (new weight=0)

Item 2: My respiratory problems are a nuisance to my family, friends or neighbours
1 = true (new weight=79.1)
0 = false (new weight=0)

Item 3: I get afraid or panic when I cannot catch my breath
1 = true (new weight=87.7)
0 = false (new weight=0)

Item 4: I feel that I am not in control of my respiratory problems
1 = true (new weight=90.1)
0 = false (new weight=0)

Item 5: Exercise is not safe for me
1 = true (new weight=75.7)
0 = false (new weight=0)

Item 6: Everything seems too much of an effort
1 = true (new weight=84.5)
0 = false (new weight=0)

Part 2 Section 6: We would like to know how your respiratory problems usually affect your daily life.

Item 1: I cannot play sports or do other physical activities
1 = true (new weight=64.8)
0 = false (new weight=0)

Item 2: I cannot go out of the house to do the shopping
1 = true (new weight=81.0)
0 = false (new weight=0)

Item 3: I cannot do household chores
1 = true (new weight=79.1)
0 = false (new weight=0)

Item 4: I cannot move far from my bed or chair
1 = true (new weight=94.0)
0 = false (new weight=0)

Item 5: Now please check the box (one only) that you think best describes how your respiratory problems affect you:
0 = does not stop me (new weight=0)
1 = stops one or two things (new weight=42.0)
2 =stops most things (new weight=84.2)
3 = stops me doing everything I would like to (new weight=96.7)

- **OUTLINE OF SCORING ALGORITHM**

Summary

Three component scores are calculated: Symptoms; Activity; Impacts.

One Total score is also calculated.

Principle of Calculation

Each questionnaire response has a unique empirically derived 'weight'. The lowest possible weight is zero and the highest is 100.

Each component of the questionnaire is scored separately in three steps:

i. The weights for all items with a positive responses are summed.
ii. The weights for missed items are deducted from the maximum possible weight for each component. The weights for all missed items are deducted from the maximum possible weight for the Total score.
iii. The score is calculated by dividing the summed weights by the adjusted maximum possible weight for that component and expressing the result as a percentage :

$$\text{Score} = 100 \times \frac{Summed\ weights\ from\ positive\ items\ in\ that\ component}{Sum\ of\ weights\ for\ all\ items\ in\ that\ component}$$

The Total score is calculated in similar way:

$$\text{Score} = 100 \times \frac{Summed\ weights\ from\ positive\ items\ in\ the\ questionnaire}{Sum\ of\ weights\ for\ all\ items\ in\ the\ questionnaire}$$

Sum of maximum possible weights for each component and Total:

Symptoms 490.3

Activity 744.5

Impacts 1483.5

Total 2718.3

(Note: these are the maximum possible weights that could be obtained for the worst possible state of the subject).

PureTech LYT 100, Inc.

Protocol No: LYT-100-2020-02

CP Project ID: PTH20312

A Phase 2 Randomized, Double-blind, Placebo-controlled and Open Label Extension to Evaluate the Safety and Efficacy of Deupirfenidone (LYT-100) in Post-acute COVID-19 Respiratory Disease

Statistical Analysis Plan for Part B (The Open-Label Extension)

Version: 1.0

Date: 15AUG2022

Based on Protocol Version V8.2, 17Mar2022 (US Sites Only) and

Protocol Version V8.0, 26Jan2022 (All Sites except US)

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1 Introduction

1.1 Preface

The objective of this document is to detail the statistical methodology to be used for the final statistical analysis for Part B of study LYT-100-2020-02. The statistical methodology of Part A was provided in a separate document.

The statistical analysis plan is based on the following information and documents:

- LYT-100-2020-02 Protocol 8.0/ Date: 26Jan2022 (All sites except US country)
- LYT-100-2020-02-US Protocol 8.2/ Date: 17Mar2022 (US sites only)
- LYT-100-2020-02 Subject Case Report Forms V14.0/ Date: 26APR2022

Note that Part B is an open-label extension to the first Part (Part A), which double-blind and placebo-controlled. In contrast, all patients treated in Part B will be given LYT-100 in an unblinded fashion, and without a control arm. Statistical analyses will be based on assessments of the longer-term safety and tolerability of LYT-100 with continued treatment from Part A and the persistence of any treatment benefits as noted during Part A. Data from Part A will therefore necessarily be included in the analysis of the Part B/OLE outcomes.

1.2 Timing of statistical analyses

The following statistical analyses are planned for this study:

Final analysis: When all subjects have completed the study of Part B and the database is locked.

2 Modification History

2.1 Changes to the study protocol

Not applicable.

2.2 Changes to previous SAP versions

The following changes were made compared to the first version of the SAP:

Version	Date	Author	Significant Changes from Previous Authorized Version
1.0	21May2021	Derrick Gallagher	Initial version

3 Study Design

Indication	Post-acute Coronavirus Disease 2019 (COVID-19) Respiratory Disease
Design	Part A: Randomized, Double-blind, Placebo-controlled study Part B: All patients who participate in Part B will be treated with the same dosing regimen shown in Table 2. Patients will receive LYT-100 500 mg BID for the first three days of Part A, and then LYT-100 750 mg BID thereafter.
Phase	Phase II
Primary Objective	To assess the longer-term safety, tolerability, and efficacy of LYT-100 through up to 182 days of treatment.
Exploratory Objectives	During Part B, all patients will receive active study drug (and thus there is no control arm). Exploratory assessment of the longer-term outcomes of treatment with LYT-100 on efficacy measures will be performed to inform as to the general pattern of improvement in these measures with the extended treatment. In general, the focus of this assessment will be on those patients in the LYT-100 to LYT-100 group, but analysis will also be performed for the Placebo to LYT-100 group. Description of the following outcomes through up to 182 days of treatment with LYT-100 will therefore be performed: 1. Change in distance walked on the six-minute walk test performed in line with the American Thoracic Society/European Respiratory Society Guidelines. 2. Dyspnoea-12
Endpoints	• Safety Endpoints Safety and tolerability endpoints include: Adverse events, concomitant medications, clinical laboratory findings (chemistry, hematology, coagulation, urinalysis), physical examinations, ECGs, and vital signs. These will be tabulated or summarized descriptively, where appropriate. Outcomes such as mortality and duration of hospital stay are considered efficacy outcomes in the context of the study objectives and disease being

	studied but will be included in the overall discussion of the safety and tolerability of LYT-100. • Exploratory Efficacy Endpoints The efficacy endpoints in Part B are considered exploratory. 1. 6-minute walk test (6MWT) 2. Dyspnoea-12 (D-12)
Treatments	LYT-100
Number of subjects	Only subjects who complete 91 days of treatment in Part A will be eligible for participation in Part B.
Data Safety Monitoring Board	An independent, unblinded DSMB will assist with oversight of patient safety during this study. The DSMB will meet approximately monthly during the study (as per the DSMB Charter) to review unblinded safety and efficacy data (where warranted per the DSMB Charter) of all subjects.
Planned enrolment	Approximately 35 study centers in Europe, United States, Asia, and South America.

