16.1 STUDY INFORMATION

16.1.1 Protocol and Protocol Amendments

Amendment #7: Protocol Version 8.0 Global Protocol dated 26 January 2022

Amendment #9: Version 8.2 U.S. dated 17 March 2022

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

Protocol Number: LYT-100-2020-02

Authors: PureTech LYT 100, Inc.

Development Phase: Phase 2
Document Version: Protocol Version 1.0 dated June 17, 2020
Amendment #1: Protocol Version 2.2 dated September 03, 2020
Amendment #2: Protocol Version 3.1 dated October 20, 2020
Amendment #3: Protocol Version 4.0 dated December 22, 2020
Amendment #4: Protocol Version 5.0 dated March 12, 2021
Amendment #5: Protocol Version 6.0 April 27, 2021
U.S. Specific Amendment #6: Protocol Version 7.0 September 23, 2021
Amendment #7: Protocol Version 8.0 January 26, 2022

Number of Pages: 126

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PROTOCOL AUTHORIZATION

Title: 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

As PureTech LYT 100, Inc. ("Sponsor") representative, I confirm that the study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (IP), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki and the International Council for Harmonization guidelines on Good Clinical Practice (GCP).

DocuSigned by:
Heather Paden
Signer Name: Heather Paden
Signing Reason: I approve this document
Signing Time: 27-Jan-2022 | 17:22 EST
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27-Jan-2022 | 17:22 EST

Heather Paden Date

INVESTIGATOR'S AGREEMENT

Title: 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

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s) (IB), electronic Case Report Forms (eCRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Human Research Ethics Committee (HREC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the appropriate Ethics Committee, except where necessary to avert an immediate hazard to the patients.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), in accordance with the current version of International Conference on Harmonization (ICH) guidelines for GCP, and in accordance with the current version of National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (updated 2018). The conduct of the study will also be in accordance with the Integrated Addendum to ICH E6 (R1), Guideline for GCP ICH E6 (R2).

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigational Site

Printed name of Investigator

Signature of Investigator

Date

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
PureTech LYT 100, Inc.

Name of Investigational Product:
Deupirfenidone Capsules

Name of Active Ingredient:
Deupirfenidone (LYT-100)

Protocol Number:
LYT-100-2020-02

Title of Study: 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

Study Centre(s): Approximately 35 study centers in Europe, United States, Asia and South America. Other regions may be added as the pandemic mandates (i.e., India).

Studied Period (Years):	**Phase of Study:**
Estimated date first Participant enrolled: Q4 2020 Estimated date last Participant completes double-blind treatment, Part A: Q1 2022 Estimated date first Participant enrolled to open-label extension, Part B: Q2 2021 Estimated date last Participant completes open-label extension, Part B: Q2 2022	Phase 2

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. Other regions may be added as the pandemic mandates (i.e., India).

PART A:

After informed consent is obtained, patients will enter a screening phase for 5 days, to determine eligibility. The screening period may be extended up to a total of 10 days to allow for evaluation of all screening assessments required for study inclusion. Patients are required to have all screening assessments, including a training session for the 6-minute walk test (6MWT), and meet all

inclusion/exclusion criteria for the trial prior to randomization. Approximately 168 eligible patients who previously hospitalized, but no longer require mechanical ventilation, extracorporeal membrane oxygenation, non-invasive ventilation (ie continuous positive airway pressure, high-flow nasal oxygen therapy or other high flow oxygen with FiO2 ≥35% and flow rate ≥ 8 lpm) for at least 72 hours prior to the screening visit, will be randomized to receive LYT-100 or placebo, in a ratio of 1:1, respectively, in conjunction with institutional standard of care for COVID-19. Enrollment in the United States may remain open in order for an additional approximately 30 subjects randomized to Part A to allow for evaluation of U.S. specific COVID Symptoms Assessments and Qualitative Interviews. Two 6MWT will be performed at baseline, with the longest distance recorded for the baseline measure. These tests can take place on Days -1 and/or Day 1, prior to dosing.

Patients randomized will be assigned to stratification levels as shown in Table 3. The primary analysis will be based on all data. Subgroup analysis may be performed as the data warrant, although the sample size for subgroups may not be sufficient for definitive conclusions to be drawn. Standard of care will be administered as per investigator's medical judgement, based on the severity of the disease, and according to local government and/or institutional guidelines. LYT-100 or placebo will be administered daily for up to 91 days, with an optional extension of open-label LYT-100 administration for up to an additional 91 days for those patients who qualify. Patients will start participation in the study while either hospitalized, or at time of hospital discharge / post-discharge from hospital for COVID-19 respiratory disease.

The timing of randomization into Part A is dependent on type of qualifying respiratory support and date of initial confirmed COVID-19 diagnosis, as described below in Table 1.

Table 1. Timing of Randomization Relative to COVID-19 Diagnosis and Qualifying Respiratory Support

Qualifying Respiratory Support	Initial Confirmed Diagnosis of COVID-19
Any form of supplementary oxygen treatment other than ECMO or MV	Within 90 days
ECMO or MV	Within 132 days

During Part A, treatment assignments will remain blinded to the patient, study staff, and sponsor. Patients will be seen either on the hospital ward and/or in the ICU during hospital stay or at discharge, or on a rehabilitation ward, an outpatient clinic or at the patient's home post-discharge. Note that for patients who were hospitalized and are discharged during the study, these patients will continue with study visits according to the Schedule of Events for Part A. For all patients, study follow-up visits will occur at Days 14, 28, 56, and 91. In Part A, patients who discontinue early or elect to not continue into Part B will also have a follow-up visit 14 days, post-completion of study treatment. (See Figure 1.)

For those patients who are eligible and who elect to continue into **Part B**, the open label extension, study visits will occur at Days 105, 119, 147 and Day 182. Part B patients who discontinue early will also have a follow-up visit 14 days, post-completion of Part B treatment. (See Figure 1.)

Study Objectives- Part A

COVID-19 respiratory disease is a multi-faceted indication, and thus this clinical study includes several objectives (and corresponding endpoints) to adequately describe the effects of study treatment. To that end, there are primary and key secondary objectives that form the basis for study success, while other secondary objectives will inform overall conclusions and allow for assessment of a preponderance of evidence as to the benefit of LYT-100 in this population.

Primary Objective:

To evaluate the effect of LYT-100 on the change in distance walked on the six-minute walk test performed in line with the American Thoracic Society/European Respiratory Society Guidelines.

Key Secondary Objective:

To evaluate the effect of 91 days of treatment with LYT-100 compared to placebo on 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 WHO Ordinal Scale for Clinical Improvement
4. Quality of Life 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 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 X-ray
12. Length of hospital stay
13. All-cause mortality
14. Use of supplemental oxygen from Baseline to end of treatment

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 Objectives:

To evaluate the plasma concentration vs. time data via population pharmacokinetic analysis of LYT-100 and its metabolite(s).

Study Objectives- Part B

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:

- Change in distance walked on the six-minute walk test performed in line with the American Thoracic Society/European Respiratory Society Guidelines.
- Dyspnoea-12
- Saint George Respiratory Questionnaire-I (SGRQ-I)
- The Modified Borg
- Dyspnoea Scale (mBDS).
- The WHO Ordinal Scale for Clinical Improvement
- Quality of Life assessment as collected using the SF-36 (v2), including 8 domains and 2 component scores.
- Number of lung segments involved using CT Scan and QLF assessment
- Pulmonary exacerbations, severe and non-severe
- All-cause rehospitalizations
- Severity of lung lobe(s) involvement, using CT Scan
- Pulse oximetry
- Chest X-ray
- Length of hospital stay
- All-cause mortality
- Use of supplemental oxygen from Baseline to end of treatment

Data Safety Monitoring Board (DSMB)

An independent, unblinded DSMB will assist with oversight of patient safety during both Parts A and B. A Charter will be written to describe the purpose, members, meeting frequency, and data to be reviewed by the DSMB.

Study Drug Dosage and Mode of Administration

Patients will receive LYT-100 (deupirfenidone) formulated as powder in 250 mg capsules or matching placebo. Dosing will be provided as shown in Table 2. In both Part A and Part B, an initial dosage of 500 mg BID will be given the first 3 days of dosing, followed by 750 mg BID thereafter. Patients will take LYT-100 study medication, or placebo (in Part A), orally and preferably with food (solid or nutritional supplements, whenever possible), with approximately 10 to 12 hours between the two daily doses.

Table 2: Dosing Regimens for Parts A and B

Part A: Double-Blind		**Part B: Open-Label Extension**	
Day 1 to Day 3	**Day 4 through Day 91**	**Day 91 through Day 93**	**Day 94 through Day 182**
[1]LYT-100 **500 mg BID** or matching Placebo[2] x 3 days	[1]LYT-100 **750 mg BID** or matching Placebo[2] x 88 days	[1]LYT-100 **500 mg BID**[2] x 3 days	[1]LYT-100 **750 mg BID**[2] x 88 days

[1]Patients will take study medication orally and preferably with food (solid or nutritional supplements, whenever possible), with approximately 10 to 12 hours between the two daily doses.

[2] Doses may be adjusted according to safety and tolerability to avoid toxicity by adjusting to lower doses in response to patient safety and tolerability issues, including: Skin reactions to sunlight; Significant changes to liver enzymes, and/or Gastrointestinal (GI) side effects. See protocol Section 5.2 for details.

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.

All patients will be monitored following screening for completion of clinical efficacy and safety assessments of LYT-100 at time points delineated in the Schedule of Events (Part A: Table 4; Part B: Table 5).

Number of Patients (Planned)

Approximately 168 patients with post-acute, documented COVID-19 will 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.

Enrollment in the United States may remain open in order for an additional approximately 30 subjects randomized to Part A to allow for evaluation of U.S. specific COVID Symptoms Assessments and Qualitative Interviews.

Eligibility Criteria- Part A

The following Inclusion and Exclusion must be met before randomization into the study.

Inclusion Criteria- Part A

1. Positive result of a molecular RT-qPCR diagnostic test, RNA or antigen test for SARS-CoV-2 result from a clinical specimen deemed clinically associated with the current episode of illness, warranting hospital admission as per investigator's judgement, or previously hospitalized (central and/or local laboratory COVID-19 test results are accepted from any biological material source)
2. Hospitalization for COVID -19 respiratory disease and treated with supplemental oxygen (including MV, ECMO or any other means of oxygen administration) in hospital

   Note: Admission to a hospital Emergency Department, temporary hospital or any other hospital-affiliated facility used to treat acutely ill subjects in which the subject would otherwise be admitted to the hospital but due lack of bed space/ capacity in response to the COVID-19 pandemic, or otherwise treated by hospital staff, falls under the category of hospitalization.

   Also note: Hospitalization can be any length of time on at least one calendar day and does not need to be greater than or equal to 24 hours.
3. Written, electronic, or oral informed consent from the patient or Legally Authorized Representative prior to any study procedures in a manner approved by an IRB or Ethics Committee
4. Male or female, aged ≥18 to ≤80 years of age, inclusively at the time of informed consent
5. Able to perform and willing to comply with all study procedures and requirements
6. Able to bear weight and ambulate a minimum of 10 m distance (use of inhaled oxygen permitted)
7. Randomization day is dependent on type of qualifying respiratory support and date of initial confirmed COVID-19 diagnosis as described in Table 1
8. COVID-19 pneumonia findings on imaging (chest X-ray or CT Scan) with a minimum of two lung lobes involvement
9. Shortness of breath ≥ grade 3 on mBDS dyspnea scale
10. Laboratory parameters (CBC, biochemistry) deemed by the investigator as acceptable and/or not clinically significant to enroll the patient

11. Women of childbearing potential (WOCBP) must be non-pregnant and non-lactating, and must be abstinent from heterosexual intercourse for 90 days following last dose of study medication or agree to use one of the acceptable, highly effective double contraception:
    a. oral, intravaginal, or transdermal combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation
    b. oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
    c. intrauterine device (IUD)
12. Male patients must be surgically sterile (> 30 days since vasectomy with no viable sperm), abstinent, or if engaged in sexual relations with a WOCBP, the participant and his partner must be surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method from screening until study completion, including the follow-up period and an additional 90 days after the last dose of study medication
13. Males will not donate sperm for at least 90 days after the last dose of study medication
14. Partners of male patients and female patients will report pregnancy occurring within 90 days from cessation of study medication
15. Patients can be on other medication (on and off label), apart from the ones specifically outlined in the Exclusion Criteria to treat COVID-19 respiratory disease that the investigator deems clinically relevant in combination with the study drug
16. Patients can concomitantly receive any standard of care as per investigators' clinical decision; standard of care may encompass any approved medication, on or off label apart from the ones specifically outlined in the exclusion criteria. Concomitant medication may be other medication(s) apart from the ones specifically outlined in the Exclusion Criteria

Exclusion Criteria- Part A

1. Patients who cannot follow-up with study participation requirements
2. Investigator considers patient is inappropriate to enroll in the trial
3. Pre-existing chronic respiratory condition(s), obstructive or restrictive, for which the patient is actively taking concomitant medication are excluded. Patients with history of Idiopathic Pulmonary Fibrosis (IPF), lung cancer, pulmonary arterial hypertension, other interstitial lung diseases, severe cardiac insufficiency (grade IV) are excluded irrespective of whether they are actively being medicated for those conditions or not
4. Pre-existing co-morbid conditions preventing outcome assessments, e.g., neurological, medical, orthopedic injury/disability, disease or condition that would prevent ability to transfer and walk for 6 minutes, prior to confirmed COVID-19 diagnosis
5. Co-morbid diagnosis of tuberculosis
6. Unstable angina or myocardial infarction in the last month prior to screening
7. Pre-existing co-morbidity associated with life expectancy less than 1 year
8. Present life expectancy less than 3 days and/or LDH > 360

   Note: If in the opinion of the Investigator an elevation of LDH > 360 at the time of screening is likely due to persistent effects from COVID-19 infection and expected to improve over time by ruling out all other potential causes or contributory factors for elevated LDH, the Investigator may use clinical judgement to enroll the patient and monitor LDH levels per protocol.
9. Body mass index ≥ 50 kg/m^2
10. Resting heart rate of ≥ 120 bpm, systolic blood pressure of > 180 mm Hg and a diastolic blood

pressure of > 100 mm Hg and/or or a fall in pulse oximetry oxygen saturation (SpO_2) to <80% upon ambulation

11. Sepsis, septic/hypovolemic/cardiogenic/neurogenic shock
12. Patients on MV, ECMO, NIV, HFNO and/or other high flow oxygen FiO2 ≥35% and ≥ 8 lpm within the last 72 hours prior to screening. Low flow supplemental oxygen is allowed.
13. History of anaphylactic reaction (particularly reactions to general anesthetic agents); allergic reaction due to any drug which led to significant morbidity; prior allergic reaction to pirfenidone
14. Known symptoms of dysphagia or known difficulty in swallowing capsules and/or total gastrectomy
15. Patients undergoing dialysis or hemoperfusion, or with a history of dialysis or hemoperfusion, or anticipated to require dialysis or hemoperfusion within 72 hours of screening or severe renal impairment (defined as creatinine clearance rate <30 mL/min) at the time of screening/ baseline
16. Use of any of the following drugs:
    a. Fluvoxamine, enoxacin, ciprofloxacin.
    b. Treatment with steroids under institutional protocols and guidelines to manage COVID-19 pneumonia/respiratory symptoms is allowed. Use of steroids off-label to treat non-COVID-19 related conditions is not allowed.
    c. Any Investigational Agents (i.e., non-approved or nonauthorized drugs), with the exception of those used for COVID-19 respiratory diseases that the investigator deems clinically relevant in combination with the study drug, as described below:

       i. Allowed agents
       - Patients who had received prior investigational agents for COVID-19 but are no longer taking those drugs are allowed.
       - Inhaled corticosteroids are allowed.
       - Patients that received prior convalescent plasma are allowed; however, concomitant convalescent plasma is excluded.

       ii. Excluded agents
       - Patients on concomitant experimental anti-viral, anti-fibrotic or anti-inflammatory therapies are excluded.
       - Any investigational agent not explicitly on this list should be reviewed by the medical monitor prior to initiating therapy or enrolling participant

    d. Other inhibitors of CYP1A2 (including but not limited to methoxsalen or mexiletine)
    e. Inducers of CYP1A2 (such as phenytoin), CYP2C9 or 2C19 (including but not limited to carbamazepine or rifampin)
    f. Drugs associated with ***substantial risk for prolongation of the QTc interval*** (including but not limited to moxifloxacin, quinidine, procainamide, amiodarone, sotalol). Note that QTc prolongation is not an all / nothing drug effect, and specifically the administration drugs such as hydroxychloroquine do not preclude participation in this trial but does mandate measurement of the QTc every 6 hours until deemed necessary in accordance with investigator judgement
    g. Vaccination with a live vaccine is not permitted during the period from 4 weeks prior to screening to 4 weeks after the last dose
    h. Tobacco and nicotine product and/ or a positive cotinine test at screening

i. Pirfenidone or nintedanib

17. Any other reason that, in the opinion of the Investigator, might interfere with the evaluation required by the study
18. For baseline AST ≥2.5xULN, ALT ≥2.5xULN and/or total bilirubin >1.5xULN (in the absence of history of Gilbert syndrome and/or the absence of alkaline phosphatase ≥2xULN or clinical evidence of cholestasis), or severe hepatic impairment
19. Patients requiring surgery due to an acute onset condition prior to randomization
20. Patients experiencing tachypnea. For the purposes of this study, tachypnea is defined as a resting respiratory rate ≥ 25 per minute.

Eligibility Criteria- Part B

The following Inclusion and Exclusion must be met before the patient can continue into the Open Label Extension.

Inclusion Criteria- Part B

1. Patient must have completed Part A of the study, through Day 91 of treatment.
2. In the opinion of the Investigator, the patient is a good candidate for continued treatment.

Exclusion Criteria- Part B

Patients ***must not meet*** any exclusion criteria listed for Part A.

Duration of Study and Study Treatment

Part A- Double-Blind

Over five days (up to 10 days to allow for evaluation of all screening assessments), patients will be screened and complete baseline assessments. Randomization occurs on the day following the Baseline Visit/assessment, i.e., shortly prior to the first dose of double-blind study medication.

All patients will be treated up to 91 consecutive days. Follow-up of study assessments post-randomization are at Days 14, 28, 56 and Day 91. For hospitalized patients who are discharged during the study, these patients will continue with study visits according to the Schedule of Events for Part A (Table 4).

A follow-up post-treatment completion visit will occur within 14 days of last day of study treatment.

The total duration of the study for each participant in Part A is up to 118 days, including screening and baseline of 5 days (up to 10 days to allow for evaluation of all screening assessments), treatment period of 91 days and off-treatment safety follow-up of 14 days including a 3-day study window for last visit.