3.1 Sample size estimation

The sample size for Part A was based on both the 6MWT and the mBDS. Please refer to SAP for Part A for the details. A sample size of N=84 per arm will provide over 80% power to detect statistically significant differences. Only subjects who complete 91 days of treatment in Part A will be eligible for participation in Part B.

The sample size for Part B is based on patients who complete Part A, and is not based on any power or hypothesis-testing considerations.

3.2 Randomisation, blinding and unblinding procedures

There is no randomization for Part B. All patients will be given open-label LYT-100, and patients, investigational staff, and the Sponsor will be UNBLINDED to study treatment.

4 Analysis Sets

4.1 Study Safety Population (SSP)

The Study Safety Population is defined as all subjects who received at least one dose of either placebo or LYT-100.

All subjects who receive any study drug, including placebo and LYT-100.

4.2 OLE Safety Population (OLE)

The Open-Label Extension (OLE) Safety Population is defined as all patients who are treated with at least one dose of LYT-100 during Part B. This is the primary analysis population for which all endpoints (including efficacy) will be assessed. Note that only patients who are treated with LYT-100 during Part B will be included in the Part B analysis.

5 General Statistical Methods and Definitions

5.1 General statistical methods

The statistical analyses will be presented by treatment group of Part B for the OLE Safety Population analysis set as defined in section 4. Summary tables will be structured with a column for each treatment sequence in the order of "Placebo to LYT-100", "LYT-100 to LYT-100", and (where appropriate) "All Subjects". "Placebo to LYT-100" indicates subjects who are treated with placebo in double-blinded Part A and LYT-100 in open-label extension Part B, whereas LYT-100 to LYT-100" indicates subjects who are treated with LYT100 for both Part A and Part B.

In general, continuous variables will be summarised using descriptive statistics, i.e. generally displaying number of subjects in the respective analysis population, number of subjects with data, number of subjects with missing values, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum.

Categorical and ordinal variables will be summarised by using frequency counts and percentages. In addition, the number of subjects with missing values will be displayed.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Means, medians and quartiles will be presented by 1 additional decimal place and standard deviation will be presented by 2 additional decimal places than the standard presentation level of the respective subject data. Minimum and maximum values will be presented using the same number of decimal places as the patient data. Percentages will be presented to 1 decimal place if not otherwise stated.

If the number of subjects in a category is 0, then percentage will not be displayed, and only a count of 0 will be shown.

All p-values will be two-sided and reported to 3 decimal places (e.g., 0.XXX). Values < 0.001 will be reported as < 0.001.

All data collected as part of the study will be reported in data listings, sorted by Site, Subject, and visit/study day.

5.2 Covariates and Strata

In Mixed-effect model repeated measures (MMRM) analysis, the baseline value of the endpoint and study center will be considered as covariates for efficacy endpoints, where appropriate.

5.2.1 Multicenter Studies

This study will be conducted by multiple investigators at various centres (Approximately 35 study centers in Europe, United States and Asia). Data from individual centers may be combined prior into 'pooled centers' for use in the analysis as a covariate. This pooling would be performed via regions

(United States, East Europe, West Europe, and others) and by actual number of patients enrolled, where applicable.

5.2.2 Output Presentations

Appendix II details the conventions for presentation of data in outputs.

The TFL shells provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by Clinipace Biostatistics.

5.3 Subgroups

No subgroup efficacy analyses will be performed for Part B.

5.4 Missing data

Missing data imputation will not be performed for the analysis of Part B.

5.5 Observation and analysis times

5.5.1 Study Days

Reference start date is defined as the day of first dose of study medication in Part A and study day relative to the reference start date will appear in every listing where an assessment date or event date appears.

Study day will be calculated from the reference start date and will be used to show start/stop day of the assessments and events relative to the first administration of study treatment.

- If the date of the event is on or after the reference date, then:
  Study day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  Study day = (date of event – reference date).

Thus, the date of first dose study drug is defined as Study Day 1, with the day prior defined as Study Day -1.

In case of that event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix III, Partial Date Conventions.

5.5.2 Definition of baseline values

For efficacy endpoints, we will be using the Part A double-blind (DB) Baseline. That will allow us to examine the full ~184-day profile of the efficacy in the clinical trial.

5.5.3 Study periods or stages

This study of Part A includes screening, study treatment, and post-treatment periods.

- Over five days, patients will be screened and complete baseline assessments. Randomization (Day 1) occurs on the day following the Baseline Visit/assessment.

- All patients will be treated up to 91 consecutive days during the study treatment period. Study assessments are at Days 14, 28, 56 and Day 91 ± 3 days.

This study of Part B includes study treatment and post-treatment periods.

- All patients will be treated up to 91 consecutive days during the study treatment period. Study assessments are at Days 91, 105, 119 Day 147 , and Day 182 ± 3 days.
- A follow-up post-treatment completion visit will occur within 14 days of last day of study treatment ± 3 days.

5.5.4 Definition of analysis timepoints or time windows

The following table outlines the analysis visits that data will be mapped to for analysis of efficacy, safety and pharmacodynamics data collected during the study, except that the 6MWT baseline visit will be determined by the longest distance of the two tests conducted between Day 1 and Day -1. If after mapping, multiple data points share the same analysis visit, the data point closest to the expected study visit will be used; if the two tests are the same number of days from the target day for the visit, the earliest of the two will be used.

Study Visit	**Target Day***	**Study Day Interval***	**Analysis Visit**
Baseline (pre-treatment) This window is intended to capture any data collected prior to first dose of study medication.	-1	-10 to 1	Baseline
Day 1	Day 1	1	Day 1
Day 14	Day 14	4 to 20	Day 14
Day 28	Day 28	21 to 42	Day 28
Day 56	Day 56	43 to 73	Day 56
Day 91 (Last Day of Double-Blind Treatment)	Day 91	74 to 98	Day 91
Day 105	Day 105	99 to 111	Day 105
Day 119	Day 119	112 to 133	Day 119
Day 147	Day 147	134 to 164	Day 147

Early Termination/Day 182	Day 182	165 to 189	Day 182
Post-Treatment Safety Follow up Visit/Day 196	Day 196	190 to 202	Day 196

*Relative to the first day of study drug or placebo taken in Part A.
Note: Due to the Covid pandemic, some centers had scheduling changes to accommodate local regulations as the local situation evolved. In particular, Philippines center 601 and Argentina center 802 had Day 91 visits that occurred beyond the window in this table (ie, the window is 74 to 98, but these patients had actual Study Days out to as far as 107). Because these visits were intended to be targeted for the last double-blind study visit per the protocol, these visits have been windowed into the Day 91 analysis window accordingly. Therefore, for any site, if the EDC lists the visit as Day 91, but the visit is out of the 74 to 98 window, those visits up through day 107 were set the analysis visit to day 91.

For the laboratory, vital signs, and ECG assessments, the baseline is determined on the basis of LYT-100 treatment. The baseline will be the last value before first dose of open-label treatment with LYT-100 in Part B. The analysis visits for these assessments will be re-visited as the following.

Study Visit	**Target Day#**	**Study Day Interval#**	**Analysis Visit**
Day 91 (First Day of Open Label Study Period)	Day 91	74 to 98	Screening for laboratories and ECG; Baseline for vital signs
Day 105	Day 105	99 to 111	Day 14
Day 119	Day 119	112 to 133	Day 28
Day 147	Day 147	134 to 164	Day 56
Early Termination/Day 182	Day 182	165 to 189	Day 91
Post-Treatment Safety Follow up Visit/Day 196	Day 196	190 to 202	Day 105

*Relative to the first day of study drug taken. Study Day 1 is the day of first dose of study medication, while Study Day -1 is the day immediately prior.

5.6 Multiple Comparison/Multiplicity

The efficacy endpoints are regarded as exploratory analyses in support of the Part A double-blind analysis outcomes. Adjustment for multiplicity is not under consideration for Part B.

6 Subject Accounting and Disposition

6.1 Subject accounting

The number and relative frequencies of subjects in each analysis set as defined in section 4 Analysis Sets will be performed by Enrolled Population and presented overall and by treatment sequence. Number and percentage of subjects enrolled in Part B will be provided.

6.2 Disposition and withdrawals

A clear accounting of the disposition of all subjects who enter Part B will be provided. The subject disposition outcomes will be tabulated including the number and percent of subjects who are enrolled, who receive treatment, who complete the treatment, and who complete the post-treatment follow-up. In addition, reasons for treatment discontinuation and study withdrawal will be presented. The summary will be performed by OLE Safety Population.

6.3 Important protocol deviations

Protocol deviations will be presented in a listing including severity, protocol deviation type, and the action taken, if any. The protocol deviation which impacts subject safety, ICH-GCP compliance, or efficacy endpoints could be marked as major protocol deviation per study team's approval prior to database lock during the blinded data review meeting. The decision whether a protocol deviation is major or minor will be made on a case-by-case basis.

7 Demographics and Background Characteristics

7.1 Demographics

Analysis of demographics data will be performed for the OLE Safety Population. Demographics will be carried over from Part A and summarized using appropriate descriptive statistics.

Demographics will be summarized by overall subjects and treatment sequence, with corresponding listing as follows:

- Age (years)
- Age Group (< 65, ≥ 65 years old)
- Sex (Female, Male)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, and Unknown)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple and Other)
- Weight (kg) at baseline
- Height (cm) at baseline
- BMI (kg/m^2) at baseline
- Days since discharge from hospital (days), derived from the date of first dose of study drug minus the date of discharge for the qualifying hospitalization from eCRF form "Qualifying Hospitalization Discharge Date".

Baseline characteristics will be carried over from Part A and summarized as follows:

- 6MWT distance (m), for each of the first and the second attempts 6MWT distance (m) for the attempt used as 'baseline' for purposes of analysis
- The number (%) of patients where the first and where the second attempt was used as baseline for purposes of analysis
- 6MWT distance status at baseline (10 to <100 m, 100 to 200 m, > 200m)
- mBDS at baseline
- Prior Mechanical Ventilation/Prior ECMO Status (Yes, No)
- Charlson Comorbidity Index at baseline

Charlson Comorbidity Index (CCI) will be calculated using the following table and add all items of the comorbidity score. The score ranges from 0 to 33. A higher score indicates worse health condition.

Disease	Points
Myocardial Infarction	1
Congestive Heart Failure	1
Peripheral Vascular disease	1
Cerebrovascular disease	1
Dementia	1
COPD	1
Connective Tissue disease	1
Peptic Ulcer disease	1
Diabetes Mellitus	1 point if uncomplicated 2 points if end-organ damage
Moderate to severe CKD	2
Hemiplegia	2
Leukaemia	2
Malignant Lymphoma	2
Solid Tumour	2 points 6 points if metastatic
Liver disease	1 point if mild 3 points if moderate to severe
AIDS	6 points

7.2 Medical history

Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA® version 24.0 (or later)) and will be classified as follows:

- Previous medical history: medical conditions that stopped prior to start of treatment
- Ongoing (concomitant) medical conditions: medical conditions still present after start of treatment. Medical conditions with onset or end-date on the date of the first dose of study medication will be considered concomitant.

Frequency and percentage of medical history and concomitant medical conditions will be summarized by system organ class (SOC) and preferred term (PT) by OLE Safety population. The number (%) of subjects reporting each condition will be presented by overall and treatment sequence. If subjects have more than one disease within an SOC or PT they will be counted only once for the respective SOC or PT.

8 Exposure and Compliance

8.1 Extent of Exposure

Duration of study drug exposure, defined as the number of days between the date of first dose and the date of the last dose, will be summarized using descriptive statistics by treatment sequence and overall. The duration of study drug exposure focus on the LYT-100 treatment only. For LYT-100 to LYT-100 arm, the date of first dose taken is the first dose in Part A whereas for placebo to LYT-100 arm, the date of first dose taken is the first dose in Part B. Therefore, the duration will range from 1 to 182 for LYT-100 to LYT-100 arm, and from 1 to 91 days for placebo to LYT-100 arm.

Duration (days) will be calculated as date of last dose – date of first dose + 1.

If the date of first intake of study medication is missing, it will be assumed to be identical to the date of randomization for LYT-100 to LYT-100 arm and assumed to be identical to the date of ICF signed for placebo to LYT-100 arm.

Descriptive statistics for the treatment duration will be presented using OLE Safety Populations.

8.2 Compliance

Similar to the extent of exposure, the compliance will only calculate the compliance of LYT-100 treatment only. For LYT-100 to LYT-100 arm, the date of first dose taken is the first dose in Part A whereas for placebo to LYT-100 arm, the date of first dose taken is the first dose in Part B.

8.2.1 Placebo-LTY100 Compliance

Compliance will be based on the protocol-defined planned 91 days of study drug dosing in Part B OLE. The total amount (in mg) of study drug will be determined for each patient, and then compared to the total EXPECTED amount (135,000 mg) of study drug that would be given if a patient completed exactly 91 days of treatment (as per protocol).

The expected amount of study drug is derived based on both the titration period (first 3 days) and then the remaining full-dosage days, as follows:

- Days 91 through 93 (3 days): 1000 mg/day x 3 days = 3000 mg during titration period
- Days 94 through 182 (88 days): 1500 mg/day x 88 days = 132,000 mg.
- TOTAL: 135,000 mg expected.

The actual mg taken by each patient will be calculated using the start and stop dates for each dose level, multiplied by the dosage given from the study drug adjustment eCRF page dataset. As an example, the following patient titrated to full dose, had a dose interruption for 13 days, and then restarted study drug but at half the prescribed dosage for the remainder of study participation.

- Start Day 91 and Stop Day 93 (total daily dose 1000mg): Total mg given=3,000
- Start Day 94 and Stop Day 116 (total daily dose 1500mg): Total mg given=33,000

- Start Day 117 and Stop Day 167 (total daily dose 0mg, dose interrupted): Total mg given=0
- Start Day 117 and Stop Day 167 (total daily dose 750mg, reduced dose): Total mg given=37,500
- Total mg given to subject=73,500

Compliance (expressed as a percent) would then be calculated as:

$$\frac{\text{Total mg given}}{\text{Total mg expected}} = \frac{73{,}500}{135{,}000} = \mathbf{54.4\%}$$

The second example below is a patient who had the Day 182 study visit a full 10 days after the target study day (Day 182) and yet who continued taking double-blind study medication.