Part B- Open Label Extension

Following completion of treatment in study Part A, all patients will be treated up to 91 consecutive days. Follow-up of study assessments post- randomization are at Days 105, 119, 147 and Day 182. For hospitalized patients who are discharged during the study, these patients will continue with study visits according to the Schedule of Events for Part B (Table 5).

A follow-up post-treatment completion visit will occur within 14 days of last day of study treatment.

The total duration of the study for each participant who completes both Parts A and B is up to 209 days, including screening and baseline of 5 days (up to 10 days to allow for evaluation of all screening assessments), treatment period of 91 days for Part A, treatment period of 91 days for Part B, and off-treatment safety follow-up of 14 days including a 3-day study window for last visit.

Endpoints - Part A

Efficacy Endpoints

The efficacy endpoints are consistent with the primary and secondary objectives of the study. 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:

- *6-minute walk test (6MWT)* is the primary efficacy endpoint. All patients will complete a 6MWT test according to the Schedule of Assessments and aligned with the American Thoracic Society/European Respiratory Society Guidelines with COVID-19 modifications provided in the 6MWT study procedural manual. 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. This is a self-paced test. Patients choose their own intensity of exercise and may stop and rest during the test. Changes from baseline in the 6MWT distance will be assessed using covariates in a mixed model. Dyspnea and fatigue are also assessed prior to the 6MWT and end of the test (Table 14).

Key Secondary Efficacy Endpoints:

- *Dyspnoea-12 (D-12)* measures "breathlessness severity" without reference to current activity and was developed for use in interstitial lung disease and COPD. current experience (““these days”) and is assessed ”, at baseline and at follow-up visits. The tool generates a total score using 12 descriptor items including seven physical and rive affective items with response optionsnone (0), mild (1), moderate (2) or severe (3). The total score ranges from 1 to 36 whereby the higher score correlates with greater breathlessness severity (Table 17).

Other Secondary and Exploratory Efficacy Endpoints:

- *Saint George Respiratory Questionnaire-I (SGRQ-I)* is an idiopathic pulmonary fibrosis disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with interstitial lung disease. There are 34 self-completed items with 3 domain component scores (Symptoms, Activities, and Impacts), with higher scores indicating more limitations. Changes from baseline in the component scores of the SGRQ-I will be assessed (Table 16).
- *Modified Borg Dyspnoea Scale (mBDS)* is a measure of dyspnea. The mBDS is a self-administered unidimensional assessment tool that analyzes breathlessness under exertion. Changes over time will be derived (Table 13).
- *WHO Ordinal Scale for Clinical Improvement* will be assessed for changes from baseline over time. The WHO ordinal scale has the following nine categories: (0) Uninfected (No clinical or virological evidence of infection); (1) Ambulatory (No limitation of activities); (3) Hospitalized Mild Disease (Hospitalized, no oxygen therapy); (4) Oxygen by mask or nasal prongs; (5) Hospitalized Severe Disease (Non-invasive ventilation or high-flow oxygen); (6) Intubation and mechanical ventilation; (7) Ventilation plus additional organ support (i.e. extracorporeal life support (ECLS), continuous renal replacement therapy (CRRT), vasopressors); (8) Dead (Death); (Table 10).
- The *SF-36* (v2) is a self-administered questionnaire containing 36 items that measures functional status, well-being and overall evaluation of health in 8 domains and 2 component summary scores. It requires approximately 5-10 minutes to complete and uses scaled, ordinal responses (e.g., All of the time, Most of the time, A good bit of the time, etc.) Changes in the standardized component scores and domain scores will be calculated (Table 18).

- The proportion of patients with "normal" CT scan images will be defined in a responder analysis. Patients with pre-existing chest pathology pre-COVID-19 should be considered "normal" for those pre-existing items/findings. Chest CT scans will be performed according to the CT Scan manual. Lung lobe involvement will be assessed for each of five lobes via central read with the terms defined by the Fleischner Society (Hansell et al 2018). CT scans may also be analyzed with semi-Quantitative Lung Fibrosis (QLF) and computer-Aided Diagnosis (CAD) QLF Scores (Kim et al, 2010). Table 11 shows how each lobe will be scored, the total score for each finding per lobe (range 0 to 5), each finding across the lung (range 0-25) and total score (range 0 to 100) will be derived accordingly. Changes from baseline in this total score will be assessed. A responder analyses will be performed, in which the proportion of patients showing ground glass opacities, fibrosis, consolidation, reticulation/bronchiectasis, and other radiographic abnormality improvement(s) by determining at least a 2-point score improvement for each abnormality across the five lobes (range 0-25), will be derived. 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 12. Shifts in these characteristics over the course of treatment will be of interest.
- *Biomarker* changes in will be assessed, including C-reactive protein (CRP), lymphocyte count, d-dimer, cardiac troponin, ferritin, lactate dehydrogenase (LDH), IL-6, TGF-β1, TNF-α, IL-1β, PDGF- β, GCSF, and VEGF.
- The proportion of patients with *'normal' chest X-ray* will be defined in a responder analysis. Patients with pre-existing chest pathology pre-COVID-19 should be considered 'normal' for those pre-existing items/findings.
- *Pulse oximetry* will be performed at rest and changes over time will be determined.
- *Number of hospital stay days* and *time to all-cause mortality* will be assessed.
- Percentage of patients who develop *respiratory exacerbations, severe or non-severe*
- *All-cause rehospitalizations*. Patients who are hospitalized at the time of randomization would need to have been discharged and readmitted for inclusion in this assessment.
- *Use of supplemental oxygen* from Baseline to end of treatment

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.

Population PK

Using plasma concentration versus time data, population pharmacokinetic analysis will be performed to assess the exposure-response characteristics of LYT-100 and its metabolite(s).

Endpoints- Part B

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, and all are as described for Part A (see above).

- 6-minute walk test (6MWT)
- Dyspnoea-12 (D-12)
- Modified Borg Dyspnoea Scale (mBDS)
- Saint George Respiratory Questionnaire-I (SGRQ-I)
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2)
- The proportion of patients with "normal" CT scan images will be defined in a responder analysis.
- The proportion of patients with 'normal' chest X-ray will be defined in a responder analysis.
- Pulse oximetry
- Number of hospital stay days and time to all-cause mortality
- Percentage of patients who develop respiratory exacerbations, severe or non-severe
- All-cause rehospitalizations.
- Use of supplemental oxygen

Statistical Methods for Part A:

The primary focus of the statistical analysis is on the double-blind comparison of LYT-100 to placebo (Part A). The following methods describe those for Part A; Part B methods are provided at the end of this section. Note that a comprehensive SAP will be written, in which the methods of statistical analysis will be described separately for Part A from Part B.

Sample Size

The study will utilize a suite of endpoints to measure patient clinical function and health-related quality of life. The sample size was based on both the 6MWT (a measure of patient clinical function) and the mBDS, a measure of patient health related quality of life (HRQoL).

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 patients 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., patients 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 estimation.

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 of 75 meters, estimated correlation between observations on the same subject of 0.50, and an alpha of 5%.

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.

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Randomization Stratification:

Approximately 168 patients will be randomized to Part A to receive LYT-100 or placebo in a 1:1 ratio. Enrollment in the United States may remain open in order for an additional approximately 30 subjects randomized to Part A to allow for evaluation of U.S. specific COVID Symptoms Assessments and Qualitative Interviews. The randomization will be stratified by the longest distance measured from two 6MWT at baseline and risk factors (

Table 3). The intent of the use of these strata in the randomization is to ensure similar distribution of disease severity to the two treatment arms.

Table 3. Randomization Stratification Levels (Study LYT-100-2020-02)

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**

Study Populations

- The Safety Population is defined as all patients who received at least one dose of study treatment. All safety endpoints will be assessed using this population. Patients will be analyzed according to the treatment they actually received, regardless of which treatment they were randomized to.
- The Intent to Treat (ITT) population is defined as all randomized patients. All efficacy endpoints will be assessed using this population, with primary conclusions regarding study drug effect to be based on the ITT population outcomes (with the FAS and PP populations assessed for sensitivity and to support the ITT conclusions). Patients will be analyzed according to the treatment group they were randomized to, regardless of which treatment they actually received.
- 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 6-minute walk test. 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.

- The Per-Protocol (PP) population is 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 have no major protocol deviations that could affect interpretability of the efficacy outcome. Subjects who died or discontinued due to TEAE will be included in this population.
- The Pharmacokinetic (PK) Population is defined as all patients who receive study treatment and provide at least one plasma concentration measure. This population will be determined by the study pharmacokineticist.

General Statistical Plan

A comprehensive statistical analysis plan will be written that will include details regarding the statistical analysis. The methods described below summarize the general approach.

Demographic information and patient disposition outcomes will be tabulated (including the number and percent of patients who are enrolled, who receive treatment, who prematurely discontinue and reasons for discontinuation, and who complete the study). Summary statistics for days of exposure and concentration of exposure will be provided.

The baseline for each variable (except the 6MWT) will be the last measurement obtained prior to first dose of study treatment. For the 6MWT distance, the longest distance of the two Day -1/ Day 1 distances will be used as baseline for purposes of analysis.

All efficacy analyses will be based on the ITT population unless otherwise specified. Baseline patient / clinical data, and all secondary endpoints will be presented descriptively as means, medians, or proportions with appropriate measures of variance, e.g., range, 95% CI).

The primary method of analysis for continuous endpoints is consistent with the sample size methodology and will thus utilize mixed models for repeated measures (MMRM), assuming a Gaussian distribution, an unstructured covariance matrix, and the Kenward-Roger approximation for denominator degrees of freedom. Fixed effects will include treatment, visit, the treatment by visit interaction, the baseline value of the endpoint as a covariate, and study center; however, the SAP may specify additional covariates to be added to the model. By-visit pairwise comparisons will be assessed. A sensitivity analysis of the primary and key secondary endpoints will be performed using a nonparametric Wilcoxon rank sum test to test the active vs. placebo comparison at each time point.

Categorical endpoints will be assessed at each time point using a Cochran-Mantel-Haenszel (CMH) test, stratified by center. For ordinal and other categorical endpoints, analysis using a Cochran-Mantel-Haenszel test with modified ridit scores to assess the differences in row mean scores between the treatment groups (referred to as a CMH-RMS) test statistic from the SAS PROC FREQ procedure will be used,

Kaplan-Meier plot and log-rank tests may assess time to all-cause mortality (if sufficient mortality data exist) as well as time to discharge from hospital (in days) and other time-to-event parameters, as the data permit. The proportion of all-cause mortality (deaths) through Day 91 will be tabulated.

Correlational analysis may also be undertaken to identify patient factors and potential biomarkers that are associated with overall survival and successful resolution of all signs and symptoms of the disease. Statistical analyses will be performed using SAS, version 9.4. (SAS, Cary, NC).

Inferential Testing and Multiplicity Considerations

The significance level of all tests will be a 2-tailed alpha level of 0.05. There is one key secondary efficacy endpoint. Efficacy 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.

Safety Analysis

Safety analyses will be performed using the Safety Population. Adverse events, concomitant medications, clinical laboratory findings, physical examinations, ECGs, and vital signs for each participant will be tabulated or summarized descriptively, where appropriate.

Treatment-emergent adverse events and changes in laboratory, vital signs, and ECG parameters will be summarized. Shift tables will also be provided for clinical laboratory results. ECG results will be classified as normal and abnormal and summarized. ECG results for QTcF will also be classified as <450 msec, 450-500 msec or >500 msec.

Population PK (Part A only)

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.

Part B Methods

Part B is characterized by open-label treatment, and thus the analysis will be descriptive in nature. Where inferential methods are used, these will be used to better-inform as to the relative magnitudes of the longer-term effects from treatment with LYT-100, and not for hypothesis testing purposes.

The focus of the Part B analysis will be on the LYT-100 to LYT-100 group (as these patients will have been treated with up to 182 days with active treatment), but the Placebo to LYT-100 group will also be analyzed, with a focus on whether there are any meaningful differences in these exploratory efficacy endpoints from Part A compared to Part B.

OLE Safety Population: 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 will be assessed. Other analysis populations may be defined to help inform as to characteristics of the safety and exploratory efficacy profiles.

The primary objective of Part B is to assess safety and tolerability, and thus tabulations will be presented with this goal in mind. Analysis will include data from Part A, so that the slopes of changes over time from Study Day 1 through Study Day 182 can be described.

Table 4: Study Schedule of Assessments for Part A: Double-Blind Placebo-Controlled (Study LYT-100-2020-02)

	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								
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
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
Pregnancy test[8]	X				X	X	X	X	X
Urine Cotinine[9]	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
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.
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.

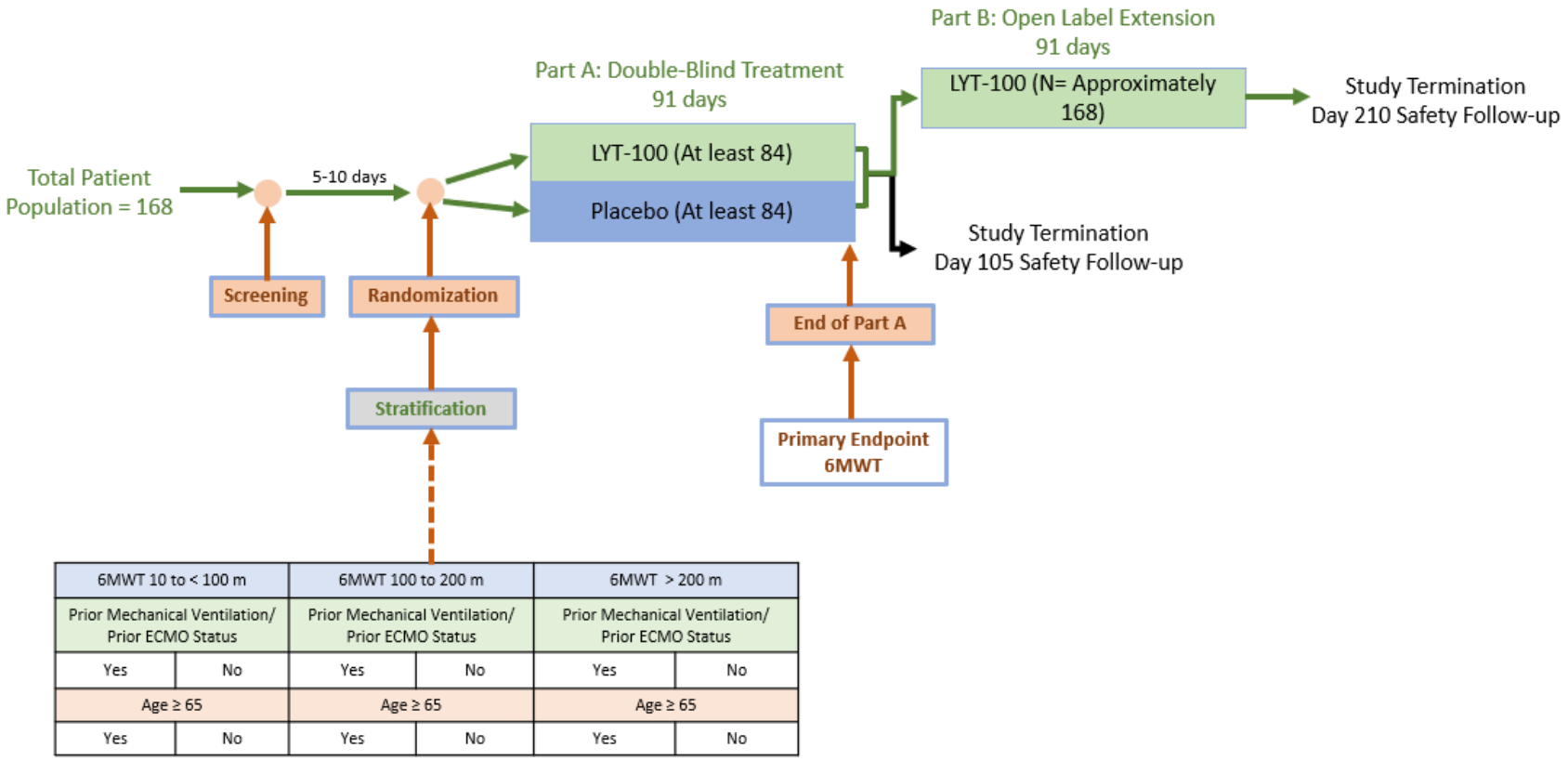
Table 5: Study Schedule of Assessments for Part B: Open Label Extension (Study LYT-100-2020-02)

	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 and/or rehabilitation, and hospitalization status		X	X	X	X	X	X
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
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. Abbreviated symptom directed physical examination will be performed.
3. 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,
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.

Figure 1: Study Design (Study LYT-100-2020-02)



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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
AUC	Area under the curve
AE	Adverse Event
ALB	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BASO	Basophils
BICARB	Bicarbonate
BID	Twice daily
BILI	Total Bilirubin
BILIDIR	Direct Bilirubin
BIPAP	Bilevel positive airway pressure
BMI	Body Mass Index
BP	Blood pressure
bpm	Beats per minute
CA	Calcium
cGMP	Current good manufacturing practice
CI	Confidence interval
CL	Chloride
COVID-19	Coronavirus 2019
CoV	Coronavirus
CPK	Creatine phosphokinase
CPAP	Continuous Positive Airway Pressure
CREAT	Creatinine
CRO	Clinical Research Organization
CRP	C-reactive protein
CRU	Clinical research unit
CSR	Clinical study report
DLCO	Diffusing capacity of the lungs for carbon monoxide
DLCOpp	Diffusing capacity of the lungs for carbon monoxide, percent predicted
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case Report Form
EOS	End of study
ESN	Eosinophils
EMA	European Medicines Agency
FDA	Food and Drug Administration
FEV	Forced Expiratory Capacity
FEV1	Forced Expiratory Capacity inf the first second
FEV1/FVC	Ratio between FEV1 and FVC
FiO2	Fraction of inspired oxygen

Abbreviation or Specialist Term	Explanation
FSH	Follicle-stimulating hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GI	Gastrointestinal
GLOBUL	Globulin
GLU	Glucose
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HCV	Hepatitis C virus
HGB	Hemoglobin
HFNO	High-Flow Nasal Oxygen
HR	Heart rate
HREC	Human Research Ethics Committee
HRQol	Health related quality of life
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
INR	International normalized ratio
IP	Investigational product
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IV	Intravenous
K	Potassium
LDH	Lactate dehydrogenase
LFT	Liver function test
LYM	Lymphocytes
MedDRA®	Medical Dictionary for Regulatory Activities
mBDS	Modified Borg Dyspnoea scale
MERS	Middle east respiratory syndrome coronavirus
MM	Medical Monitor
MV	Mechanical ventilation
n	Number
NA	Sodium
NEUT	Neutrophils
NHMRC	National Health and Medical Research Council
NIV	Non-invasive ventilation
NSAID	Nonsteroidal anti-inflammatory drug
OCCBLD	Occult Blood
OCP	Oral contraceptive pill
OLE	Open label extension
OTC	Over the counter
PD	Pharmacodynamics

Abbreviation or Specialist Term	Explanation
PDGF-β	Platelet-derived growth factor beta
PE	Physical examination
PEF	Peak Exploratory Volume
PFT	Pulmonary Function Test
PHOS	Phosphate
PI	Principal Investigator
PK	Pharmacokinetics
PLAT	Platelets
PO2	Partial pressure of oxygen
PP	Pharmacokinetic population
PR	Pulse rate
PROT	Protein
PT	Preferred term
RT-PCR	Reverse transcription polymerase chain reaction
QoL	Quality of life
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cells
RETI	Reticulocytes
RPSD	Randomization plan and specifications document
RR	Respiration rate
RV	Residual Volume
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe acute respiratory syndrome
SD	Standard deviation
SF-36 v2	36-item quality of life questionnaire; version 2
SGRQ-1	Saint George Respiratory Questionnaire - IPF version
SOC	System organ class
SpO2	Oxygen Saturation
SPGRAV	Specific Gravity
STST	Sit-to Stand test
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TGF-β1	Transforming growth factor beta 1
TID	Three times a day
TLC	Total lung capacity
TNF-α	Tumor necrosis factor alpha
TROP1	Troponin 1
VT	Tidal Volume
U	Urea
UROBIL	Urobilinogen
VEGF	Vascular endothelial growth factor
WBC	Leukocytes (white blood cells)
WHO	World Health Organization
WOCBP	Woman of childbearing potential
6MWT	Six-minute walk test

1. BACKGROUND AND INTRODUCTION

1.1. Introduction

SARS-CoV-2 virus and the resulting respiratory disease, coronavirus disease 2019 (COVID-19), is rapidly spreading around the globe, with an overall case fatality rate of approximately 5% (Wu 2020, Baud 2020, Zhu 2020). As of June 12, 2020, more than seven million and four hundred thousand deaths have been confirmed around the world (Baud 2020). These have been increasing in many countries in an exponential fashion with new regions recently reporting new outbreaks.