- Start Day 91 and Stop Day 93 (total daily dose 1000mg): Total mg given=3,000
- Start Day 94 and Stop Day 192 (total daily dose 1500mg): Total mg given=145,500
- Total mg given to subject=148,500

Compliance (expressed as a percent) would then be calculated as:

$$\frac{\text{Total mg given}}{\text{Total mg expected}} = \frac{148{,}500}{135{,}000} = \mathbf{110.0\%}$$

8.2.2 LYT100-LTY100 Compliance

Compliance will be based on the protocol-defined planned 91 days of study drug dosing in Part and repeated in Part B OLE. The total amount (in mg) of study drug will be determined for each patient, and then compared to the total EXPECTED amount (270,000 mg) of study drug that would be given if a patient completed exactly 182 days of treatment (as per protocol).

The 91 day dosing regimen is given in 2 cycles corresponding with Part A (Double Blind) and Part B (OLE). The compliance is calculated in the same manner presented above in section 8.2.1.

9 Previous and Concomitant Medications and Therapies

Prior and concomitant medications are coded according to the World Health Organization drug dictionary (WHODrug Global B3 September 2020 or later) and stored with ATC codes and generic names.

Prior medication is carried over from Part A and defined as any medication other than the study drug within 30 days prior to the first study drug administration of Part A. Medications used over the course of the study will be classified to prior or concomitant based on the imputations specified in Appendix III: Partial Date Conventions.

The summary tables by treatment sequences and overall for prior and concomitant medication will be provided detailing the number and percentage of subjects by Primary Anatomical Main Group (ATC Level 3 and preferred name using the WHO Drug Dictionary.

A table of new-onset medications will also be provided, including only those medications with a start date on or after the date of the first dose of study medication.

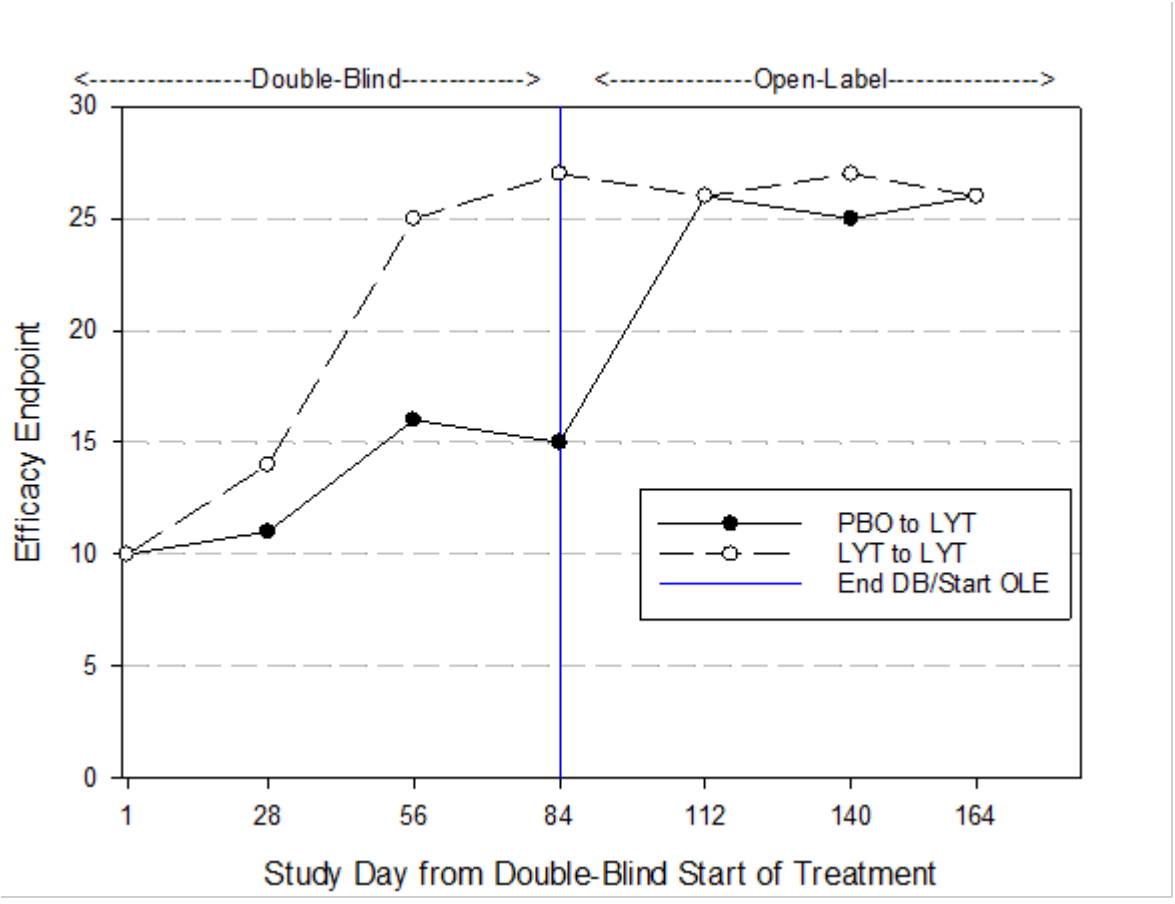
Prior and concomitant procedures will be provided in listing. In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

10 Exploratory Efficacy Analysis

For each of the following endpoints, a line plot of the LSMean (+/-SE) changes over time (by treatment group) from MMRM models using observed cases will be provided for the OLE Safety populations:

- 6MWT
- Dyspneoa 12

Efficacy will be tabulated and plotted in a fashion that allows for examination of the time course from the double-blind to the OLE period. The following sample graphic demonstrates how this may be plotted (subject to change).



10.1 6-minute Walk Test distance (6MWT)

The change from baseline to Day 182 of the 6MWT distance. Analysis of the change from baseline in 6MWT will be performed at each protocol-scheduled timepoint, including both Part A and Part B, ie, baseline, Day 14, 28, 56, 91, 105, 119, 147, and 182.

Two 6MWT will be performed on Days -1 and/or 1, at baseline of Part A, and with the longest distance will be recorded for the baseline measure. These tests can take place on Days -1 and/or Day 1, prior to dosing.

The 6MWT measures the distance a patient can quickly walk on a flat, hard surface in a period of 6 minutes. It evaluates the global and integrated response of all the systems involved during exercise.

Subjects who are unable to complete (or walk) due to disease severity will be assigned a distance of 0 (zero).

Change from baseline in 6MWT will be summarized as descriptive statistics by treatment and visit. 6MWT will be analyzed using MMRM, assuming a Gaussian distribution, an unstructured covariance matrix, the Between-Within denominator degrees of freedom approximation and the Huber-White robust sandwich estimation for standard errors. Fixed effects will include treatment, visit, the treatment by visit interaction, the baseline value of the endpoint, study center, prior mechanical ventilation/prior ECMO Status (Yes vs. No), and age group (< 65 vs. >= 65) as covariates. The visits will include Day 14, 28, 56, 91, 105, 119, 147, and Day 182. Where applicable, the study center will be pooled into regions (US, East Europe, West Europe, and others) using the designations used in Part A. The covariate of study center will then be replaced by region. However, if there is a convergence problem with the unstructured covariance matrix, then alternative covariance structures will be examined (autoregressive (1), Compound Symmetry). By-visit pairwise comparisons will be assessed. Least square means and their standard errors (SE), least square means for treatment difference along with their 95% confidence interval (CI) of will be reported.

10.2 Dyspnoea-12

Dyspnoea-12 is an instrument used to assess the dyspnea severity ”these days” reflecting breathlessness experienced in daily life. Dyspnea-12 consist of 12 descriptor items ranging from none (0), mild (1), moderate (2) or severe (3).

An overall score (range 0-36) of breathlessness severity is provided that encompasses seven physical items (Items 1-7, range 0-21) and five affective items (Items 8-12, range 0-15). The total scores range from 1 to 36 whereby the higher score correlates with greater severity. The instrument with data from more than three items missing will not be used. The method for scoring the Dyspnoea-12 with up to three missing items is detailed in the table below.

Number of items missing	Calculation to account for missing items	Dyspnoea-12 score calculation
1	36 ÷ 33 =1.09	1.1 × total Dyspnoea-12 score
2	36 ÷ 30 =1.2	1.2 × total Dyspnoea-12 score
3	36 ÷ 27 =1.3	1.3 × total Dyspnoea-12 score

It will be assessed at Day -1, 14, 28, 56, 91, 105, 119, 147, and 182. Changes from baseline in the total Dyspnoea-12 will be analyzed using MMRM method as primary efficacy endpoint by treatment group and visit. The visits will include Day 14, 28, 56, 105, 119, 147, and 182.

10.3 Other exploratory efficacy analyses

10.3.1 St. George's Respiratory Questionnaire-I

The SGRQ-I will be listed at Day -1, 28, 56, 91, 119, 147, and 182, is an idiopathic pulmonary fibrosis disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in subjects with interstitial lung disease. No statistical analysis will be performed, and data will only be presented in a listing.

10.3.2 Modified Borg Dyspnoea Scale

The modified Borg Dyspnoea Scale (mBDS) will be listed at Screening, Day -1, 1, 14, 28, 56, 91, 105, 119, 147 and 182.

10.3.3 WHO Ordinal Scale for Clinical Improvement

The WHO Ordinal Scale for Clinical Improvement will be listed at Day -1, 28, 91, 119, 147 and 182. No statistical analysis will be performed, and data will only be presented in a listing.

10.3.4 SF-36 (v2)

The SF-36 v2 is a self-administered questionnaire containing 36 items that measures health on functional status, well-being, and overall evaluation of health in 8 domains and assessed at Day -1, 28, 56, 91, 105, 119, 147, and 182.

The raw scores for each item will be presented by scale in a listing.

Scale	Item	Lowest and highest possible raw scores	Possible raw score range
Physical Functioning (PF)	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	10-30	20
Role-Physical (RP)	4a, 4b, 4c, 4d	4-20	16
Bodily Pain (BP)	7,8	2-11	9
General Health (GH)	1, 11a, 11b, 11c, 11d	5-25	20
Vitality (VT)	9a, 9e, 9g, 9i	4-20	16
Social Functioning (SF)	6, 10	2-10	8
Role-Emotional (RE)	5a, 5b, 5c	3-15	12
Mental Health (MH)	9b, 9c, 9d, 9f, 9h	5-25	20
Self-Evaluated Transition (SET)	2	1-5	4

10.3.5 Chest CT Scan

Chest CT Scan will be listed at Day -1, 91, and 182. No statistical analysis will be performed, and data will only be presented in a listing.

Table 1:Lung Lobe Involvement Scores (sample)

Lung lobe involvement – for each of the five lung lobes (Right upper, Right middle, Right lower, Left Upper, Left lower), and lingula	**Score**
Ground glass opacity (GGO) Score	
No alveolar disease	0
Ground glass opacity involving < 5% of the lobe	1
GGO involving 5-25% of the lobe	2
GGO involving 25-49% of the lobe	3
GGO involving 50-75% of the lobe	4
GGO involving >75% of the lobe	5
Fibrosis Score	
No interstitial disease	0
Interlobular septal thickening; no discrete honeycombing	1
Honeycombing (+/- septal thickening) involving up to 25% of the lobe	2
Honeycombing (+/- septal thickening) involving 25-49% of the lobe	3
Honeycombing (+/- septal thickening) involving 50-75% of the lobe	4
Honeycombing (+/- septal thickening) involving > 75% of the lobe	5
Consolidation Score	
No Consolidation	0
Consolidation involving <5% of the lobe	1
Consolidation involving 5-25% of the lobe	2
Consolidation involving 25-49% of the lobe	3
Consolidation involving 50-75% of the lobe	4
Consolidation involving >75% of the lobe	5
Reticulation/bronchiectasis Score:	
No reticulation	0
Reticulation involving < 5% of the lobe	1
Reticulation involving 5-25% of the lobe	2
Reticulation involving 25-49% of the lobe	3
Reticulation involving 49-75% of the lobe	4
Reticulation involving >75% of the lobe	5

10.3.6 Chest X-Ray

Chest X-Ray will be listed at Screening, 91 and 182. No statistical analysis will be performed, and data will only be presented in a listing.

10.3.7 Pulse Oximetry (SpO2)

Pulse-Oximetry (SpO2) will be listed at Screening, Day -1, 1, 14, 28, 56, 91, 105, 119, 147, 182, and 196. No statistical analysis will be performed, and data will only be presented in a listing.

10.3.8 Length of Hospital Stay and Mortality

Total number of days of hospital stay (Length of Hospital Stay) will be listed. Date of (original) admission, date of (original) discharge and rehospitalization(s) and subsequent discharge(s) will be collected.

The length of original hospital stay from admission will be derived by taking the date of discharge minus the date of admission and adding one. Subjects who die or withdraw from the study while in hospitalization will be censored on the date of death/withdrawal. Subjects will be censored on the visit date of Day 196 if they are still hospitalized at this timepoint.

The length of original hospital stay from first study drug administration will also be derived by taking the date of discharge minus the date of first dose of study drug in Part A and adding one. Subjects who die or withdraw from the study while in hospitalization will be censored on the date of death/withdrawal. Subjects will be censored on the visit date of Day 196 if they are still hospitalized at this timepoint.

Total duration of hospitalization during the study will be summed up for the days of hospitalization from the first dose of study drug in Part A to last date of the study (Day 196/End of Study) including the days of rehospitalization from any cause. If a subject is discharged prior to end of study, the original hospital stay will be calculated as date of discharge minus the date of first study drug and plus one, and add the number of stay of rehospitalization which will be calculated as discharge date minus admission date and plus one.

The length of hospitalization prior to enrolment will be carried from Part A calculated for the original hospitalization from the date of admission to date of enrolment of Part A, i.e. Study Day 1.