The most common presenting symptoms of COVID-19 are cough, fever, and malaise (Guan 2020, Huang 2020, Jiang 2020). In moderate to severe cases worsening pulmonary function, pneumonia, lung damage, and death can ensue (Chen 2020a). Chest radiographs may show evidence of pneumonia which is typically bilateral, while CT scans show ground glass opacity, smooth or irregular, interlobular septal thickening, ill-defined margins, air bronchograms, crazy paving pattern, thickening of the adjacent pleura, nodules, cystic changes, bronchiolectasis, pleural effusion, or lymphadenopathy (Zhao 2020). The presence of significant radiologic abnormalities in the lung are indicative of progression and poor prognosis. COVID-19 survivors have lung fibrosis and reduced pulmonary function. Data from other relevant causes of lung injury informs the potential long-term consequences of COVID-19 (Chesnutt 1997; Ichikado 2012). ARDS and mechanical ventilation—both of which can occur in COVID-19—cause persistent lung fibrosis, pulmonary dysfunction, and diminished of quality of life (Cabrera-Benitez 2014). Similarly, previous viral pneumonias related to SARS-CoV-2 have also caused lung fibrosis and pulmonary dysfunction that continues after the acute infection has resolved. In the case of SARS, these issues have persisted for nearly 15 years (Zhang 2020). COVID-19 post-discharge studies suggest a similar phenomenon, further reinforcing the need for early intervention to prevent lung fibrosis.

While the epidemiology of COVID-19 disease is influenced in part by test sampling practices and demography in different countries, a wide range of severity of illness has been recognized. Cases frequently occur with minimal symptomatology and detection in asymptomatic individuals has been well documented (Wang 2020). On the other hand, severe cases with fulminant multisystem involvement may occur (Hu 2020, Greenland 2020). Among cases admitted to ICUs requiring mechanical ventilation, ARDS occurs in one-third to one-half, and ten percent or more of ICU patients will have complicating acute renal failure (Yang 2020). The median time from ICU admission to death in an early series of 52 patients in China was 7 days (Yang 2020). While older age and the presence of comorbidities portends a worse prognosis, fatal cases have occurred in otherwise young and/or healthy individuals. While too soon to know the long-term effects among survivors, based on experience with other severe viral infections delayed morbidity and mortality, including development of pulmonary fibrosis, is expected (Venkataraman 2017).

The understanding of the pathophysiology of COVID-19 related lung damage is rapidly evolving. Post-mortem samples from patients with COVID-19 show diffuse alveolar damage suggestive of acute respiratory distress syndrome (ARDS), which has previously been identified in patients of related coronaviral infections like SARS and MERS (Xu 2020). ARDS in coronaviral infection likely results from inflammation, fluid accumulation in the lungs, and progressive fibrotic changes that interfere with gas exchange necessary for respiration. Specifically, the initial viral replication generates an immune response, including increases in

pro-inflammatory cytokines like IL-6, TNFα, and IL-1β, which recruit immune cells that cause local tissue damage and fibrosis (Gralinski 2018, Sun 2020). Ultimately, progressive lung damage from this inflammation and tissue re-modelling contributes to respiratory failure and is thought to be the ultimate cause of death in most patients. Preliminary reports from COVID-19 suggest a similar process, with striking increases in pro-inflammatory cytokines like IL-6 and TNF and development of radiological signs of inflammatory and fibrotic lesions in the lungs (Shi 2020).

1.2. Therapeutic Options for COVID-19 (Supportive, Antiviral, and Adjunctive)

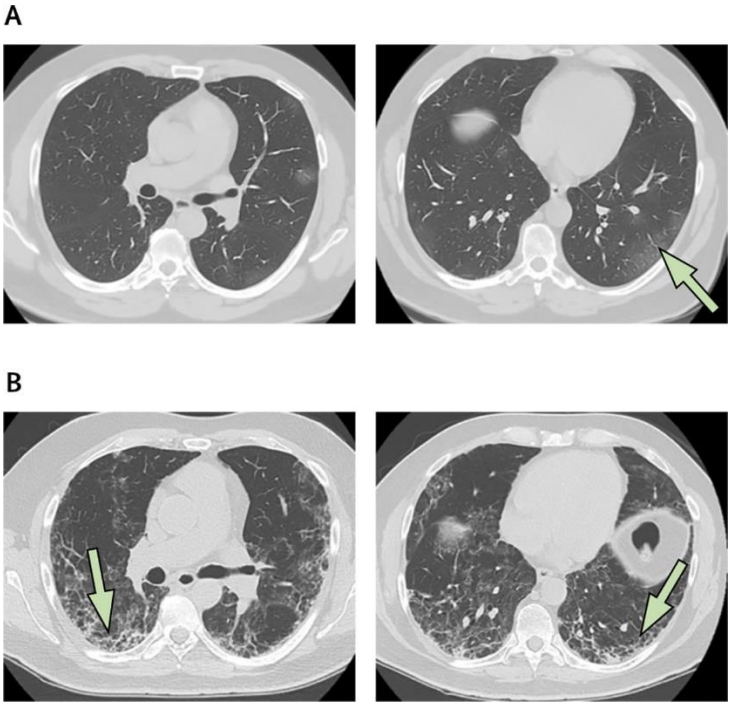
No effective specific treatment for COVID-19 has yet been identified. Although rapidly evolving as clinical experience is gained, principles of therapy are extrapolated from other life-threatening lung disease and include supportive respiratory therapies, anti-viral drugs, and adjunctive treatments. A vast array of anti-viral agents has been proposed and these are under investigation in more than 200 registered clinical trials. These agents include ritonavir boosted lopinavir, arbidol, remdesivir, and favipiravir among others (Cao 2020, Gautret 2020, Dong 2020). However, in general there is limited data for these agents to date with regards to clinically important outcomes. Adjuvant agents are those that do not have direct anti-viral effects per se but manage the complicating immune and other host inflammatory processes. These agents include immunomodulators such as tocilizumab, corticosteroids, convalescent plasma, and immune globulins, all of which are under current investigation (Mehta 2020, Wu 2020, Zhou 2020). The focus of most of these research efforts is early-phase disease, with the hope of preventing progression to critical illness. Few trials are focusing on patients who have progressed to requiring critical care, and even fewer on preventing progression to the fibrotic phase of ARDS, which appears to be when the number of deaths begins to peak.

Coronavirus Disease 2019 (COVID-19) is an acute respiratory disease caused by the coronavirus SARS-CoV-2. In some patients, COVID-19 is marked by rapid respiratory and systemic decline which can lead to death or lasting disabilities in survivors. 20-30% of hospitalized COVID-19 patients presenting with pneumonia will require intensive respiratory support (Chen 2020b; Guan and Zhong 2020). COVID-19 disease severity and mortality are largely driven by inflammatory and vascular destruction of tissue (Conti 2020). The early immune response to SARS-CoV-2 infection can progress to inflammation in both lungs, resulting in consolidation lesions and fibrosis (Li 2020b; Shi 2020). The initial SARS-CoV2 viral replication elicits an increase in pro-inflammatory cytokines like IL-6, TNF-α, TGF-β, and others. In some patients, an uncontrolled inflammatory response (Mehta 2020) results in acute respiratory distress syndrome (ARDS), which can necessitate mechanical ventilation (Wang 2020a).

In survivors, disease and invasive treatment both create fibrotic scarring and the risk of persistently diminished lung function (Chung 2020). Lung scarring can reduce the function of the lung, as reflected by changes in pulmonary function tests. These in turn reflect a patient's difficulties in everyday situations. For example, in interstitial lung disease, reduction in the diffusion capacity predicts oxygen desaturation during exercise (Rizzi 2015). In COVID-19, clinicians are already documenting rapid progression to lung fibrosis (Figure 2). The potential for fibrosis-mediated lung damage and the unprecedented scale of the current pandemic creates an enormous public health challenge: patients who have recovered from the acute symptoms of COVID-19 yet have persistent pulmonary dysfunction. New therapeutic options are needed to

address the underlying inflammation and fibrotic mechanisms that lead to lung scarring and long-term respiratory complications in COVID-19 survivors. Here we propose an approach using LYT-100, a clinical-stage, antifibrotic and anti-inflammatory drug for the treatment of COVID-19 related respiratory complications.

Figure 2: Lung CT of a patient with coronavirus disease 2019.



(A) Images of peripheral mild ground glass opacities in the left lower lobe (arrow). (B) Three weeks later, at the same lung zones, the disease has rapidly progressed, and fibrotic changes are now evident (arrows). Source: 10.1016/S2213-2600(20)30222-8

In COVID-19, acute disease course can be modeled in three stages: 1) an initial response mounted by the immune system to the virus, 2) a potential secondary interferon-driven immune response leading to tissue damage, and 3) a final hyperinflammation in which an inflammatory macrophage response leads to aberrant tissue repair and ultimately fibrosis (Merad and Martin 2020; Siddiqi and Mehra 2020). In earlier stages, the presence of serum cytokines and other inflammatory markers are predictors of disease severity and death (Chen 2020a; Ruan 2020; Zhou 2020) and can be used to predict patients at critical risk (Yan 2020). As the disease progresses, more severe patients have an imbalanced macrophage population in lung tissue tilted toward inflammation (Liao 2020). These infiltrating macrophages carry a gene signature associated with tissue repair and fibrosis. The immune system transitions from repelling the initial insult to repair, but inflammation can lead instead to fibrosis or scarring. A similar phenomenon has been observed in patients with ARDS undergoing mechanical ventilation (Cabrera-Benitez 2014).

The transition from inflammation to fibrosis can be visualized in COVID-19 patients with pneumonia. Early imaging shows inflammation-related opacification, while later tests reveal a

characteristic pattern of lung damage due to interstitial lung remodeling, likely alveolar epithelial cell injury (Shi 2020). Chest X-rays show evidence of pneumonia, while CT scans show ground glass opacity, smooth or irregular, interlobular septal thickening, ill-defined margins, air bronchogram, "crazy-paving" pattern, thickening of the adjacent pleura, nodules, cystic changes, bronchiolectasis, pleural effusion, or lymphadenopathy. In more severe cases of COVID-19, the process of lung fibrosis likely begins early, and histological changes including fibrotic organizing pneumonia are present (Polak 2020). Antemortem and postmortem studies have revealed diffuse alveolar damage (Barton 2020) and microvascular thrombosis that add to the risk of lung fibrosis, if not already present (Polak 2020).

The COVID-19 pandemic has been underway for less than a year, and post-discharge data are rapidly emerging. A high proportion of mild, moderate and severe COVID-19 patients (17-53%) show signs of lung fibrosis already at three weeks post symptom onset (Li 2020a; Ye 2020). Clinician investigators are also reporting lung fibrosis that persists beyond the acute infection, and follow-up CT scans are being considered to evaluate permanent lung scarring (Hosseiny 2020). Of COVID-19 patients with pneumonia, 44% of patients had fibrosis on CT imaging at 9 days post-discharge (Yu 2020). The group of patients with fibrosis had higher CRP and IL-6 during their hospitalization, supporting the link between inflammation in the acute phase and fibrosis during the transition to recovery. Compared to the worst CT scan, the follow-up CT scan fewer involved segments and more intense ground glass opacification. While features like interstitial thickening and crazy paving pattern mostly resolved, other more fibrotic patterns like irregular interface and parenchymal band emerged or persisted.

Fibrosis in the lungs can impair lung capacity, pulmonary function, and gas exchange. COVID-19 patients with lung fibrosis had higher rates of shortness of breath, or dyspnea, than those without (Yu 2020). Emerging data from pulmonary function testing also suggest quantitative changes in COVID-19 survivors who were hospitalized. After discharge, COVID-19 patients had reduced diffusing capacity of the lung for carbon monoxide percent predicted, DLCO%, as well as an abnormal ratio of first forced expiratory volume (FEV1) to forced vital capacity (FVC), FEV1/FVC%. These deficits can improve somewhat with respiratory rehabilitation but do not return to normal (Liu 2020). Another study in COVID-19 that included mild and severe cases found that nearly half (47%) of all patients had impairments in gas exchange, including 30% of mild patients (Mo 2020). These deficits in DLCO were accompanied by less common abnormalities in spirometry, including changes in FVC, FEV1, and FEV1/FVC. The DLCO% reflects the ability of the lungs to conduct gas exchange, and impairment in gas exchange results from reducing the available pulmonary vascular surface and thickening of the alveolar wall. Fibrosis in the alveolar wall can impair the diffusion of oxygen. This can lead to impaired respiratory function and serve as a predictor for deleterious outcomes. For example, in SARS, changes in DLCO% were thought to be more sensitive than high-resolution CT scans, as radiologic changes might lag behind functional changes (Xie 2005).

COVID-19 patients with post-acute impairment in lung function from fibrosis or residual inflammation can have dyspnea and deficits in pulmonary function testing. These deficits can translate into problems with physical functioning, similar to those observed after ARDS or SARS. The 6-minute walk test (6MWT) is a simple to administer and interpret test of functional capacity, including exercise endurance and cardiopulmonary function. The 6MWT has been used to test pulmonary function in fibrotic pneumonias, including IPF interstitial pneumonia (Eaton et al., 2004). The 6MWT has also been used to characterize physical

functioning after viral pneumonias or ARDS, where the expected course is a recovery from an acute event. For example, a meta-analysis of post-SARS complications found a reduced 6MWT distance, which had the ability to improve some improvements up to 3-6 months but plateauing recovery after 6-12 months (Ahmed et al., 2020). Critical illness in general is associated with 6-minute walk test distance (6MWD) decline, but ARDS in particular results in lower 6MWD across a year of follow-up (Parry et al., 2019). Although ARDS patients recover over this year, the recovery is blunted compared to other critically ill patients, and patients with mechanical ventilation have even lower 6MWD values initially and through recovery (Li et al., 2006).

1.2.1. Pirfenidone

Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone; Deskar; Esbriet; AMR-69; S-7701) is an orally active small molecule and the first treatment that has been shown in clinical trials to slow the progression of idiopathic pulmonary fibrosis (IPF), a chronic, progressive, fibrosing interstitial lung disease with unknown etiology (Nathan 2017, King 2014a, King 2014b). It is approved for the treatment of IPF in many countries in Europe, North America, Latin America and Australasia. Pirfenidone has been shown to be generally well tolerated; the most common adverse events (AEs) are gastrointestinal symptoms (nausea, diarrhea, dyspepsia, vomiting), fatigue, rash, and photosensitivity reactions. This novel pyridine compound has anti-inflammatory, antioxidant, and antifibrotic properties. Among many other demonstrated effects, pirfenidone attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as TGF β and platelet-derived growth factor, or PDGF (Schaefer 2011). Pirfenidone has demonstrated activity in nonclinical models for multiple other fibrotic conditions, including those of the lung, kidney and liver (Schaefer 2011, Scriabine 2009).

1.2.2. LYT-100 (Deupirfenidone)

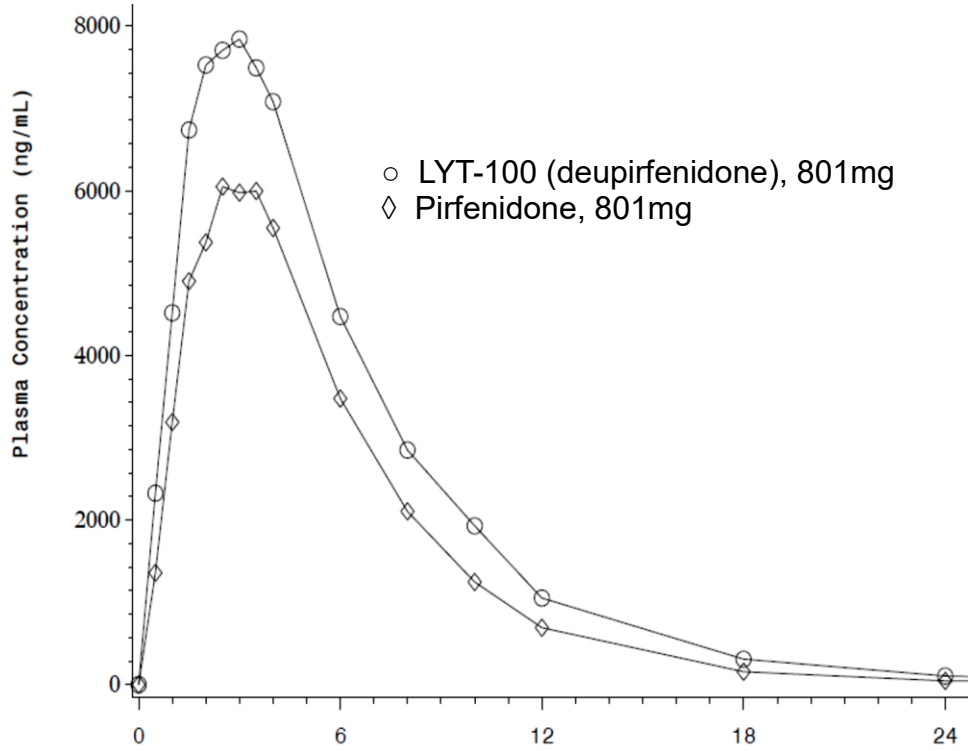
LYT-100 (deupirfenidone) is a selectively deuterated form of pirfenidone. While pirfenidone has established efficacy in treating fibrotic conditions such as IPF, the short half-life of the drug requires that it be dosed at least three times per day. In addition, metabolism of pirfenidone, primarily by CYP1A2, has the potential to lead to interpatient variability in pharmacokinetics, safety, and efficacy. To address the possible limitations of pirfenidone, a selectively deuterated form of pirfenidone (LYT-100) has been developed, which is expected to be metabolized more slowly and with less variability between patients, compared with non-deuterated pirfenidone. LYT-100 therapy may therefore result in improved tolerability and efficacy compared with pirfenidone.