10.3.9 Pulmonary Exacerbations, Severe and Non-severe

The occurrence of pulmonary exacerbations will be listed by either severe or non-severe.

11 Safety

Safety conclusions will be based on outcomes from the OLE Safety Population.

11.1 Adverse events

An AE is defined as any event, side-effect, or other untoward medical occurrence that occurs in conjunction with the use of a medicinal product in humans, whether considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavourable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product.

Treatment emergent adverse events (TEAE) are defined as an AE that occurs or worsened on or after the first dose of study medication and will be evaluated from the first administration of study drug until the End of Study (EOS) visit. AEs which occurred (start) prior to the first dose of study medication will be classified as pre-treatment AEs. The classification of TEAEs of the imputations for partial dates is specified in Appendix III: Partial Date Conventions.

All adverse events will be coded using the MedDRA Version 23.0 (or later); this version has the most up-to-date COVID-19 coding terms. The analysis will focus on the TEAEs.

Number and percent of subjects with TEAEs and number of events will be given by SOC and by PT within each SOC by placebo group of Part A (first 91 treatment period), both treatment sequences of Part B (placebo to LYT-100 arm and LYT-100 to LYT-100 arm) and both periods of LYT-100 group (Combination of Part A and Part B) for the following:

- All TEAEs with 95% confidence interval about the point estimate based on the Clopper Pearson method
- All TEAEs and all TEAEs judged by the investigator to be at least possibly related
- All TEAEs by severity (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5)
- All TEAE related to study treatment (i.e. considered as possible and probable)
- Drug-related TEAEs with severity of Grade 3 or higher
- Serious TEAEs and Serious TEAE related to study drug (i.e. considered as possible and probable)
- TEAEs leading to study drug dose reduction
- TEAEs leading to study drug discontinuation and also those related to study drug (i.e. considered as possible and probable)
- TEAEs leading to death
- Pre-treatment AE

Unless otherwise specified, at each level of summarization a subject will be counted once if they reported one or more events at that level of summarization. If more than one occurrence of an event is reported, the event of the worst severity or the worst-case relationship assessment will be summarized.

Subject listings will be provided for TEAEs, treatment related TEAEs, SAEs, TEEs leading to study drug discontinuation, and TEAEs leading to death. The listings will also include subjects enrolled but not randomised. If AEs are reported prior to study drug, they will be listed in a SEPARATE data listing from the TEAEs.

Based on the established safety profile for pirfenidone and the nonclinical and clinical development programs for LYT-100 the following AEs are considered of special interest (AESI). AESIs will be evaluated and discussed in the clinical study report with special consideration as prospectively defined events. These AESIs, which will be identified from a pre-unblinding medical review of all TEAEs, will be binned according to MedDRA system organ class and tabulated, generally as follows (exact details to be determined prior to unblinded):

1) General disorders and Administrative site conditions: anorexia, decreased appetite, fatigue
2) Cardiac Disorders: e.g., primarily arrhythmias, syncope
3) GI disorders: diarrhea, nausea, vomiting
4) Investigations, e.g., hepatic laboratory abnormalities: increase in transaminases
5) Skin and subcutaneous tissue disorders, e.g., photosensitivity reaction, rash

Exploratory analysis of TEAEs may be considered to best assess the safety/tolerability profile of LYT-100 in this Covid population.

11.2 Deaths

Deaths will be presented as listing in detail by using "Death Details" form of eCRF. Additional analysis of death is planned as part of the efficacy assessments.

11.3 Laboratory Evaluations

Laboratory test will include hematology, biochemistry, coagulation and urinalysis and it will be performed at the time points specified in the study schedules (Screening, Day -1, 14, 56, 91, 105, 119, 147, 182 and 196). No statistical analysis will be performed, and data will only be presented in a listing.

- Hematology test: Haemoglobin (HGB), Haematocrit (HCT), Erythrocytes (RBC), Platelets (PLAT), Leukocytes with differential (including Eosinophils (ESN), Neutrophils (NEUT), Basophils (BASO), Lymphocytes (LYM - collected with biomarkers) and Reticulocytes (RETI)
- Biochemistry tests: C-reactive protein (CRP- collected with biomarkers), Urea (U), Creatinine (CREAT), Total Bilirubin (BILI) and Direct Bilirubin (BILIDIR), Blood Urea Nitrogen (BUN), Albumin (ALB), Globulin (GLOBUL), Alkaline Phosphatase (ALP), Creatine phosphokinase (CPK), Troponin 1 (TROP1- collected with biomarkers), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma- glutamyl transpeptidase (GGT), Glucose (GLU), Sodium (NA), Potassium (K), Calcium (CA), Chloride (CL), Phosphate (PHOS), Bicarbonate (BICARB), Lactate dehydrogenase (LDH- collected with biomarkers and at screening), Ferritin (collected with biomarkers and at screening).
- Coagulation test: INR, Prothrombin time, APTT, d-dimer (collected with biomarkers)
- Dipstick Urinalysis test: pH (PH), Specific Gravity (SPGRAV), Creatinine (CREATININE), Protein (PROT), Glucose (GLUC), Ketones (KETONES), Total Bilirubin (BILI), Occult Blood (OCCBLD), Nitrite (NITRITE), Urobilinogen (UROBIL), Leukocytes (WBC)
- Urine Cotinine – collected at screening, Days 28, 91, and 182.
- Serum pregnancy test

11.4 Vital signs

Vital signs (weight, temperature, blood pressure, heart rate, respiratory rate, and BMI) including SpO2 will be measured at every study visit (Screening, Day -1, 1, 14, 28, 56, 91, 105, 119, 147, 182 and 196). No statistical analysis will be performed, and data will only be presented in a listing.

11.5 Electrocardiogram

ECG values will be listed at Screening, Day 14, 91, 105, 182 and 196. No statistical analysis will be performed, and data will only be presented in a listing.

12 Interim Analyses

No interim analysis is planned.

13 Software

If not stated otherwise, the data will be analysed using SAS Version 9.4 or higher in a secure and validated environment.