Both animal models and preclinical toxicology studies have been completed with LYT-100 that demonstrate its biologic activity and safety. These were followed by a phase I randomized, double-blind, single-dose crossover study to compare the pharmacokinetics, safety, and tolerability of LYT-100 with pirfenidone in healthy volunteers. Twenty-four subjects received a comparable single 801 mg oral dose of either LYT-100 or pirfenidone in Period 1 and, following washout, crossed over to receive the other treatment in Period 2.

Pharmacokinetic results demonstrated that deuteration of pirfenidone in LYT-100 resulted in an approximately 25% higher C_{max} and 35% higher overall exposure relative to the non-deuterated form, pirfenidone, as shown in Figure 3. Note that, in humans, approximately 80% of an oral

pirfenidone dose is excreted in urine, with the majority of recovered drug material (>95%) excreted as the 5-carboxy-pirfenidone metabolite and less than 1% as unchanged pirfenidone.

Figure 3: LYT-100 increases C_{max} and AUC compared to pirfenidone when administered at an equal dose in healthy volunteers (Study SD-560-C-22)



1.2.3. Pirfenidone and LYT-100 as candidate adjunct therapies for severe COVID-19 disease

Pirfenidone has been suggested for the treatment or prevention of ARDS because of its multiple effects on the underlying inflammatory and fibrotic mechanisms. In rodent models of ARDS, pirfenidone ameliorates pulmonary inflammation and fibrosis induced by LPS, reducing cytokines like IL-1β and fibrotic regulators like TGF-β in the lungs (Corbel 2001). Pre-treatment with pirfenidone also reduces immune cell activation and levels of cytokines and TGF-β (30). Other potential mechanisms include the role of pirfenidone as a scavenger molecule protective against reactive oxygen species in the progression of lung damage. In an oleic-acid induced acute lung injury model, early treatment with pirfenidone reduced the severity of lung damage by physiology and histology (Mei 2005).

Clinicians have reported experiences with pirfenidone in non-viral acute respiratory distress, both in a pre-treatment and treatment regimen. IPF patients who are already receiving pirfenidone treatment have better outcomes measured by survival when admitted into respiratory intensive care units with progression to ARDS, and this pre-treatment with pirfenidone may prevent inflammatory and fibrotic processes and lead to chronic lung damage (Vianello 2019).

Anecdotal case reports and series in patients with post viral pneumonia raise the further possibility of a therapeutic effect.

The known effectiveness of pirfenidone in treatment of pulmonary fibrosis as well as the putative mechanism of action and clinical observations suggest that either pirfenidone or LYT-100 holds significant promise as adjuvant therapies for severe COVID-19 disease. The more favorable PK characteristics of LYT-100 suggest this is the better candidate to take forward into clinical trials in COVID-19 patients.

1.3. Summary of Nonclinical and Clinical Studies with LYT-100

1.3.1. Nonclinical Studies

LYT-100 has been evaluated in limited pharmacology, PK, metabolism and toxicity studies via the oral route (along with a pirfenidone comparator arm), since extensive nonclinical and clinical data are available for pirfenidone (CDER, 2014) including pharmacology; safety pharmacology; absorption, distribution, metabolism and excretion; toxicology studies with durations up to 6 months in rats and 9 months in dogs; reproductive toxicity; genotoxicity; carcinogenicity in mice and rats; and photosafety.

A brief summary of the non-clinical pharmacology, pharmacokinetics and toxicology of LYT-100 is provided in the following sections. More detailed information is provided in the LYT-100 Investigator's Brochure.

1.3.1.1. Pharmacology

In vitro and *in vivo* pharmacology studies conducted with LYT-100 have verified that deuteration does not alter the pharmacodynamics (PD) of pirfenidone with respect to its anti-fibrotic and anti-inflammatory mechanisms of action.

Safety pharmacology studies have not been conducted with LYT-100, as data on a full battery of safety pharmacology studies are available for pirfenidone including assessments of neurological, cardiovascular, respiratory, and gastrointestinal effects.

1.3.1.2. Pharmacokinetics

Single dose absorption and PK of LYT-100 and pirfenidone and the resulting metabolites have been studied in rats, dogs and chimpanzees, as summarized in the Investigator Brochure.

In brief, studies of the *in vitro* hepatic microsomal stability of pirfenidone and LYT-100 in human, monkey, dog, rat, and mouse liver microsomes demonstrated that deuteration improved the metabolic stability of pirfenidone in all species. An *in vitro* comparative mass balance study of pirfenidone and LYT-100 in human and rat liver microsomes and a comparative study of pirfenidone and LYT-100 metabolites in rat, dog, mouse and monkey liver microsomes revealed that metabolism of both compounds was qualitatively similar and showed that deuteration did not introduce novel metabolites, although metabolism of LYT-100 occurred more slowly. No studies have been carried out examining the potential for LYT-100 to interact with human transporter proteins, although pirfenidone does not appear to be a substrate for multiple transporters tested. The major human metabolite of pirfenidone, 5-carboxy pirfenidone, did not inhibit transporters except for OAT1 and OAT3. Metabolite 5-carboxy pirfenidone is a substrate of human breast cancer resistance protein and P-glycoprotein.

1.3.1.3. Toxicology

A comparative dose range finding study of a single dose (male and female rats) or two daily oral doses (female rats) of LYT-100 and pirfenidone demonstrated findings consistent with previous reports on pirfenidone, and supported dose selection for a subsequent 4-/13-week oral toxicity study in rats, as described briefly below.

The objective of the sub-chronic, repeat-dose study was to evaluate the toxicity of LYT-100 (250, 500, and 750 mg/kg/day) or pirfenidone (750 mg/kg and 875 mg/kg) when administered orally once daily for 91 consecutive days to Sprague Dawley rats and to evaluate the potential reversibility of any findings following a 4-week recovery period. In addition, the toxicokinetic characteristics of LYT-100 and pirfenidone were determined.

There were no LYT-100- or pirfenidone-related ophthalmic, group mean body weight changes, clinical pathology or gross pathology findings. Non-adverse LYT-100- and pirfenidone-related changes were observed in clinical observations, body weight gain, feed consumption, organ weights and histopathology. Test article-related organ weight changes included increased mean liver weights in males and females for both drugs. Increased liver weight was correlated histopathologically with centrilobular hepatocyte hypertrophy (believed to be an adaptive change associated with drug metabolizing enzyme induction). These findings were not considered adverse and were correlated with LYT-100 C_{max} of up to 187,476 ng/mL (female) and 135,080 ng/mL (male) on Day 1.

Toxicokinetic analysis revealed that exposure to LYT-100 at a dose of 750 mg/kg was similar to the exposure to the same dose of pirfenidone.

1.3.2. Clinical Studies

The pharmacokinetics, safety, tolerability and food effect of LYT-100 has been tested in two studies in healthy volunteers:

- A Phase 1, randomized, double-blind, single-dose crossover study to compare the PK, safety, and tolerability of LYT-100 with pirfenidone in 24 healthy volunteers.
- A Phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose design to assess the safety, tolerability, PK and food effect profile of multiple doses of LYT-100 in healthy volunteers.

Single 801 mg oral doses of LYT-100 and pirfenidone were well tolerated and had a comparable safety profile. A total of 44 treatment-emergent adverse events (TEAEs) were reported during the study by 14 (58%) of the 24 participants enrolled. Most of these events were mild in severity and there were no events rated as severe. There were no deaths, serious adverse events (SAEs), or AEs leading to withdrawal of study drug reported during the study. The most common AE following either treatment was headache, reported by 21% of participants during each treatment. No significant changes in laboratory parameters, vital signs, or ECGs were observed following either treatment.

The pharmacokinetics of the single 801 mg dose of LYT-100 demonstrated an approximately 25% higher C_{max} and 35% higher overall exposure relative to pirfenidone. The C_{max} and overall exposure were not associated with an appreciable difference in elimination $t_{½}$. Increased systemic exposure of LYT-100 was associated with a corresponding decrease in C_{max} and overall

exposure of the most abundant circulating metabolite (5-carboxy metabolite). (See Figure 3 above).

Five dose levels of LYT-100 ranging from 100 mg BID to 1000 mg BID were assessed in the multiple ascending dose study. While the data remains blinded at this time, the TEAE profile demonstrates that LYT-100 is well tolerated over five days of BID dosing up to 1000 mg (2000 mg daily dose). There were no clinically relevant findings in vital signs, electrocardiograms, biochemistry, hematology, urinalysis, or coagulation parameters. In total, 33 subjects experienced a total of 72 AEs. All AE's were graded as mild, and less than half of these AEs (33 of 72) were considered possibly related to treatment. The most common TEAE was headache (25% of subjects). There have been no SAEs

Pharmacokinetic data for the five dose levels of LYT-100 showed a dose proportional increase in AUC and Cmax for both LYT-100 and the major metabolite, 5-carboxy-pirfenidone. C_{trough} was similar between subjects at each dose level, and no obvious durg accumulation was observed.

In a subsequent cohort, a food effect for LYT-100 was noted on C_{max}, with a 23% lower C_{max} in the presence of food. The AUC0-∞ was similarly decreased by 19% in the presence of food. It should be noted that the food effect for pirfenidone is even more pronounced, with a 49% decrease in the C_{max} in the presence of food. The decrease in the pirfenidone AUC0-∞ is similar to that of LYT-100 in the presence of food (16% and 19%, respectively).

No food effect was observed on either Cmax or AUC0-∞ for the three metabolites measured, and there was no food effect on T_{max} for any analyte. This is different from the effect observed on pirfenidone, where food slows the absorption of the drug, with a median Tmax shift from 0.5 to 3.0 hours.

Additional details for both studies are provided in the Investigator's Brochure.

1.4. Summary of Clinical Studies of Pirfenidone

The safety of pirfenidone has been evaluated in over 1500 healthy volunteers and patients with IPF, including four Phase 3 multicenter, double-blind, placebo-controlled, randomized studies. Three multinational studies (CAPACITY 004 and CAPACITY 006, N=779 patients; ASCEND, N=555 patients) included a total of 1,334 patients (King 2014b, Noble 2011). A study conducted in Japan included 275 patients (Taniguchi 2010).

Following treatment for up to 72 weeks with either pirfenidone 801 mg TID (three times a day), 399 mg TID, or placebo, the majority of patients (98%) in both the CAPACITY 004 and 006 studies (Nobel 2011), experienced at least one treatment-emergent AE. The most common AEs in the pooled pirfenidone 801 mg TID group, with at least a 1.5-times increased incidence relative to placebo, were GI events (nausea, dyspepsia, vomiting, and anorexia), skin-related events (rash, photosensitivity), and dizziness; a dose-response in frequency was noted. Most AEs were assessed as mild to moderate in severity. Serious AEs were reported in 33% of the pooled pirfenidone group and 31% of the pooled placebo group. The incidence of patients discontinuing pirfenidone due to adverse events was low (15% of pooled pirfenidone group; 9% of pooled placebo group).

In the ASCEND study (King 2014b), gastrointestinal and skin-related events were more common in the pirfenidone group than in the placebo group; most AEs were assessed as mild to moderate in severity. The incidence of patients discontinuing pirfenidone due to adverse events was low

(14% of pirfenidone group; 11% of placebo group). Excluding patients with worsening fibrosis, serious AEs were reported in 18.7% of patients in the pirfenidone group and 20.2% of patients in the placebo group.

In the Japanese study (Taniguchi 2010), photosensitivity, anorexia, dizziness and elevated γ-glutamyl-transpeptidase were significantly more common (≥5%; $p<0.05$) in the high-dose (600 mg TID) group than in the placebo group. Skin-related (photosensitivity, asteatotic eczema) and gastrointestinal AEs (abdominal discomfort) as well as decrease in white blood cells were more common in the low-dose (400 mg TID) group than in the placebo group. Photosensitivity was the major AE observed in 51% of the patients in the high-dose group and 53% in low-dose group. Of the patients who developed photosensitivity, most had mild events (70% in the high-dose group and 80% in the low-dose group), and the remainder had moderate events. Most of the AEs resolved after decreasing the pirfenidone dose or temporarily withholding the pirfenidone. The incidence of participants discontinuing pirfenidone due to adverse events was low in both dose groups (18% of high-dose pirfenidone group, 20% of low-dose pirfenidone group, 13% of placebo group).

Overall, pirfenidone was well tolerated in the Phase 3 studies. The most common AEs were gastrointestinal AEs (e.g., nausea, dyspepsia, diarrhea, vomiting), fatigue, anorexia, dizziness, rash and photosensitivity reactions. Serious AEs occurred infrequently and with similar incidence for pirfenidone and placebo participants. AEs leading to discontinuation of study treatment were infrequent and included nausea, rash and photosensitivity reactions.

Further information on clinical experience with LYT-100 and pirfenidone is provided in the Investigator's Brochure.

1.5. Summary of Potential Risks and Benefits of LYT-100

In nonclinical studies to date, no meaningful differences have been observed in the *in vivo* pharmacology and toxicology profiles of LYT-100 when compared with pirfenidone. In humans, LYT-100 is expected to have an AE profile similar to that of pirfenidone when participants achieve comparable systemic exposure. Therefore, AEs associated with the use of pirfenidone are considered expected with use of LYT-100 and prescribing recommendations for pirfenidone are expected to be applicable for LYT-100.

1.6. Study Rationale

Given the high case-fatality, incidence, and therefore expected mortality burden associated with COVID-19 disease, new therapeutic agents are emergently needed. Deupirfenidone is a promising candidate adjunctive therapy that may offer potential survival benefit when added to supportive care and anti-viral therapies. Additionally, while it may attenuate the severe complications acutely, by means of its anti-fibrotic properties it may also hold significant potential for long term functional and survival benefits. A clinical trial is needed before this agent can be added to the therapeutic armamentarium. In addition, critically ill patients have substantially different dosing requirements to patients with normal organ function due to abnormalities in volumes of distribution, fluid shifts, altered metabolism, and risk of adverse reactions (Roberts 2016). While evaluating the effect of deuterated pirfenidone (LYT-100) in pulmonary complications related to COVID-19, the safety and tolerability effects of LYT-100 at

a lowered dose and twice per day dosing regimen will also be monitored closely in this post-acute adult patient population.

This study will be conducted in patients who test positive for COVID-19 and will aim to address issues in post-acute patients with COVID-19 infection. The study will be conducted at multiple study centers in Asia, the United States and Europe. Other regions may be added as the pandemic mandates (i.e., South America). Screening period will not exceed 10 days. Only patients who meet all the applicable inclusion and none of the applicable exclusion criteria per study part will be enrolled.

1.7. Treatment Periods

This study includes screening, study treatment, and post-treatment periods. The treatment periods will be conducted in two parts, A and B.

- Patients will be screened and complete baseline assessments. Randomization (Day 1) occurs on the day following the Baseline Visit/assessment.
- Part A: 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.
- For patients who choose to terminate early, or who complete Part A but do not elect to continue in Part B, a follow-up post-treatment completion visit will occur within 14 days of last day of study treatment ± 3 days.
- Part B: Patients who complete 91 days of treatment in Part A and who are eligible may elect to participate in Part B. All patients will be treated in Part B up to 91 consecutive days, with study assessments on Days 91, 105, 119, 147 and 182.
- For patients who terminate early from Part B, or after completion of Part B, a follow-up post-treatment completion visit will occur within 14 days of last day of study treatment ± 3 days.

The total duration of the study for each participant in Part A is up to 118 days, including screening and baseline of 5 days (up to 10 days to allow for evaluation of all screening assessments), treatment period of 91 days and off-treatment safety follow-up of 14 days including 3-day study window for last visit.

The total duration of the study for each participant who completes both Parts A and B is up to 209 days, including screening and baseline of 5 days (up to 10 days to allow for evaluation of all screening assessments), treatment period of 91 days for Part A, treatment period of 91 days for Part B, and off-treatment safety follow-up of 14 days including a 3-day study window for last visit.

1.8. Participant Population

This study will enroll adults age 18 to 80 diagnosed as post-acute, COVID-19 patients, warranting hospital admission as per investigator's judgement, or previously hospitalized.

For the purposes of this study, "post-acute" is defined as patients who require ***none*** of the following:

- mechanical ventilation (MV);

- extracorporeal membrane oxygenation (ECMO);
- non-invasive ventilation (NIV); (i.e. continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP));
- high-flow nasal oxygen therapy (HFNO); and/or
- other high flow oxygen with FiO2 ≥35% and flow rate ≥ 8 lpm.

Diagnosis of COVID-19 may be done at a central or local laboratory test from any biological material source. The accepted tests include positive result of a validated molecular RT-PCR diagnostic test or SARS-CoV-2 RNA result from a clinical specimen deemed clinically associated with the current episode of illness.

Women of childbearing potential will be included and are subject to contraceptive requirements during the study from Screening until study completion, including the follow up period (see Section 4.6.1). Women of childbearing potential must demonstrate negative pregnancy testing at Screening and prior to study drug administration on Day 1 and be willing to have additional pregnancy tests as required throughout the study. This is in line with regulatory Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, FDA 2006.

1.9. Ethical Principles

This study will be conducted in accordance with the principles of the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and with the NHMRC National Statement on Ethical Conduct in Human Research (updated 2018). The conduct of the study will be in accordance with the ICH Integrated Addendum to E6(R1): Guideline for Good Clinical Practice ICH E6(R2).

This study will be conducted under a protocol reviewed and approved by an IEC / IRB / HREC and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

2. TRIAL OBJECTIVES AND PURPOSE

2.1. Objectives- Part A

This study 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. The objectives are consistent with the study design. Efficacy endpoints are defined in Section 15.7.

COVID-19 respiratory disease is a multi-faceted indication, and thus this clinical study includes a number of objectives (and corresponding endpoints) to adequately describe the effects of study treatment. To that end, there are primary and key secondary objectives that form the basis for study success, while other secondary objectives and exploratory objectives will inform overall conclusions and allow for assessment of a preponderance of evidence as to the benefit of LYT-100 in this population.

2.1.1. Primary Objective

To evaluate the effect of LYT-100 on the change in distance walked on six-minute walk test (6MWT) performed and must conform to the American Thoracic Society/European Respiratory Society Guidelines (Crapo et al 2002).

2.1.2. Key Secondary Objective

To evaluate the effect of 91 days of treatment with LYT-100 compared to placebo on dyspnoea-12

2.1.3. 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 WHO Ordinal Scale for Clinical Improvement
4. Quality of Life 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 QLF assessment
6. Inflammatory, fibrosis and other biomarkers
7. Pulmonary exacerbations, severe and non-severe
8. All-cause rehospitalizations. (Patients who are hospitalized at the time of randomization would need to have been discharged and readmitted for inclusion in this assessment.)
9. Severity of lung lobe(s) involvement, using CT Scan
10. Pulse oximetry
11. Chest X-ray
12. Length of hospital stay
13. All-cause mortality
14. Use of supplemental oxygen from Baseline to end of treatment

2.1.4. 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.

2.1.5. Pharmacokinetic Objective

To evaluate the plasma concentration vs. time data via population pharmacokinetic analysis of LYT-100, and its metabolite(s)

2.2. Objectives- Part B

2.2.1. Primary Objective

To assess the longer-term safety, tolerability, and efficacy of LYT-100 through up to 182 days of treatment.

2.2.2. 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:

- Change in distance walked on six-minute walk test (6MWT) performed and must conform to the American Thoracic Society/European Respiratory Guidelines (Crapo et al 2002)
- Dyspnoea-12
- Saint George Respiratory Questionnaire-I (SGRQ-I)
- The Modified Borg Dyspnoea Scale (mBDS)
- The WHO Ordinal Scale for Clinical Improvement
- Quality of Life assessment as collected using the SF-36 v2, including 8 domains and 2 component scores
- Number of lung segments involved using CT Scan and QLF assessment
- Pulmonary exacerbations, severe and non-severe
- All-cause rehospitalizations
- Severity of lung lobe(s) involvement, using CT Scan
- Pulse oximetry
- Chest X-ray
- Length of hospital stay
- All-cause mortality

- Use of supplemental oxygen from Baseline to end of treatment

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This study is 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-100 750 mg, twice per day (BID) compared to placebo. Part B is an open label extension study for patients who complete Part A.

This study will enroll adults age 18 to 80 diagnosed as post-acute, COVID-19 patients, warranting hospital admission as per investigator's judgement, or previously hospitalized.

For the purposes of this study, "post-acute" is defined as patients who require ***none*** of the following:

- mechanical ventilation (MV);
- extracorporeal membrane oxygenation (ECMO);
- non-invasive ventilation (NIV); (i.e. continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP));
- high-flow nasal oxygen therapy (HFNO)[1]; and/or
- other high flow oxygen with FiO2 ≥35% and flow rates ≥ 8 lpm (i.e. venturi or non-rebreather masks).

Diagnosis of COVID-19 may be done at a central or local laboratory test from any biological material source. The accepted tests include positive result of a validated molecular RT-PCR diagnostic test, RNA or antigen test for or SARS-CoV-2 result from a clinical specimen deemed clinically associated with the current episode of illness.

The study will be performed in approximately 35 clinical sites in Europe, the US, Asia, and South America. Other regions may be added as the pandemic mandates (i.e. India).

After informed consent is obtained, patients will enter a screening phase for 5 days (up to 10 days to allow for evaluation of screening assessments), to determine eligibility. Patients are required to have all screening assessments, including training for the 6-minute walk test, and meet all inclusion/exclusion criteria for the trial prior to randomization. Eligible patients will be randomized to receive LYT-100 or placebo in Part A, in a ratio of 1:1, in conjunction with current standard of care for COVID-19. The randomization will be stratified by 6MWT baseline and other risk factors (see Table 7, below).

Standard of care will be administered as per investigator's medical judgement, based on the severity of the disease, and according to local government and/or institutional guidelines. LYT-100 or placebo will be administered daily for up to 91 days. Patients will start participation in the

[1] High Flow Nasal Oxygen (HFNO) consists of nasal cannula connected to an oxygen flow meter with an air–oxygen gas blender and gas analyzer allowing FIO2 delivery of up to 100%. HFNO with **maximum** gas flow rates typically set between 40 and 60 liter per min, depending on the device, and provides an anatomical oxygen reservoir within the nasopharynx and oropharynx which is transmitted to the lower airways to generate positive end expiratory pressure (PEEP).

study while either hospitalized, or at time of hospital discharge or post-discharge from hospital for COVID-19 respiratory disease.

The timing of randomization is dependent on type of qualifying respiratory support and date of initial confirmed COVID-19 diagnosis.

- Patients who have received any form of supplemental oxygen (except ECMO or MV) must initiate treatment within 90 days of initially confirmed COVID-19 diagnosis by molecular RT-qPCR
- Patients who were previously treated with ECMO or MV must initiate treatment within 132 days from initial confirmed diagnosis of COVID-19. See Table 6, below.

Table 6. Timing of Randomization Relative to COVID-19 Diagnosis and Qualifying Respiratory Support

Qualifying Respiratory Support	Initial Confirmed Diagnosis of COVID-19
Any form of supplementary oxygen other than ECMO or MV	Within 90 days
ECMO or MV	Within 132 days

Treatment assignments will remain blinded to the patient, study staff, and sponsor.

Patients will be seen either on the hospital ward and/or in the ICU during hospital stay or at discharge, or on a rehabilitation ward, an outpatient clinic or at the patient's home post-discharge. Note that for patients who were hospitalized and are discharged during the study, these patients will continue with study visits according to the Schedule of Events for Part A. For all patients, study follow-up visits will occur at Days 14, 28, 56, and 91. Patients in Part A who terminate early or elect to not continue will also have a follow-up visit 14 days, post-completion of study treatment in Part A. (See Figure 1.)

For those patients who qualify for Part B and enter the open label extension, study visits will occur at Days 91, 105, 119, 147 and Day 182. Patients in Part B who terminate early or elect to not continue will also have a follow-up visit 14 days, post-completion of study treatment in Part B. (See Figure 1.)

3.2. Number of Patients

Approximately 168 eligible patients who no longer require mechanical ventilation, extracorporeal membrane oxygenation, non-invasive ventilation(ie continuous positive airway pressure, high-flow nasal oxygen therapy or other high flow oxygen (with FiO2 ≥35% and flow rate ≥ 8 lpm)) at the time of randomization, will be randomized in Part A to receive LYT-100 or placebo, in a ratio of 1:1, with at least 84 patients randomized to LYT-100 and at least 84 patients randomized to placebo. Enrollment in the United States may remain open in order for an additional approximately 30 subjects randomized to Part A to allow for evaluation of U.S. specific COVID Symptoms Assessments and Qualitative Interviews.

Only patients who complete 91 days of treatment in Part A will be eligible for participation in Part B.

3.3. Treatment Assignment and Randomization

The randomization for Part A will be stratified by 6MWT baseline and other risk factors (Table 7).

Table 7: Randomization Stratification Levels (Study LYT-100-2020-02)

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

Patients who elect to continue in Part B will not be re-randomized. Their original stratification for Part A will carry over into Part B.

3.4. Criteria for Study Termination

The study will be completed as planned unless:

- New information or other evaluation regarding the safety of the study medication indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for patients participating in the study. This may be determined by the Sponsor in conjunction with the Medical Monitor, Investigator, DSMB, and/or regulatory authorities.
- The study is terminated by the Sponsor for administrative reasons.

If the Sponsor elects to terminate or suspend the study or the participation of the investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor. The procedure will be followed by the investigational site during the course of termination or study suspension.

3.5. Data Safety Monitoring Board (DSMB)

An independent, unblinded DSMB will assist with oversight of patient safety during both Parts A and B of this study. A Charter will be written to describe the purpose, members, meeting frequency, and data to be reviewed by the DSMB.

The DSMB will meet approximately monthly during enrollment and treatment to review unblinded safety data of all patients.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Participant Inclusion Criteria-Part A

To be eligible for this study, patients must meet ***all*** of the following inclusion criteria:

1. Positive result of a molecular RT-qPCR diagnostic test, RNA or antigen test SARS-CoV-2 result from a clinical specimen deemed clinically associated with the current episode of illness, warranting hospital admission as per investigator's judgement, or previously hospitalized (central and/or local laboratory COVID-19 tests are accepted from any biological material source)
2. Hospitalization for COVID -19 respiratory disease and treated with supplemental oxygen (including MV, ECMO or any other means of oxygen administration) in hospital.

   Please note that admission to a hospital Emergency Department, temporary hospital or any other facilities used to treat acutely ill subjects which would otherwise be admitted to the hospital due to the total number of patients admitted to the facility exceeding capacity and response to the COVID-19 pandemic, or otherwise treated by hospital staff, falls under the category of hospitalization.

   Please also note that hospitalization can be any length of time on at least one calendar day and does not need to be ≥ 24 hours
3. Signed (written, electronic, or oral) consent on an IRB or Ethics Committee approved informed consent from the patient or Legally Authorized Representative prior to any study procedures
4. Male or female, aged ≥18 to ≤80 years of age, inclusively at the time of informed consent
5. Able to perform and willing to comply with all study procedures and requirements
6. Able to bear weight and ambulate a minimum of 10 m distance (use of inhaled oxygen permitted)
7. Randomization day is dependent on type of qualifying respiratory support and date of initial confirmed COVID-19 diagnosis as described in Table 6, above.
8. COVID-19 pneumonia findings on imaging (chest X-ray or CT Scan) with a minimum of two lung lobe involvement
9. Shortness of breath ≥ grade 3 on mBDS dyspnea scale
10. Laboratory parameters (CBC, biochemistry) deemed by the investigator as acceptable and/or not clinically significant to enroll the patient
11. Women of childbearing potential (WOCBP) must be non-pregnant and non-lactating, and must be abstinent from heterosexual intercourse for 90 days following last dose of study medication or agree to use one of the acceptable, highly effective double contraception:
    a. oral, intravaginal, or transdermal combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation
    b. oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
    c. intrauterine device (IUD)

12. Male patients must be surgically sterile (> 30 days since vasectomy with no viable sperm), abstinent, or if engaged in sexual relations with a WOCBP, the participant and his partner must be surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method from screening until study completion, including the follow-up period and an additional 90 days after the last dose of study medication
13. Males will not donate sperm for at least 90 days after the last dose of study medication
14. Partners of male patients and female patients should report pregnancy occurring within 90 days from cessation of study medication
15. Patients can be on other medication (on and off label), apart from the ones specifically outline in the Exclusion Criteria, to treat COVID-19 respiratory disease, that the investigator deems clinically relevant in combination with the study drug
16. Patients can concomitantly receive any standard of care as per investigators' clinical decision; standard of care may encompass any approved medication, on or off label apart from the ones specifically outlined in the exclusion criteria. Concomitant medication may be other medication(s) apart from the ones specifically outlined in the Exclusion Criteria.

4.2. Participant Exclusion Criteria-Part A

To be eligible for this study, patients ***must not meet any*** of the following exclusion criteria:

1. Patients who cannot follow-up with study participation requirements
2. Investigator considers patient is inappropriate to enroll in the trial
3. Pre-existing chronic respiratory condition(s), obstructive or restrictive, for which the patient is actively taking concomitant medication are excluded. Patients with history of Idiopathic Pulmonary Fibrosis (IPF), lung cancer, pulmonary arterial hypertension, other interstitial lung diseases, severe cardiac insufficiency (grade IV) are excluded irrespective of whether they are actively being medicated for those conditions or not.
4. Pre-existing co-morbid conditions preventing outcome assessments, e.g., neurological, medical, orthopedic injury/disability, disease or condition that would prevent ability to transfer and walk for 6 minutes, prior to confirmed COVID-19 diagnosis
5. Co-morbid diagnosis of tuberculosis
6. Unstable angina or myocardial infarction in the last month prior to screening
7. Pre-existing co-morbidity associated with life expectancy less than 1 year
8. Present life expectancy less than 3 days and/or LDH > 360

   Note: *If in the opinion of the Investigator an elevation of LDH > 360 at the time of screening is likely due to persistent effects from COVID-19 infection and expected to improve over time by ruling out all other potential causes or contributory factors for elevated LDH, the Investigator may use clinical judgement to enroll the patient and monitor LDH levels per protocol.
9. Body mass index ≥ 50kg/m^2
10. Resting heart rate of ≥ 120 bpm, systolic blood pressure of > 180 mm Hg and a diastolic blood pressure of > 100 mm Hg and/or or a fall in pulse oximetry oxygen saturation (SpO_2) to <80% upon ambulation

11. Sepsis, septic/hypovolemic/cardiogenic/neurogenic shock
12. Patients on MV, ECMO, NIV, HFNO or other high flow oxygen (FiO2 ≥35% and flow rate ≥ 8 lpm) within the last 72 hours prior to screening
13. History of anaphylactic reaction (particularly reactions to general anesthetic agents); allergic reaction due to any drug which led to significant morbidity; prior allergic reaction to pirfenidone.
14. Known symptoms of dysphagia or known difficulty in swallowing capsules and/or total gastrectomy
15. Patients undergoing dialysis or hemoperfusion, or with a history of dialysis or hemoperfusion, or anticipated to require dialysis or hemoperfusion within 72 hours of screening or severe renal impairment (defined as creatinine clearance rate <30 mL/min) at the time of screening/baseline.
16. Use of any of the following drugs:
    a. Fluvoxamine, enoxacin, ciprofloxacin
    b. Treatment with steroids under institutional protocols and guidelines to manage COVID-19 pneumonia/respiratory symptoms is allowed. Use of steroids off-label to treat non-COVID-19 related conditions is not allowed.
    c. Any Investigational Agents (i.e., non-approved or nonauthorized drugs), with the exception of those used for COVID-19 respiratory diseases that the investigator deems clinically relevant in combination with the study drug, as described below:

       i. Allowed agents
          - Patients who had received prior investigational agents for COVID-19 but are no longer taking those drugs are allowed.
          - Inhaled corticosteroids are allowed.
          - Patients that received prior convalescent plasma are allowed; however, concomitant convalescent plasma is excluded.

       ii. Excluded agents
          - Patients on concomitant experimental anti-viral, anti-fibrotic or anti-inflammatory therapies are excluded.
          - Any investigational agent not explicitly on this list should be reviewed by the medical monitor prior to initiating therapy or enrolling participant.
    d. Other inhibitors of CYP1A2 (including but not limited to methoxsalen or mexiletine)
    e. Inducers of CYP1A2 (such as phenytoin), CYP2C9 or 2C19 (including but not limited to carbamazepine or rifampin)
    f. Drugs associated with ***substantial risk for prolongation of the QTc interval*** (including but not limited to moxifloxacin, quinidine, procainamide, amiodarone, sotalol). Note that QTc prolongation is not an all / nothing drug effect, and specifically the administration drugs such as hydroxychloroquine do not preclude participation in this trial but does mandate measurement of the QTc every 6 hours until deemed necessary in accordance with investigator judgement

g. Vaccination with a live vaccine is not permitted during the period from 4 weeks prior to screening to 4 weeks after the last dose
h. Tobacco and nicotine products and/ or a positive a cotinine test at screening
i. Pirfenidone or nintedanib

17. Any other reason that, in the opinion of the Investigator, might interfere with the evaluation required by the study
18. For AST ≥2.5xULN, ALT ≥2.5xULN and/or total bilirubin >1.5xULN (in the absence of history of Gilbert syndrome and/or the absence of alkaline phosphatase ≥2xULN or clinical evidence of cholestasis), or severe hepatic impairment
19. Patients requiring surgery due to an acute onset condition prior to randomization.
20. Patients experiencing tachypnea. For the purposes of this study, tachypnea is defined as resting respiratory rate ≥ 25 per minute.

4.3. Participant Inclusion Criteria-Part B

1. Patients must have completed Part A of the study, through Day 91 of treatment.
2. In the opinion of the Investigator, the patient is a good candidate for continued treatment with LYT-100.

4.4. Participant Exclusion Criteria- Part B

Patients ***must not meet any*** of the exclusion criteria as listed for Part A.

4.5. Participant Withdrawal Criteria

Patients may withdraw their consent to participate in the study at any time. If a participant withdraws consent, the date and reason for consent withdrawal should be documented. Participant data will be included in the analysis up to the date of the withdrawal of consent.

Apart from withdrawal of consent, reasons for early termination of individual patients can include:

- Protocol deviations or participant non-compliance (must be specified on the appropriate electronic Case Report Form [eCRF]);
- Related serious or severe AEs;
- Administrative decision by the Investigator or the Sponsor;
- Death;
- Other (must be specified).

Patients will be encouraged to return to the clinical research unit to complete all necessary assessments and until the Investigator deems that it is safe to be discharged. Wherever possible, the tests and evaluations, including those listed for the final visit, should be performed for all patients who discontinue treatment prior to the completion of the study. For patients who discontinue treatment due to a related adverse event per investigator's decision, these patients should remain in the study after being discontinued from treatment and be followed for all

scheduled assessments. Subjects will only be removed from the study due to withdrawal of consent or loss of follow up.

4.6. Concomitant Medications and Other Therapies

The following drugs are not permitted during the study, and they must be discontinued at least 28 days or 10 half-lives (whichever is the longer) prior to study drug dosing:

- Fluvoxamine, enoxacin, ciprofloxacin;
- Other inhibitors of CYP1A2 (including but not limited to methoxsalen or mexiletine);
- Inducers of CYP1A2 (such as phenytoin), CYP2C9 or 2C19 (including but not limited to carbamazepine or rifampin);
- Any drug associated with prolongation of the QTc interval (including but not limited to moxifloxacin, quinidine, procainamide, amiodarone, sotalol). Note that QTc prolongation is not an all / nothing drug effect, and specifically the administration drugs such as hydroxychloroquine do not preclude participation in this trial but does mandate measurement of the QTc every 6 hours until deemed necessary in accordance with investigator judgement.

Vaccination with a live vaccine is not permitted during the period from 4 weeks prior to screening to 4 weeks after the last dose.

Immunosuppressants or other immune-modifying drugs are not permitted, except for corticosteroids at the discretion of the Investigator as part of standard of care for COVID-19 respiratory pathology, and remdesivir where it is provided as part of standard of care for the treatment of COVID-19. Dexamethasone or other corticosteroids may be administered under institutional SOC to manage COVID-19 pneumonia/respiratory symptoms. If no institutional protocols or guidelines are in place, dexamethasone may be administered up to a total daily dose of 6 mg either by oral or intravenous routes for up to 10 days, as supported by the recent RECOVERY trial (Horby et al 2020), or until hospital discharge, whichever comes first. If the use of corticosteroids is extended, then they may be used for up to 3 weeks concomitantly with LYT-100. In that period use of corticosteroids should be limited to prednisone (up to 1 mg/kg/day), methylprednisolone (up to 1/mg/kg/day), or hydrocortisone (up to 160 mg). Inhaled corticosteroids are allowed. Any significantly immune-suppressing or anti-inflammatory drug used off-label, including experimental therapies as part of a clinical trial must be discontinued at least 3 months prior to screening or 5 half- lives, whichever is longer.