14 Abbreviations

AE	Adverse Event
ALB	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BASO	Basophils
BICARB	Bicarbonate
BID	Twice daily
BILI	Total Bilirubin
BILIDIR	Direct Bilirubin
BMI	Body Mass Index
CA	Calcium
CCI	Charlson Comorbidity Index
CI	Confidence interval
CL	Chloride
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus 2019
CoV	Coronavirus
CPK	Creatine phosphokinase
CREAT	Creatinine
CRP	C-reactive protein
CS	Clinically significant
CT	Computed tomography
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case Report Form
ENR	Enrolled population
EOS	End of study
ESN	Eosinophils
FAS	Full analysis population
GCSF	Granulocyte colony stimulating factor
GCP	Good Clinical Practice
GH	General health
GLOBUL	Globulin
GLU	Glucose
HCT	Haematocrit
HCV	Hepatitis C virus
HGB	Haemoglobin
HR	Heart rate
ICH	International Council for Harmonisation
IL-6	Interleukin 6
IL-1β	Interleukin-1β

INR	International normalised ratio
ITT	Intent-to-treat
K	Potassium
LDH	Lactate dehydrogenase
LYM	Lymphocytes
MedDRA®	Medical Dictionary for Regulatory Activities
mBDS	Modified Borg dyspnoea scale
MCS	Mental component summary
MH	Mental health
MM	Medical Monitor
MMRM	Mixed model for repeated measures
MV	Mechanical ventilation
n	Number
NA	Sodium
NCS	Not clinically significant
NEUT	Neutrophils
OCCBLD	Occult Blood
PCS	Physical component summary
PDGF-β	Platelet derived growth factor-β
PE	Physical examination
PF	Physical functioning
PHOS	Phosphate
PK	Pharmacokinetic population
PLAT	Platelets
PopPK	Population Pharmacokinetics
PP	Per protocol population
PROT	Protein
PT	Preferred term
RP	Role-physical
RT-PCR	Reverse transcription polymerase chain reaction
QLF	semi-Quantitative Lung Fibrosis
QoL	Quality of life
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cells
RE	Role-emotional
RETI	Reticulocytes
RMS	Row mean score
SAE	Serious Adverse Event
SAF	Safety analysis population
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SD	Standard deviation
SDTM	Study Data Tabulation Model
SET	Self-evaluated transition
SF	Social functioning
SGRQ	Saint George Respiratory Questionnaire
SOC	System organ class
SpO2	Oxygen Saturation

SPGRAV	Specific Gravity
TEAE	Treatment-emergent adverse event
TGF-β1	Transforming Growth Factor Beta 1
TNF-α	Tumor Necrosis Factor - alpha
TROP1	Troponin 1
U	Urea
UROBIL	Urobilinogen
VEGF	Vascular endothelial growth factor
Vs.	Versus
VT	Vitality
WBC	Leukocytes (white blood cells)
WHO	World Health Organization
6MWT	Six-minute walk test

15 References

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2. LYT-100-2020-02-US Protocol V8.2/ Date: 17Mar2022 (US sites only)
3. LYT-100-2020-02 Subject Case Report Forms V11.0/ Date: 19Nov2021
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6. Janelle Yorke, Paul W Jones, and Jeffrey J Swigris. Development and validity testing of an IPF-specific version of the St George's Respiratory Questionnaire. Thorax. 2010 Oct; 65(10): 921–926.
7. J Yorke, S H Moosavi, C Shuldham, P W Jones. Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12. Thorax. 2010 Jan;65(1):21-6.

16 Appendices

Appendix I: Schedule of assessments and Procedures

Appendix II: Programming Conventions for Outputs

Appendix III: Partial Date Conventions

Appendix IV: Scoring Algorithm for SGRQ-I

Appendix I. Schedule of Assessments for Part B

	Study Treatment						Post-treatment
	Target Days ± 3 day window						
Study Day	**91**	**105**	**119**	**147**	**182**	**Early Termination[6]**	**Day 196: End of Study**
Visit Number	**7B**	**8B**	**9**	**10**	**11**	**ET**	**12**
Informed consent[1]	X						
Eligibility	X						
Physical Exam [2]		X			X	X	X
Weight		X	X	X	X	X	X
Vital signs (BP, HR), Respiratory Rate, SpO_2, Contactless, Tympanic or oral Temperature[3]		X	X	X	X	X	X
Standard 12-lead ECG[3]		X			X	X	X
Charlson Comorbidity Index					X		
Chest CT Scan					X		
Chest X-ray					X	X	X
6-minute Walk Test (end of visit)		X	X	X	X	X	
Modified Borg (Dyspnoea) Scale (start of visit)		X	X	X	X	X	
Dyspnoea-12 (start of visit)		X	X	X	X	X	
St. George's Respiratory Questionnaire (start of visit)			X	X	X		
WHO Ordinal Scale for Clinical Improvement			X	X	X	X	
SF-36 v2 (start of visit)			X	X	X	X	
Supplemental oxygen use, pulmonary exacerbation		X	X	X	X	X	X

	Study Treatment						Post-treatment
	Target Days ± 3 day window						
Study Day	**91**	**105**	**119**	**147**	**182**	**Early Termination[6]**	**Day 196: End of Study**
and/or rehabilitation, and hospitalization status							
Hematology		X	X	X	X	X	X
Blood chemistry and Coagulation		X	X	X	X	X	X
Urinalysis		X	X	X	X	X	X
Pregnancy test[4]			X	X	X	X	X
Urine Cotinine	X				X		
Study Drug Administration/Accountability[5]	X	X	X	X	X		
Adverse Events/ Mortality	X	X	X	X	X	X	X
Concomitant Meds		X	X	X	X	X	X

1. Informed consent via written, electronic, or verbal must be documented before any study-specific screening procedures are performed. In order to continue in study Part B the patient must consent on day 91 of study Part A prior to confirming eligibility for study Part B and continuation on open-label LYT-100.
2. 4. Not required for amenorrhoeic female patients. Where required by local regulations, a serum pregnancy test should be conducted in addition to the urine pregnancy test. If a urine pregnancy test is positive, a serum pregnancy must also be performed as confirmation.
5. All medication from Part A should be returned by patients at Visit 7A, and drug accountability for Part A conducted as part of Visit 7A (see Table 4.) Following confirmation of Eligibility for Part B, a new drug supply will be distributed to patients in the OLE as part of Visit 7B. Study visit 7A (Part A) and study visit 7B (Part B) should be conducted on the same day. All doses are to be administered with meals and approximately 10 to 12 hours apart.
6.. Patients are required to complete their End of Study or Termination Visit within 2 weeks of the last study drug treatment administered to the patient, ± 3 days. All patients will be encouraged to return for all remaining study visits through Day 196 even if not on study medication.

Appendix II: Programming Conventions for Outputs

❖ Clinipace Output Conventions

Outputs will be presented according to the Clinipace general guidelines and template for outputs conventions.

❖ General Rules

The following conventions will be applied for reporting descriptive statistics of all continuous data.

Means, medians, Q1, and Q3, will be reported at 1 more significant digit than the precision of the data. Minimum, and Maximum will have the same precision as Raw data (number of digits) for non-derived data (*e.g.* weight). SD will be presented with one digit more than mean.

Statistics on derived data (*e.g.* treatment exposure time in days) will be rounded to reasonable number of digits.

Qualitative variables will be summarized by counts and percentages. Unless otherwise stated, the calculation of proportions will be based on the number of available subjects. Therefore, counts of missing observations will not be included in the denominator and not presented as a separate category.

❖ Dates & Times

Depending on data available, dates and times will take the form YYYY-MM-DD and HH:MM.

❖ Spelling Format

English US

❖ Presentation of Treatment Groups

All listings will be ordered by the following (unless otherwise indicated in the template):

- Center-subject ID
- Treatment sequence
- Date (where applicable)

All tables containing coded terms (CM, MH, AE), coded records will be sorted in frequency order.

Appendix III: Partial Date Conventions

Partial dates for Adverse Events and Previous/Concomitant Medications

In cases of incomplete dates (e.g., pertaining to AE, concomitant medication, medical history, etc.), the missing component(s) will be assumed as the most conservative value(s) possible.