Use of concomitant pirfenidone and/or nintedanib is excluded.

Prior and/ or concurrent physical and/ or pulmonary rehabilitation is allowed and will be documented in the eCRF.

4.6.1. Contraception

Estrogen preparations (e.g., oestradiol, ethinyloestradiol or gestodene) may be used throughout the trial for contraception, hormone replacement therapy, or menopausal replacement therapy.

Acceptable, highly effective double contraception is defined as a condom AND one other form of the following:

- Established hormonal contraception (oral contraceptive pills [OCPs], long-acting implantable hormones, injectable hormones);
- A vaginal ring or an intrauterine device (IUD);
- Documented evidence of surgical sterilization at least 6 months prior to Screening (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy for women or vasectomy for men [with appropriate post -vasectomy documentation of the absence of sperm in semen] provided the male partner is a sole partner).

Women not of childbearing potential must be postmenopausal for ≥12 months. Postmenopausal status will be confirmed through testing of follicle-stimulating hormone levels (FSH) ≥ 40 IU/mL at Screening for amenorrhoeic female participants. Females who are abstinent from heterosexual intercourse will also be eligible.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered highly effective methods of birth control. Participant complete abstinence for the duration of the study and for 1 month after the last study treatment is acceptable.

Female patients who are in same sex relationships are not required to use contraception.

Males must be surgically sterile (>30 days since vasectomy with no viable sperm), abstinent, or if engaged in sexual relations with a WOCBP, the participant and his partner must be surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method from Screening until study completion, including the follow-up period and an additional 90 days after the last dose of study medication. Acceptable methods of contraception include the use of condoms and the use of an effective contraceptive for the female partner that includes: OCPs, long-acting implantable hormones, injectable -hormones, a vaginal ring or an IUD. Patients with same sex partners (abstinence from penile-vaginal intercourse) are eligible when this is their preferred and usual lifestyle.

5. TREATMENT OF PATIENTS

5.1. Description of Study Drug

The LYT-100 drug product and matching placebo are presented as follows:

- LYT-100, 250 mg and matching placebo – Size 1, Swedish orange opaque, hard-gelatin capsules.

The capsules are packaged in high-density polyethylene (HDPE) bottles and a white, polypropylene screw cap with an induction sealed aluminum inner seal. The IPs should be stored at a controlled room temperature of 15°C -25°C [59°F to 77°F]. Capsule count *per bottle* is 102 capsules, which is equivalent to a 14-day supply + 3 additional days of 750 mg twice per day. Three additional days of drug are provided in each bottle in the event of lost capsules or use of allowable 3-day study window extension. Two bottles will be provided *per single kit* to supply study medication for 28 days and includes a total of 6 extra days.

Patients will take LYT-100 study medication, or placebo, orally and preferably with food (solid or nutritional supplements, whenever possible), with approximately 10 to 12 hours between the two daily doses. Doses may be adjusted according to safety and tolerability to avoid toxicity.

Note that, for the first 3 days of treatment, the dose of LYT-100 will be 500 mg BID (or 2 capsules of matching placebo). Day 4 through Day 91 the dose of LYT-100 will be 750 mg BID (or 3 capsules of matching placebo). If dosing titration is not well tolerated, doses may be adjusted according to safety and tolerability to avoid toxicity by adjusting to lower doses in response to patient safety and tolerability issues. Adjustments may be made as follows: reduction to 1 capsule, BID X 2 days (may be longer if needed), 2 capsules, BID X 2 days (may be longer if needed), 3 capsules, BID, thereafter.

Table 8 provides the dosing regimens to be used during the 91-day treatment period.

Table 8: Dosing Regimens for Days 1 through 3 and Thereafter (Study LYT-100-2020-02)

Part A: Double-Blind		**Part B: Open Label Extension**	
Days 1 through 3	**Days 4 through 91**	**Days 91 through 93**	**Days 94 through 182**
[1]LYT-100 **500 mg BID** or matching Placebo[2] x 3 days	[1]LYT-100 **750 mg BID** or matching Placebo[2] x 88 days	[1]LYT-100 **500 mg BID**[2] x 3 days	[1]LYT-100 **750 mg BID**[2] x 88 days

[1] Patients will take study medication orally and preferably with food (solid or nutritional supplements, whenever possible), with approximately 10 to 12 hours between the two daily doses.
[2] Doses may be adjusted according to safety and tolerability to avoid toxicity by adjusting to lower doses in response to patient safety and tolerability issues, including: Skin reactions to sunlight; significant changes to liver enzymes, and/or gastrointestinal (GI) side effects. See Section 5.2 for details.

In Part B, in order to maintain the study blind in Part A, all patients will be treated with the same dosing regimen shown in Table 8. All patients entering Part B will receive LYT-100 500 mg BID for three days, followed by LYT-100 750 mg BID thereafter.

5.2. Dose Adjustment

5.2.1. Gastrointestinal Events

Patients who experience intolerance to therapy due to gastrointestinal side effects should be reminded to take LYT-100 with food. If gastrointestinal events do not improve, or worsen in severity, dose reduction may be considered per Investigator judgment.

5.2.2. Photosensitivity Reaction or Rash

Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded to avoid exposure to the sun and to use a sunblock daily when going outdoors even if they will not be exposed to direct sunlight. Dose reduction may be considered per Investigator judgment.

5.2.3. Other

If dosing titration is not well tolerated or the dose needs to be reduced due to toxicity, adjustments to dosing may be made as follows:

- Days 1-3: reduction from 2 capsules, BID, to 1 capsule, BID, x 2 days (may be longer if needed);Days 4-91: reduction from 3 capsules, BID, to 2 capsules, BID x 2 days (may be longer if needed); and if reduction from 750 mg to 500 mg of Investigational Product BID is not sufficient to address difficulties with tolerability or toxicity, further reduction to 250 mg BID is allowed.
- Days 4-91: following dose reduction return to 3 capsules, BID, at Investigator's discretion.

5.3. Prior and Concomitant Medications

5.3.1. Prior Medications

All medications, including OTC medications, vitamins, and herbal supplements, taken during the 30 days prior to the first study drug administration will be recorded and reviewed by the Investigator to determine whether the participant is suitable for inclusion in the study.

Please note: For any subject who receives a COVID-19 vaccination, the type (e.g., Pfizer, Moderna, Janssen/ J&J) of vaccine and date(s) of administration must be reported as a prior medication.

5.3.2. Concomitant Medications

All medications, including OTC medications, vitamins, and herbal supplements, taken by patients during the course of the study will be recorded in the eCRF and coded using the most current World Health Organization (WHO) drug dictionary. Prior and concomitant medications will be listed by participant and summarized by anatomical therapeutic chemical (ATC) and Preferred Term (PT).

Please note: For any subject who receives a COVID-19 vaccination, the type (e.g., Pfizer, Moderna, Janssen/ J&J) of vaccine and date(s) of administration must be reported as a concomitant medication.

5.4. Treatment Compliance

Patients will be provided with enough LYT-100 study medication bottles to cover the prescribed daily dose until their next study visit. The number of capsules dispensed at each study visit will be recorded in the patient's source documents. Patients will be instructed to retain and return all emptied and non-emptied bottles to each study visit. Study drug capsule counts returned at each visit will be totaled and recorded in the patient's source document record. The difference in the number of capsules dispensed and number of capsules returned will be reconciled against the anticipated number capsules administered to account for all dosing intervals since the last study visit to determine study drug medication compliance.

A phone application to provide medication reminders will be used to assist the patient with medication adherence during the study treatment phase of the trial.

5.5. Blinding- Part A Only

Blinding procedures for Part A of the study will be described in detail in a separate randomization plan and specifications document.

The Sponsor, Investigator, Medical Monitor, study personnel, and patients are not to make any effort to determine which study drug therapy is being received.

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 participant'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 may break the study code for that participant only using the Interactive Web Response 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 adverse event), must be documented in the participant's medical records. The study monitor should be promptly informed of premature unblinding.

As soon as possible, and without revealing the participant's study treatment assignment (unless important to the safety of patients remaining in the study), the Investigator must notify the Sponsor by telephone and then in writing if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to unblinding.

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

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Supplies

The Sponsor will supply the study drug to the investigational site. The study drug provided for this study was manufactured under current Good Manufacturing Practices (cGMP) and will be suitable for human use.

6.2. Study Drug Packaging and Labelling

The Sponsor is responsible for the preparation and labelling and providing details of batch numbers, safety, and stability data.

The study drug is labelled in accordance with local regulatory requirements and will be shipped at a temperature of 15°C-25°C [59°F to 77°F].

6.3. Study Drug Storage

Upon receipt, the study drug must be stored at 15°C-25°C [59°F to 77°F].

The Investigator will be fully responsible for the security, accessibility, and storage of the study drug while it is at the investigational facility.

6.4. Study Drug Preparation

Procedures relating to study drug preparation and dispensing are outlined in the Pharmacy Manual.

6.5. Administration

The Investigator is responsible for the education of study staff and patients as to the correct administration of the study drug.

6.6. Study Drug Accountability

A record will be maintained by the investigational site that will account for all dispensing and return of any used and unused study drug. At the end of the study, the study drug will be reconciled, and a copy of the record given to the study monitor.

6.7. Study Drug Handling and Disposal

On completion of the study, any surplus study drug supplies will be destroyed upon receipt of written approval from the Sponsor and evidence of destruction supplied to the study monitor. If no supplies remain, this will be documented in the dispensing record.

7. STUDY SCHEDULE

Please see Table 4 for Schedule of Assessments-Part A, and Table 5 for Schedule of Assessments- Part B. Where possible, assessments should be conducted in order of least invasive to most invasive. Study manuals will be described for certain endpoints (e.g., 6MWT, Chest x-ray, CT Scans) that will define how procedures will be performed. The sections below describe the general procedures to be performed each day.

In general, patient-reported quality of life scales (e.g., SF-36 v2, mBDS, SGRQ-I) should be performed at the beginning of each visit, with the remaining procedures (e.g., blood collections, 6-minute walk tests) performed after.

Throughout patient participation, patients should be warned to avoid exposure to sunlight and avoid sunlamps. They should be encouraged to wear sunscreen and protective clothing on a daily basis to avoid potential for skin reactions.

Throughout the conduct of the study, patients and study staff should take appropriate precautions to mitigate or minimize infection risks. This includes the use of personal protective equipment (masks, gowns, gloves) and hand washing, as appropriate for the situation.

7.1. Screening and Baseline

7.1.1. Screening- Visit 1 (Day -10 to Day -2)

Over five days (up to 10 days to allow for evaluation of all screening assessments), patients will be screened and complete baseline assessments. Patients are required to have all screening assessments, including training for the 6-minute walk test, and meet all inclusion/exclusion criteria for the trial prior to randomization.

At Screening, patients will be provided with full information concerning details of the study assessments and procedures. They will also be provided with an informed consent form (ICF). Prior to being asked to sign the consent form, patients will be given time to review study information and ask any questions.

After the Informed Consent Form is obtained (written, electronic, or oral), screening assessments will be carried out as follows:

- Confirmation of a positive RT-PCR diagnostic test / RNA or antigen SARS-CoV-2
  Note: COVID positive diagnostic test results of tests conducted prior to ICF should be used even if this date predates the screening period and does not need to be repeated as part of screening.
- Eligibility - inclusion/exclusion criteria
- Recording of demographic information
- Pertinent Medical History
- Modified Borg Dyspnoea Scale (mBDS) - conduct this at beginning of visit
- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral,

contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)

- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Chest x-ray
- Confirmation of prior requirement for NIV, ECMO, MV, HFNO, and/or other supplemental oxygen during hospitalization, with current need for NIV, ECMO, MV, HFNO, and/or other high flow oxygen (FiO2 ≥ 35% and flow rate ≥ 8 lpm) excluding the subject
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis, urine cotinine, and FSH for post-menopausal females only)
- Urine pregnancy test (WOCBP only). (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
- Brief training for the 6 Minute Walk Test at the end of the screening visit. Following verbal instructions from a qualified staff member, the patient will practice the 6 MWT for approximately 2 minutes
- Pre-treatment adverse events
- Prior and concomitant medications - include medications 30 days prior to screening

Note: AEs and changes in concomitant medications will be recorded from the time of informed consent. They will be recorded, and 'pre-treatment' will be noted for AEs and concomitant medications taken prior to first dose of study medication.

Please also note the following clarifications with regards to screening activities

- When evaluating eligibility, if screening lab values are exclusionary, and the Investigator's judgement believes the values are likely due to persistent effects from the COVID infection and are expected to improve over time (e.g., liver function tests), these labs may be re-drawn during the screening period.
- Rescreening of subjects is allowed with prior approval from the Sponsor.
- Screening labs collected as part of standard of care are acceptable to be used for eligibility assessments and do not need to be repeated as long as they are collected within the screening window.
- The protocol allowed screening window, of up to 10 days, is to allow for all study procedures to be performed and evaluated prior to baseline

7.1.2. Baseline-Visit 2 (Day -1 to Day 1)

The following assessments will be carried out over the course of 1 to 2 calendar days:

- Modified Borg Dyspnoea Scale - collect this at beginning of visit

- Abbreviated symptom-directed physical examination
- Measurement of height and weight, and calculation of Body Mass Index
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- Charlson Comorbidity Index
- Chest CT Scan (If a CT scan without contrast was obtained within 7 days of Baseline, and there have been no significant changes in signs and symptoms of respiratory complications in those 7 days, then an additional CT scan will not need to be collected. However, the prior CT scan must have been done without contrast.)
- Dyspnoea-12 - collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2) - collect this at beginning of visit
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Biomarkers - time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)
- Pre-treatment adverse events
- Concomitant medications.
- 6-minute Walk Test – Two tests must be conducted between Day -1 and Day 1, and the longest distance recorded for the baseline measure. There should be a minimum of 30 minutes between the two tests if both are conducted on Day -1. The second test can also be performed on Day 1.
  - Patients who complete both baseline 6MWTs on Day -1 may be randomized on the same day using the study EDC system, following completion of all Day -1 assessments and confirmation that the patient meets all eligibility criteria. Following randomization, the subject should take their first dose of study medication while onsite (preferably with food, solid or nutritional supplements, whenever possible). Vital signs (BP, HR, RR, SpO2, Temperature) and Modified Borg (Dyspnea) Scale are repeated post study medication administration and recorded in the Study Treatment Day 1 eCRF.
  - Patients who complete the first baseline 6MWT on Day -1 and the second 6MWT on Day 1 will be randomized on Day 1 using the study EDC system following confirmation that the patient meets all eligibility criteria. Following randomization, the subject should take their first dose of study medication while onsite (preferably with food, solid or nutritional supplements, whenever possible).

7.2. Study Treatment Period- Part A

The study treatment period includes visits at Day 1, 14, 28, 56, and 91.

7.2.1. Day 1-Visit 3 (First Dose of Study Medication)

- Patients will be randomized prior to dosing on Day 1 (see Section 3.3).
- 6-minute walk test for baseline measure (only if a second test was not conducted on Day -1; see above); prior to study medication administration
- Study Drug Administration/Accountability - doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- After dosing, the following should be performed:
- Post-treatment vital signs (blood pressure, heart rate, respiratory rate, SpO_2 after participant has been resting in a supine position for at least 5 minutes and prior to blood draws), oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- Post-treatment Modified Borg Dyspnoea Scale
- Post-treatment Adverse Events
- Post-treatment Concomitant medications

7.2.2. Day 14- Visit 4

Assessments will be conducted as follows:

- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Abbreviated symptom-directed physical examination
- Weight and Body Mass Index calculation
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Dyspnoea-12 - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Biomarkers - time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)
- Study Drug Administration/Accountability - doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- PK blood sample- collect the time of the last dose taken prior to blood collection; one PK sample is collected at visit and the corresponding time interval must be recorded as one of the following: 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 interval within the same patient at future visits.

- Adverse Events / Mortality
- Concomitant medications.
- 6-minute Walk Test - conduct this at end of visit

7.2.3. Day 28- Visit 5

Assessments will be conducted as follows:

- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Weight and calculation of Body Mass Index
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- Dyspnoea-12 - collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2) - collect this at beginning of visit
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Urine Cotinine
- Biomarkers - time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)
- Study Drug Administration/Accountability - doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- PK blood sample- collect the time of the last dose taken prior to blood collection; one PK sample is collected at visit and the corresponding time interval must be recorded as one of the following: 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 interval within the same patient at future visits.
- Adverse Events / Mortality
- Concomitant medications.
- 6-minute Walk Test - conduct this at end of visit

7.2.4. Day 56- Visit 6

Assessments will be conducted as follows:

- Modified Borg Dyspnoea Scale - collect this at beginning of visit

- Weight and calculation of Body Mass Index
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- Dyspnoea-12 - collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) - collect this at beginning of visit
- SF-36 (v2) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Biomarkers - time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)
- Study Drug Administration/Accountability - doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- PK blood sample- collect the time of the last dose taken prior to blood collection; one PK sample is collected at visit and the corresponding time interval must be recorded as one of the following: 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 interval within the same patient at future visits.
- Adverse Events / Mortality
- Concomitant medications.
- 6-minute Walk Test - conduct this at end of visit

7.2.5. Day 91- Visit 7A

Assessments will be conducted as follows:

- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Charlson Comorbidity Index
- Chest CT scan
- Chest x-ray
- Dyspnoea-12 - collect this at beginning of visit

- St. George's Respiratory Questionnaire-I (SGRQ-I) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2) - collect this at beginning of visit
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis, urine cotinine)
- Urine pregnancy test (WOCBP only)
- Biomarkers - time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)
- Study Drug Administration/Accountability – Collect any remaining study medication from Part A.
- PK blood sample- collect the time of the last dose taken prior to blood collection; one PK sample is collected at visit and the corresponding time interval must be recorded as one of the following: 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 interval within the same patient at future visits.
- Adverse Event / Mortality
- Concomitant medications.
- 6-minute Walk Test - conduct this at end of visit

7.2.6. Early Termination (Visit ET)

An early termination visit must be conducted if the patients discontinues study medication for any reason. It should be conducted within 2 weeks of the last dose of study medication. All patients should be strongly encouraged to continue with all remaining study visits even though they are no longer on study medication.

- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Chest x-ray
- Dyspnoea-12 - collect this at beginning of visit
- SF-36 (v2) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status

- Biomarkers - time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- PK blood sample-collect the time of the last dose taken prior to blood collection; one PK sample is collected at visit and the corresponding time interval must be recorded as one of the following: 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 interval within the same patient.
- Study Drug Administration/Accountability – Collect any remaining study medication from Part A.
- Adverse Events / Mortality
- Concomitant medications.
- 6-minute Walk Test - conduct this at end of visit

Please note: Vital status, overall survival status should be collected at day 91 days (91 days from the first dosing date) for any subjects that prematurely discontinue from the study.

7.3. Post-Treatment- Day 105 End of Study- Part A (Visit 8A)

End of study is when the last visit and last assessment(s) are conducted. Assessments will be conducted as follows:

- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Chest x-ray
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Adverse Events / Mortality
- Concomitant medications

Note: While “a follow-up post-treatment visit will occur within 14-day of last day of study treatment”, if a patient discontinues study drug prematurely but continues to follow study procedures the 14-day post treatment visit is not required as long as they have been off study medication for at least 14 days at the time of their last in-clinic visit.

7.4. Study Treatment Period- Part B

The study treatment period includes visits at Day 91, 105, 119, 147, and 182.

7.4.1. Day 91; Visit 7B (First Day of Open Label Study Period)

Day 91 (Visit 7A) of Part A is the same day as the Day 91 (Visit 7B) of Part B; i.e. both visits are conducted on the same day. Dosing for Part B should be performed AFTER all assessments below are performed.

- After completion of all procedures for Visit 7A of Part A, Visit 7B is used to confirm eligibility for participating in Part B. A new ICF will be signed by each patient participating in Part B.
- Study Drug Administration/Accountability – Distribute Open Label study drug to patients. All patients entering Part B will take LYT-100 500 mg BID for three Days, and then LYT-100 750 mg BID thereafter. Doses are intended to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals.
  - All patients who are continuing into Part B should take their final dose of Part A medication in the morning, prior to returning any remaining supplies from Part A.
  - The evening dose for all patients should be taken from Part B supplies.

7.4.2. Day 105- Visit 8B

This visit corresponds to the 14-day post-treatment safety follow-up visit (Visit 8A) for patients from Part A who do NOT choose to continue in Part B. Assessments will be conducted as follows:

- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Dyspnoea-12 - collect this at beginning of visit
- Study Drug Administration/Accountability - doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- Adverse Events / Mortality
- Concomitant medications.
- 6-minute Walk Test - conduct this at end of visit

7.4.3. Day 119- Visit 9

Assessments will be conducted as follows:

- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 6-minute Walk Test - conduct this at end of visit
- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Dyspnoea-12 - collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2) - collect this at beginning of visit
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Urine Cotinine
- Study Drug Administration/Accountability - doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- Adverse Events / Mortality
- Concomitant medications.

7.4.4. Day 147- Visit 10

Assessments will be conducted as follows:

- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 6-minute Walk Test - conduct this at end of visit
- Modified Borg Dyspnoea Scale - collect this at beginning of visit

Dyspnoea-12 - collect this at beginning of visit

- St. George's Respiratory Questionnaire-I (SGRQ-I) - collect this at beginning of visit
- SF-36 (v2) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status

- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Study Drug Administration/Accountability - doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- Adverse Events / Mortality
- Concomitant medications.

7.4.5. Day 182- Visit 11

Assessments will be conducted as follows:

- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Charlson Comorbidity Index
- Chest CT scan
- Chest x-ray
- 6-minute Walk Test - conduct this at end of visit
- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Dyspnoea-12 - collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2) - collect this at beginning of visit
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis, urine cotinine)
- Urine pregnancy test (WOCBP only)
- Study Drug Administration/Accountability – Collect any remaining study medication from Part B
- Adverse Event / Mortality
- Concomitant medications

7.4.6. Early Termination (Visit ET)

An early termination visit must be conducted if a patient discontinues study medication for any reason. It should be conducted within 2 weeks of the last dose of study medication. All patients who terminate early should be strongly encouraged to continue with all remaining study visits even though they are no longer on study medication.

- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Chest x-ray
- 6-minute Walk Test - conduct this at end of visit
- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Dyspnoea-12 - collect this at beginning of visit
- SF-36 (v2) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Adverse Events / Mortality
- Concomitant medications.

7.5. Post-Treatment: Day 196 End of Study- Part B (Visit 12)

End of study is when the last visit and last assessment(s) is conducted. Assessments will be conducted as follows:

- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Chest x-ray
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Adverse Events / Mortality
- Concomitant medications

Note: While “a follow-up post-treatment visit will occur within 14-day of last day of study treatment”, if a patient discontinues study drug prematurely but continues to follow study procedures the 14-day post treatment visit is not required as long as they have been off study medication for at least 14 days at the time of their last in-clinic visit.

8. EFFICACY ASSESSMENTS AND ENDPOINTS

All efficacy endpoints will be derived at each protocol-schedule time point for which they are collected, with analysis performed (e.g., change from baseline) for each time point. A detailed description of the collection of assessments will be documented in an assessment collection and specification manual.

8.1. 6-Minute Walk Test (6MWT)

The 6-minute walk test (6MWT) is the primary efficacy endpoint. All patients will complete a 6MWT test according to the Schedule of Assessments and aligned with the American Thoracic Society/European Respiratory Society Guidelines (Crapo et al 2002) and according to the 6MWT study procedural manual. 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. The 6MWT has been used to measure physical functioning following ARDS in the setting of post-mechanical ventilation as well as recovery from other viral pneumonias (Hsieh et al., 2018).

This is a self-paced test. Patients choose their own intensity of exercise and may stop and rest during the test (Crapo et al 2002). This test should be scheduled as the last assessment collected at study visits, e.g., after vital signs, daily pulse oximetry reading, dyspnea scales, QOL and other blood collection assessments. Oxygen supplementation is allowed during the test; however, the subject must use the same device and oxygen flow rate at each 6MWT assessment. The patient's dyspnea and fatigue are also assessed prior to the 6MWT and end of test. Patients who are unable to complete (or walk) due to disease severity will be assigned a distance of 0 (zero). (Table 14).

Reproducibility and reliability of the 6MWT is critically important to the study. While not specified in the ATS guidelines as a relative contraindication, if a subject is feeling acutely ill for any reason, including after receiving a COVID-19 vaccine, visit should be rescheduled to ensure that they are not performing the 6MWT during an acute illness.
Changes from baseline in the 6MWT distance will of primary interest.

8.2. Dyspnoea-12 (D-12)

D-12 is an instrument used to assess the effect of dyspnea in interstitial lung disease and COPD, and is used in reference to the patient's breathlessness experience "these days", i.e., current at baseline and at follow-up visits, and unlike other dyspnea tools, it has no reference to activity. One of the primary complaints of post-acute respiratory complications of COVID-19 is dyspnea (Carfi et al., 2020) The tool has 12 descriptor items ranging from none (0), mild (1), moderate (2) or severe (3). An overall score of breathlessness severity is provided that encompasses seven physical items and five affective items. Table 17 provides a sample of the scale. Total scores range from 1 to 36 whereby the higher score correlates with greater severity.

8.3. Other Secondary or Exploratory Efficacy

Other secondary efficacy endpoints are intended to be supportive to the primary and key secondary efficacy endpoints.

8.3.1. St. George Respiratory Questionnaire-I (SGRQ-I)

The SGRQ-I is an idiopathic pulmonary fibrosis disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with interstitial lung disease. There are 34 self-completed items with 3 domain component scores (Symptoms, Activities, and Impacts). Higher scores indicate more limitations. Table 16 provides a sample of the scale.

Changes from baseline in the component scores of the SGRQ-I will be assessed as secondary efficacy endpoint. Further, a responder analysis will be performed in which the proportion of patients experiencing an increase of ≥4 units (vs < 4 units) will be assessed.

8.3.2. Modified Borg Dyspnoea Scale (mBDS)

The mBDS is a measure of dyspnea. The mBDS is a self-administered unidimensional assessment tool that analyzes breathlessness under exertion. Table 13 provides a sample of the scale. One of the primary complaints of post-acute respiratory complications of COVID-19 is dyspnea (Carfi et al., 2020). The primary assessment will be the changes from baseline.

8.3.3. WHO Ordinal Scale for Clinical Improvement

The WHO Ordinal Scale for Clinical Improvement (Table 10) will be assessed for changes over time of ≥ 1 point as well as a responder analysis (improvement by at least 1 point and also for at least 2 points) . 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); (3) Hospitalized Mild Disease (Hospitalized, no oxygen therapy); (4) Oxygen by mask or nasal prongs; (5) Hospitalized Severe Disease (Non-invasive ventilation or high-flow oxygen); (6) Intubation and mechanical ventilation; (7) Mechanical Ventilation plus additional organ support (i.e. extracorporeal life support (ECLS), continuous renal replacement therapy (CRRT), vasopressors); (8) Dead (Death)

8.3.4. SF-36 (v2)

The SF-36 v2 (Table 18) is a self-administered questionnaire containing 36 items that measures health on functional status, well-being, and overall evaluation of health in 8 domains. It requires 5-10 minutes to complete and uses scaled, ordinal responses (e.g., All of the time, Most of the time, A good bit of the time, etc.) (Brazier 1992). The domain scores and component summaries are as follows:

- SF-36 v2 scaled domains
    - Vitality
    - Physical functioning
    - Bodily pain
    - General health perception
    - Physical role functioning
    - Emotional role functioning
    - Social role functioning

    - Mental health
- SF-36 v2 Mental Component Summary
- SF-36 v2 Physical Component Summary

Changes in the standardized component scores and domain scores will be calculated.

8.3.5. Chest CT Scan

Qualitative assessments will be collected from chest CT Scans without contrast. The proportion of patients with "normal" CT scan images will be defined in a responder analysis. Patients with pre-existing chest pathology pre-COVID-19 should be considered "normal" for those pre-existing items/findings. Chest CT scans will be performed according to the CT Scan manual. Lung lobe involvement will be assessed for each of five lobes via central read with the terms defined by the Fleischner Society (Hansell et al 2018).

The CT images will be assessed for the presence of ground-glass opacity (hazy areas of increased attenuation without obscuration of the underlying vasculature), consolidation (homogeneous opacification with obscuration of the underlying vasculature), reticular pattern (consisting of either coarse linear or curvilinear opacity or fine subpleural reticulation without substantial ground-glass opacity), mixed pattern (combination of consolidation, ground-glass opacity, and reticular opacity in the presence of architectural distortion), and honeycomb pattern (clustered cystic air spaces). The distribution of abnormalities will be classified as predominantly subpleural (involving mainly the peripheral one-third of the lung), central (involving mainly the central two-third of the lung), or diffuse.

CT scans may also be analyzed with semi-Quantitative Lung Fibrosis (QLF) and computer-Aided Diagnosis (CAD) QLF Scores (Kim et al, 2010). Table 11 shows how each of the five lobes will be scored; the total score for each of the four 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 in this total score will be assessed.

A responder analyses will be performed, in which the proportion of patients showing ground glass opacities, fibrosis, consolidation, reticulation/bronchiectasis, and other radiographic abnormality improvement(s) by determining at least a 2-point score improvement for each abnormality across the five lobes (range 0-25) will be derived. 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 12. Shifts in these characteristics over the course of treatment will be of interest.

8.3.6. Biomarkers (Part A only)

Changes in biomarkers will be assessed, including C-reactive protein (CRP), lymphocyte count, d-dimer, cardiac troponin, ferritin, lactate dehydrogenase (LDH), IL-6, TGF-β1, TNF-α, IL-1β, PDGF- β, GCSF, and VEGF (see Section 9.1.2).

8.3.7. Chest X-Ray

Qualitative assessments will be collected from chest X-rays. The proportion of patients with "normal" chest X-ray will be defined in a responder analysis. Patients with pre-existing chest pathology pre-COVID-19 should be considered "normal" for those pre-existing items/findings.

8.3.8. Pulse Oximetry (SpO_2)

In patients requiring oxygen supplementation, ensure oxygen is administered at the prescribed rate for a minimum of 15 minutes prior to SpO_2 assessment. Changes over time in SpO2 will be assessed.

8.3.9. Length of Hospital Stay and Mortality

Total number of days of hospital stay will be assessed. Date of (original) admission, date of (original) discharge and rehospitalization(s) and subsequent discharge(s) will be collected. Methods for handling hospitalization days and patients who die or discontinue treatment prematurely will be addressed in the SAP. Time to all-cause mortality will be assessed if the data permit.

8.3.10. Other clinical outcomes

Other clinical outcomes will be assessed, as follows:

- The percentage of patients who develop severe pulmonary exacerbations
- The percentage of patients who develop non-severe pulmonary exacerbations
- Percentage of patients who experience rehospitalization for any cause, while on treatment.
- Use of supplemental oxygen from Baseline to end of treatment.

9. PHARMACOKINETIC AND BIOMARKER ASSESSMENTS- Part A Only

9.1. Blood Collection

Blood samples (for PK and biomarker analysis) and urine samples (for screening and safety evaluations) will be obtained at the time points delineated in the Schedule of Assessments (see Table 4).

The actual collection time of each sample must be recorded in the source data documentation, on the collection tube, and in the eCRF. Please see footnotes to Schedules of Assessments for permitted time windows for sample collection.

All blood samples will be collected in accordance with the site's standard operating procedures and will be processed according to instructions provided in the Laboratory Manual at the time points delineated in the Schedule of Assessments.

The total volumes of blood to be taken from each participant are detailed in Appendix 2, Table 19.

The Sponsor will supply complete written instructions for handling, processing, storage, and shipping of samples prior to study initiation.

9.1.1. Pharmacokinetics

Blood samples for population pharmacokinetics will be collected on Study Days 14, 28, 56, and 91. When pharmacokinetic levels are collected, the last dose of study medication taken prior to blood collection will be recorded, including the date and the time. Each participant will provide up to a minimum of 1 sample at each timepoint in reference to dosing: Pre-dose (Hour 0), 1 to <2 h, 2 to <4 h, 4 to <8 h, 8 to 12 h. Sites should avoid on-treatment duplications of the same timepoint interval within the same patient. The following is an example of blood collection options:

- Day 14 (**4 to <8 h** sample collected)
- Day 28 (**Pre-dose** (Hour 0) sample collected; *patient should bring medication with them to the visit*)
- Day 56 (**1 to <2 h**, **2 to <4 h sample**, *can collect two timepoints at a visit if patient plans to be at the site for extended time*)
- Day 91 (**8 to 12 h**, *again patient should bring medication with them to the visit if next dose is due shortly after the blood collection*).

For trough or later timepoint intervals such as 8 to 12 hours, the patient should be instructed to hold their next study medication dose and bring it with them to their study visit(s) to accommodate the longer time intervals required from their last dose taken.

9.1.2. Biomarkers

Blood samples for biomarkers will be collected at Baseline and on Study Days 14, 28, 56, 91 and at Day 105/Early Termination/End of Study. 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.

The following biomarkers will be assessed: C-reactive protein (CRP), lymphocyte count, d- dimer, cardiac troponin, ferritin, lactate dehydrogenase (LDH), IL-6, TGF-β1, TNF-α, IL-1β, PDGF- β, GCSF and VEGF. Additional biomarkers may be explored at a future time following the completion of this study.

Analyses of biomarkers will include changes from baseline.

9.2. Sample Analysis

Plasma PK and biomarker sample analysis will be performed using appropriately validated procedures and methods as outlined in the Laboratory Manual.

10. ASSESSMENT OF SAFETY

This study includes many efficacy parameters that can sometimes be considered safety outcomes. Because these parameters (e.g., chest x-ray and CT scan) are included as efficacy objectives, these assessments are described in the Efficacy Assessments and Endpoints (Section 8). Further, 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. An independent, unblinded DSMB will assist with oversight of patient safety during this study by reviewing unblinded safety data on a monthly basis during enrollment and treatment (Section 3.5).

10.1. Safety Parameters

Study procedures should be completed as delineated in the Schedule of Assessments (Table 4). However, if a participant is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the Sponsor's Medical Monitor or appropriate designee. Any unscheduled procedures required for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures.

10.1.1. Demographic/Pertinent Medical History

Pertinent medical history (including alcohol, smoking status, and prior requirement for MV, ECMO, NIV, HFNO or other high flow oxygen (FiO2 ≥35% and flow rate ≥ 8 lpm), age (calculated), sex, ethnicity, and race will be recorded at Screening.

The Charlson Comorbidity Index (CCI) predicts 10-year survival in patients with multiple comorbidities (Charlson et al 1987).

10.1.2. Vital Signs

Vital signs (tympanic, contactless, or oral temperature, blood pressure, heart rate, respiratory rate, SpO2) will be measured at the time points specified in the study schedules with patients resting for at least 5 minutes in a supine position prior to assessment. When the time of vital signs measurement coincides with a blood draw, the vital signs will be taken before the scheduled blood draw where possible while ensuring the blood draw is within the window specified in the protocol.

Additional vital signs may be performed at other times if deemed necessary.

10.1.3. Weight and Height

Body height (centimeters) and body weight (kilograms) will be measured at the time points delineated in the study schedule and will be used to calculate BMI by dividing the participant's body weight in kilograms by the participant's height in meters squared (kg/m^2). Body weight and height will be obtained with the participant's shoes and jacket or coat removed.

10.1.4. Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician, qualified nurse practitioner or physician's assistant as per the PI at the time points specified in the study schedules.

- Complete physical examinations include general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes.
- Symptom-directed physical examinations include head, ears, eyes, nose, throat, chest (heart, lungs), abdomen, skin, musculoskeletal, and lymph nodes and any pertinent system based on any prior findings.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

10.1.5. Electrocardiogram

A 12-lead ECG will be taken at the time points delineated in the study schedules. Additional ECG monitoring may be performed at other times if deemed necessary.

ECGs will be performed prior to vital signs with patients in a supine position. Patients must be in this position for at least 5 minutes before the ECG is taken.

All ECG tracings will be reviewed by the PI or designee.

When the time of ECG monitoring coincides with a blood draw, the ECG will be taken before the scheduled blood draw while ensuring the blood draw is within the window specified in the protocol.

10.1.6. Laboratory Assessments

Safety laboratory tests (hematology, biochemistry, coagulation, urinalysis and urine cotinine) will be performed at the time points specified in the study schedules. Additional clinical laboratory tests may be performed at other times if deemed necessary based on the participant's clinical condition.

Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory.

A blood sample will be taken from each participant for hematology, coagulation and biochemistry analyses at the time points delineated in the study schedules.