For example, if the start date has a missing day value and year and month are available, the first day of the month but not before first intake of study medication will be imputed for study day computations (i.e., treatment-emergent status, etc.). The start date will be set to the first day of the year but not before first intake of study medication if month and day are missing and year is available.

If day is missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month and year components.

Date imputation will only be used for computational purposes e.g., treatment-emergent status, etc. Actual data values as they appear in the original CRFs will be shown in the data listings.

Appendix IV: Scoring Algorithm for SGRQ-I

- **ITEM WEIGHTS**

Symptoms Component

There are 6 items which displayed disordered thresholds and required adjacent response categories to be collapsed. The format for the SGRQ-I symptoms component is detailed below.

SGRQ-I Symptoms Component

Part 1 Please describe how often your respiratory problems affect you currently.
Item 1: I cough:
2 = Almost everyday (new weight=80.6)
1 = Only with infections (new weight=40.2)
0 = Not at all (new weight=0)

Item 2: I bring up phlegm:
2 = Almost everyday (new weight=76.8)
1 = Only with infections (new weight=41.4)
0 = Not at all (new weight=0)

Item 3: I have shortness of breath
2 = Almost everyday (new weight=87.2)
1 = Only with infections (new weight=50.3)
0 = Not at all (new weight=0)

Item 4: I have attacks of wheezing
2 = Almost everyday (new weight=86.2)
1 = Only with infections (new weight=51.0)
0 = Not at all (new weight=0)

Item 5: How many times in a typical week do you suffer from respiratory attacks?
1 = more than one (new weight=66.2)
0 = none (new weight=0)

Item 6: In a typical week, how many good days do you have?
2 = every day (new weight=93.3)
1 = a few days (new weight=51.2)
0 = none (new weight=0)

Activities Component
The activities component contains 10 items.

SGRQ-I Activities Component
Part 2 Section 2: Questions about what activities usually make you feel short of breath these days
Item 1: Washing or dressing yourself
1 = true (new weight=82.2)
0 = false (new weight=0)

Item 2: Walking around in the house
1 = true (new weight=80.2)
0 = false (new weight=0)

Item 3: walking outside on level ground
1 = true (new weight=81.4)
0 = false (new weight=0)

Item 4: Walking up a flight of stairs
1 = true (new weight=76.1)
0 = false (new weight=0)

Item 5: Playing sports or other physical activities
1 = true (new weight=72.1)
0 = false (new weight=0)

Part 2 Section 5: These are questions about how your activities might be affected by your respiratory problems
Item 1: Jobs such as household chores take a long time, or I have to stop to rest
1 = true (new weight=70.6)
0 = false (new weight=0)

Item 2: If I walk up one flight of stairs, I have to go slowly or stop
1 = true (new weight=71.6)
0 = false (new weight=0)

Item 3: If I hurry or walk fast, I have to stop or slow down
1 = true (new weight=72.3)
0 = false (new weight=0)

Item 4: My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, bowl or play golf
1 = true (new weight=74.5)
0 = false (new weight=0)

Item 5: My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports

1 = true (new weight=63.5)
0 = false (new weight=0)

Impacts Component

The SGRQ-I includes 18 items to calculate the impacts component.

SGRQ-I Impacts Component

Part 2 Section 1

Item 1: If you ever held a job:

1 = My lung condition interferes or made me stop work (new weight=83.3)
0 = My lung problem does not affect my job (new weight=0)

Part 2 Section 3: Some more questions about your cough and shortness of breath these days

Item 1: Coughing hurts

1 = true (new weight=81.1)
0 = false (new weight=0)

Item 2: Coughing makes me tired

1 = true (new weight=79.1)
0 = false (new weight=0)

Item 3: Short of breath when I talk

1 = true (new weight=84.5)
0 = false (new weight=0)

Item 4: Short of breath when I bend over

1 = true (new weight=76.8)
0 = false (new weight=0)

Item 5: My coughing or breathing disturbs my sleep

1 = true (new weight=87.9)
0 = false (new weight=0)

Item 6: I get exhausted easily

1 = true (new weight=84.0)
0 = false (new weight=0)

Part 2 Section 4: Questions about other effects that your respiratory problems may have on you these days.

Item 1: My cough or breathing is embarrassing in public

1 = true (new weight=74.1)

0 = false (new weight=0)

Item 2: My respiratory problems are a nuisance to my family, friends or neighbours
1 = true (new weight=79.1)
0 = false (new weight=0)

Item 3: I get afraid or panic when I cannot catch my breath
1 = true (new weight=87.7)
0 = false (new weight=0)

Item 4: I feel that I am not in control of my respiratory problems
1 = true (new weight=90.1)
0 = false (new weight=0)

Item 5: Exercise is not safe for me
1 = true (new weight=75.7)
0 = false (new weight=0)

Item 6: Everything seems too much of an effort
1 = true (new weight=84.5)
0 = false (new weight=0)

Part 2 Section 6: We would like to know how your respiratory problems usually affect your daily life.

Item 1: I cannot play sports or do other physical activities
1 = true (new weight=64.8)
0 = false (new weight=0)

Item 2: I cannot go out of the house to do the shopping
1 = true (new weight=81.0)
0 = false (new weight=0)

Item 3: I cannot do household chores
1 = true (new weight=79.1)
0 = false (new weight=0)

Item 4: I cannot move far from my bed or chair
1 = true (new weight=94.0)
0 = false (new weight=0)

Item 5: Now please check the box (one only) that you think best describes how your respiratory problems affect you:
0 = does not stop me (new weight=0)
1 = stops one or two things (new weight=42.0)
2 =stops most things (new weight=84.2)
3 = stops me doing everything I would like to (new weight=96.7)

- **OUTLINE OF SCORING ALGORITHM**

Summary

Three component scores are calculated: Symptoms; Activity; Impacts.

One Total score is also calculated.

Principle of Calculation

Each questionnaire response has a unique empirically derived 'weight'. The lowest possible weight is zero and the highest is 100.

Each component of the questionnaire is scored separately in three steps:

i. The weights for all items with a positive responses are summed.
ii. The weights for missed items are deducted from the maximum possible weight for each component. The weights for all missed items are deducted from the maximum possible weight for the Total score.
iii. The score is calculated by dividing the summed weights by the adjusted maximum possible weight for that component and expressing the result as a percentage :

$$\text{Score} = 100 \times \frac{Summed\ weights\ from\ positive\ items\ in\ that\ component}{Sum\ of\ weights\ for\ all\ items\ in\ that\ component}$$

The Total score is calculated in similar way:

$$\text{Score} = 100 \times \frac{Summed\ weights\ from\ positive\ items\ in\ the\ questionnaire}{Sum\ of\ weights\ for\ all\ items\ in\ the\ questionnaire}$$

Sum of maximum possible weights for each component and Total:

Symptoms 490.3

Activity 744.5

Impacts 1483.5

Total 2718.3

(Note: these are the maximum possible weights that could be obtained for the worst possible state of the patient).

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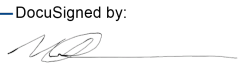
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