10.1.6.1. Hematology

Hematology parameters to be tested are:

- Hemoglobin (HGB)
- Hematocrit (HCT)
- Erythrocytes (RBC)
- Platelets (PLAT)
- Leukocytes with differential (including Eosinophils (ESN), Neutrophils (NEUT), Basophils (BASO), Lymphocytes (LYM - collected with biomarkers and at screening) and Reticulocytes (RETI)

10.1.6.2. Biochemistry

Biochemistry parameters to be tested are:

- C-reactive protein (CRP - collected with biomarkers and at screening)
- Urea (U)
- Creatinine (CREAT)
- Total Bilirubin (BILI) and Direct Bilirubin (BILIDIR)
- BUN (blood urea nitrogen)
- 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 – collection with biomarkers and at screening in PartA; collected and tested as part of blood chemistries in Part B)
- Ferritin (collected with biomarkers and at screening)
- Transforming Growth Factor Beta 1 (TGF-β1)
- Tumor necrosis factor alpha (TNF-α)
- Interleukin 6 (IL-6)
- Interleukin 1 beta (IL-1β)
- Platelet-derived growth factor- β (PDGF- β)
- Granulocyte colony-stimulating factor (GCSF)
- Vascular endothelial growth factor (VEGF)

10.1.6.3. Coagulation

Coagulation parameters to be tested are:

- INR
- Prothrombin time
- APTT
- d-dimer (collected with biomarkers)

10.1.6.4. Urinalysis

A urinalysis test (dipstick) will be performed for each participant. Urinary analysis will be performed at Screening and other times according to the study schedule. If abnormality is noted for protein, blood, nitrite or leukocyte esterase (and at the discretion of the Investigator) a microscopic examination of RBC, WBC, bacteria and casts will be performed.

Dipstick urinalysis (chemical) parameters to be tested are:

- pH (PH)
- Specific Gravity (SPGRAV)
- Protein (PROT)
- Glucose (GLUC)
- Ketones (KETONES)
- Total Bilirubin (BILI)
- Occult Blood (OCCBLD)
- Nitrite (NITRITE)
- Urobilinogen (UROBIL)
- Leukocytes (WBC)

10.1.6.5. Urine Cotinine

A urine cotinine test will be performed at screening, Days 28 and 91 (Visits 5 and 7A) in Part A, and Days 119 and 182 (Visits 9 and 11) in Part B, to measure the amount of cotinine in urine for patients exposed to nicotine.

10.1.6.6. Pregnancy and Follicle-Stimulating Testing

A pregnancy test will be performed at the screening visit and periodically during the trial in WOCBP only. 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.

Postmenopausal status will be confirmed through testing of follicle-stimulating hormone levels (FSH) ≥ 40 IU/mL at Screening for amenorrhoeic female patients. Females who are abstinent from heterosexual intercourse will also be eligible.

11. ADVERSE AND SERIOUS ADVERSE EVENTS

Safety and tolerability will be assessed throughout the study by monitoring AEs, physical examination, vital signs, 12-lead ECGs, clinical laboratory values (hematology panel, multiphasic chemistry panel and urinalysis), and concomitant treatments.

In this study, AEs will be reported for all patients from the time of consent until the completion of the Follow-up/EOS visit. AEs reported prior to the first dose will be denoted as pre-treatment. SAEs will be reported for all patients (enrolled and not enrolled) from the time of consent. AEs reported from the time of consent to confinement on Day -1 will be recorded as pre-treatment AEs.

Treatment emergent- AEs are defined as an AE that occurs following first dose of study medication and will be evaluated from the first administration of study drug until the EOS visit. AEs that are ongoing at the final onsite visit will be marked as Not Recovered/Not Resolved on the AE eCRF page (see Section 11.1.4).

All spontaneously volunteered and enquired for, as well as observed AEs, will be recorded in the participant's medical records and the eCRF.

11.1. Definition of Adverse Events

An AE is any event, side-effect, or other untoward medical occurrence that occurs in conjunction with the use of a medicinal product in humans, whether or not considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavorable 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 or not considered related to the medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition;
- New conditions detected or diagnosed after study drug administration that occur during the reporting periods, even though it may have been present prior to the start of the study;
- Signs, symptoms, or the clinical sequelae of a suspected interaction;
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or concomitant medications (overdose per se will not be reported as an AE/SAE).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure should be reported as an AE if it meets the criteria of an AE;
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital);
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

If there is evidence of an AE through report or observation, the Investigator or designee will evaluate further and record the following information:

- Time of onset and resolution
- Severity
- Causality/relation to study treatment
- Action taken regarding study drug
- Outcome

11.1.1. Severity of an Adverse Event

Severity (intensity) of AEs will be graded by the Investigator as one of:

- **Mild (Grade 1):** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate (Grade 2):** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe (Grade 3):** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- **Life-threatening (Grade 4):** A type of AE that places the participant at immediate risk of death.
- **Death (Grade 5):** Events that result in death.

11.1.2. Causal Relationship of an Adverse Event

The Investigator will assess the relationship between study drug and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to study drug will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug should be considered and investigated, if appropriate. The following definitions are general guidelines to help assign grade of attribution:

- **Not related:** The event is clearly related to other factors such as the participant's environment or clinical state, therapeutic interventions or concomitant drugs administered to the participant. This is especially so when an event occurs prior to the commencement of treatment with the study drug.
- **Possible:** The event follows a reasonable temporal sequence from the time of study drug administration or follows a known response to the study drug but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.

- **Probable:** The event follows a reasonable temporal sequence from the time of study drug administration and follows a known response to the study drug and cannot be reasonably explained by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.

11.1.3. Action Taken with Investigational Products

Should the Investigator need to alter the administration of the study drug from the procedure described in the protocol due to the well-being and safety of the participant then the action taken will be recorded on the AE eCRF page, as one of the following options:

- Dose Reduced
- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Other

11.1.3.1. Action Taken with Investigational Product: Liver Function Testing

When ALT and/ or AST are elevated, discontinuation of confounding concomitant medications should be considered. Please see Table 9 for a list of such medications.

Table 9. Medications to be Used with Caution in Combination with LYT-100

Amiodarone	Disulfiram	Levofloxacin	Probenecid
Amitriptyline	Duloxetine	Ketoconazole	Propafenone
Aprepitant	Entacapone	Methoxsalen	Quinidine
Bupropion	Ethylestradiol	Metronidazole	Sertraline
Chloramphenicol	Fenofibrate	Mexiletine	Sildenafil
Cinacalcet	Fluconazole	Modafinil	Terbinafine
Citalopram	Fluoxetine	Moxifloxacin	Topiramate
Clozapine	Fluvastatin	Nicotine	Voriconazole
Diclofenac	Insulin	Omeprazole Paroxetine	Zafirlukast
Diltiazem	Lansoprazole		

Note: Table 9 is not an exhaustive list but rather a list of commonly known concomitant medications that are known to cause elevations in Liver Function Tests and as such clinical judgment should be used to consider discontinuation of a concomitant medication in the event of LFT elevation.

When ALT and/or AST are elevated >3 x ULN with elevation of bilirubin: Study drug should be discontinued and not restarted.

When ALT and/or AST are elevated ≤3 x ULN without elevation of bilirubin (Grade 1) and in the absence of symptoms: Study drug may be continued at current dose with monitoring of LFTs weekly.

When ALT and/or AST are elevated >3 - ≤5 x ULN without elevation of bilirubin (Grade 2) and in the absence of symptoms: Study drug should be held, LFTs should be checked weekly until resolution of elevations, and then patient can be re-started on study drug at 250 mg BID

with at least weekly monitoring of LFTs for an appropriate period of time. If LFTs are within normal limits within 2 weeks of holding study medication, restarting study drug at full dose can be considered.

When ALT and/or AST are elevated >5 x ULN without elevation of bilirubin and in the absence of symptoms: Study drug should be discontinued and not restarted.

11.1.4. Outcome

Outcome of an AE will be recorded on the AE eCRF as follows:

- Recovered/Resolved
- Recovering/Resolving
- Recovered/Resolved with Sequelae
- Not Recovered/Not Resolving/Ongoing, up to a 30-day follow-up period for treatment-related AEs
- Fatal
- Unknown (or participant lost to follow-up after 4 attempts at contact over a period of 30 days).

11.2. Definition of Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up-), and at any dose of the study drug (active or placebo), that fulfils one or more of the following:

- Results in death.
- It is immediately life-threatening.
- It requires in-patient hospitalization or prolongation of existing hospitalization.
- It results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or birth defect.
- It is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above.

Important medical events that may not be one of the above may be considered an SAE by the Investigator when, based upon appropriate medical judgment, they are considered clinically significant and may jeopardize the participant, or may require medical or surgical intervention to prevent one of the outcomes listed above.

An AE is considered “life-threatening” if, in the opinion of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

11.2.1. Notification of a Serious Adverse Event

All SAEs regardless of relationship to the IP during the period starting from the time of informed consent through the Follow-up Visit, will be recorded in the eCRF. Once the Investigator becomes aware of an SAE, he/she must report the SAE to the Clinical Research Organization (CRO) Safety Department within 24 h of knowledge of the event.

A SAE report must include a full description of the event including the below parameters (include any protocol specific requirements):

- Diagnosis or description of event
- Onset date
- Severity assessment
- Causal relationship to the IP
- Assessment of seriousness of the event
- Corrective treatment administered for the SAE
- Action taken related to IP include the following: dose interruption, dose delay, dose reduction, or IP discontinuation
- Outcome of event and end date

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to CRO Safety Department as soon as information is available.

As further information regarding the SAE becomes available, such follow-up information should be documented on a new SAE report form, marked as a follow-up report, and sent electronically. Paper reporting will be used as back-up for reporting if EDC is unavailable.

Withdrawal from the study in the event of an SAE and therapeutic measures taken shall be at the discretion of the Investigator. A full explanation for the discontinuation from the study should be made in the participant's medical records and in the eCRF. All patients who discontinue study medication should be strongly encouraged to continue with all remaining study visits for follow-up on key safety and efficacy assessments.

All SAEs that occur within 30 days after the last dose of study drug should be recorded and reported as noted previously.

11.3. Clinical Laboratory Abnormalities and other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., biochemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECG and vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed **clinically significant** or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (and recorded as an SAE if they meet the criteria of being serious) as previously described. Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are included as AEs (and SAEs if serious).

The Investigator should exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the participant and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions yet be of a magnitude to require glucose administration to prevent such sequelae.

11.4. Recording Adverse Events

AEs spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded in accordance with the Investigator's normal clinical practice and on the AE page of the eCRF during the study at the investigational site.

However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs and SAEs will be collected from the time of consent until the end of the study. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the participant to discontinue the study. AEs that occur during the study must be documented in the participant's medical record, on the AE CRF and on the SAE report form. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE form, preferably with baseline values and copies of laboratory reports.

In addition, if the abnormal assessment meets the criteria for being serious, the SAE form must also be completed. A diagnosis, if known, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE/SAE page. If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded. Additional information of reporting SAEs will be provided in the Safety Management Plan.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2. An AE of severe intensity may not be considered serious.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the participant was discontinued from the study. All pregnancies should be reported within 24 hours of awareness (including pregnancies of female partners of male patients). Paper reporting will be used for documenting pregnancies and should be followed until outcome is known. Outcome of pregnancy should also be reported on a follow-up pregnancy report form.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

11.5. Reporting Serious Adverse Events

Any SAEs considered possibly or probably related to the study drug and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to the Sponsor and/or the CRO Safety Department within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE eCRF forms/pages, verify the accuracy of the information recorded on the SAE eCRF forms/pages with the corresponding source documents, and send a copy to the Sponsor and/or CRO Safety Department. Paper SAE reporting may be used as a back-up for electronic SAE reporting system when the system is not available.

Additional follow-up information, if required or available, should all be emailed to the Sponsor and/or CRO Safety Department within 24 hours of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IEC / IRB / HREC of all SAEs that occur at their site in accordance with the IEC / IRB / HREC SAE reporting policy. The Investigator will also be notified of all unexpected, serious, drug-related events that occur during the clinical trial. The investigational site is responsible for notifying its IEC / IRB / HREC of these additional SAEs.

11.6. Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs that are deemed related, possibly related or probably related to the study drug must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant dies or is lost to follow-up. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a participant dies during participation in the study or during a recognized follow-up period, the Sponsor should be provided with a copy of any post-mortem findings, including histopathology.

12. STUDY COMPLETION AND DISCONTINUATION

12.1. Participant Discontinuation

In accordance with applicable regulations, a participant has the right to discontinue participation in the study, at any time and for any reason, without prejudice to his future medical care.

If a participant discontinues study medication because of an AE, the Investigator must arrange for the participant to have appropriate follow-up care until the AE is resolved or has stabilized. Unresolved AEs will be followed until the last scheduled Follow-up visit or until the PI and Medical Monitor determine that further follow-up is no longer indicated. In addition to AEs, other reasons for removal of patients from the study might include, but are not limited to, withdrawal of consent, administrative decision by the Investigator or the Sponsor, protocol deviation, or participant noncompliance.

If a participant asks or decides to discontinue participation in the study, all efforts will be made to complete and report the observations, especially the listed primary and secondary objectives, as thoroughly as possible up to the date of withdrawal. The primary reason for withdrawal will be identified and recorded on the appropriate eCRF, along with the date of withdrawal. For patients who discontinue treatment due to a related adverse event per investigator's decision, these patients should remain in the study after being discontinued from treatment and be followed for all scheduled assessments. Subjects will only be removed from the study due to withdrawal of consent or loss of follow up.

12.2. Definition of the End of the Trial

The end of study for each participant is defined as the date of the last subject's last visit.

13. TERMINATION OR SUSPENSION OF THE STUDY

The Sponsor, Investigator and the IEC / IRB / HREC reserve the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in the eCRFs. The Investigator should notify the relevant IEC / IRB / HREC in writing of the study's completion or early discontinuation.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Monitoring will include both remote and on-site visits when this is permitted in line with national and local guidelines during the COVID-19 pandemic. An initiation visit will be performed at each site before the first subject is included. Initiation visits may be conducted remotely. Monitoring visits and contact will occur at regular intervals thereafter. A close-out visit will be performed after the database lock for Part B and resolution of all pending queries and follow-up of ongoing AEs/SAEs. Full details of the study monitoring procedures to be employed in this trial will be detailed in the Monitoring Plan.

Before an investigational site can enter a participant into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

The Sponsor will appoint a Contract Research Organization to manage and monitor the study so as to assure them of the adequate conduct of the study and to act as the contact with the investigational site. A study monitor will be identified and will be responsible for liaison with, and support of, the investigational site.

The study monitors and the regulatory authority inspectors are responsible for contacting and visiting the investigative site for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs, essential documentation, and other pertinent data) provided that participant confidentiality is respected

During the study, the monitor will have regular contacts with the investigational site for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study drug accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the CRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IEC / IRB / HREC.

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

14.2. Data Management

All data will be recorded in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF information is to be filled in by site staff as per the eCRF Completion Guidelines. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be subject to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

All eCRFs should be maintained on the system with details of any changes logged accordingly.

Two independent database locks are planned for this study: the first for the double-blind, randomized treatment portion (Part A) and the second for the open label extension (Part B).

14.3. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IEC / IRB / HREC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

15. STATISTICAL METHODS

This is a Phase 2 study in patients with active COVID-19 disease and thus has potential to be an important treatment during the current pandemic. The study is rigorously designed to collect a wide range of endpoints to assess the benefits (and risks) of treatment with LYT-100 in this population. Thus, there are several endpoints identified. Testing of primary and key secondary efficacy endpoints will be performed and will not be controlled for multiplicity. Other secondary efficacy endpoints will be tested and used to provide support as to the preponderance of evidence of the benefit/risk profile of LYT-100, with magnitude of effects, consistency of direction of effect (i.e., beneficial or harmful), and significance of inferential tests all taken into account to draw final conclusions regarding the study outcomes. Primary efficacy conclusions will be based on Day 91 (end of double-blind treatment), with supporting data from earlier timepoints included to describe the time-profile of any treatment benefits. A comprehensive statistical analysis plan will be written that will include details regarding the statistical analysis. The methods described below summarize the general approach.

Further, note that the primary focus of the statistical analysis is on the double-blind comparison of LYT-100 to placebo (Part A). The following methods describe those for Part A; Part B methods are provided at the end of the Statistical Methods section. A comprehensive SAP will be written, in which the methods of statistical analysis will be described separately for Part A from Part B.

15.1. Sample Size

The study will utilize a suite of endpoints to measure patient clinical function and health-related quality of life. The sample size was based on both the 6MWT (a measure of patient clinical function) .

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 patients 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., patients 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 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.

15.2. General Statistical Plan

The baseline value for all variables will be the last measurement obtained prior to the participant receiving the first dose of study treatment.

In general, descriptive statistics (arithmetic mean, standard deviation [SD], median, minimum and maximum) will be calculated for continuous valued safety data by specified assessment time point. Frequency summaries (i.e., number and percentage of each observed category) will be provided for categorical and ordinal safety data by time point.

Primary efficacy conclusions will be on the, Intent to Treat population, with supporting analyses performed for population definitions. Subgroup analysis for the randomization strata (or other subgroup definitions) may be performed where applicable. Safety conclusions will be based on the Safety Population.

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

Statistical methods will be further outlined in a statistical analysis plan (SAP) and approved by the Sponsor prior to any analysis. Procedures outlined in the SAP will supersede protocol specified statistical methods in the event of divergence. Part A and B will be described separately in the SAP.

15.3. Handling of Missing Data

This study is being performed in patients with active COVID-19 diagnosis. There may be restrictions beyond the patient's control that may limit the collection of study visit assessments. Attempts should be made to collect assessments at the hospital, rehab, out-patient clinic and/or patient'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 patients 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 (including topic such as imputation methods for data missing at random vs missing NOT at random) will be described in the SAP prior to unblinding.

15.4. Analysis Populations

Participant inclusion into each analysis population will be determined prior to unblinding, except the PK Population.

- The Safety Population is defined as all patients who received at least one dose of study treatment. All safety endpoints will be assessed using this population. Patients will be analyzed according to the treatment they actually receive, regardless of which treatment they were randomized to.
- The Intent to Treat (ITT) population is defined as all randomized patients. All efficacy endpoints will be assessed using this population, with primary conclusions regarding study drug effect be based on the ITT population outcomes. Patients will be analyzed according to the treatment group they were randomized to, regardless of which treatment they actually receive.
- 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.
- The Per-Protocol (PP) population is 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 have no major protocol deviations that could affect interpretability of the efficacy outcomes. Subjects who died or discontinued due to TEAE will be included in this population. The Pharmacokinetic (PK) Population is defined as all patients who receive study treatment and provide at least one plasma concentration measure. This population will be determined by the study pharmacokinetics.

15.5. Inferential Testing and Multiplicity Considerations

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, as well as the development stage of this study, 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).

15.6. Baseline Characteristics, Patient Disposition, and Medications

The baseline for each variable (except the 6MWT) will be the last measurement obtained prior to first dose of study treatment. For the 6MWT distance, the longest distance of the two tests conducted on Day -1/Day1 will be used as the baseline for purposes of analysis.

Demographic information and patient disposition outcomes will be tabulated (including the number and percent of patients who are enrolled, who receive treatment, who prematurely discontinue and reasons for discontinuation, and who complete the study). Summary statistics for days of exposure and duration of exposure will be provided.

Medical history will be coded and tabulated accordingly. Prior and concomitant medications will be coded using the current WHO drug dictionary. Prior and concomitant medications will be listed by participant and summarized by treatment using ATC and preferred term.

15.7. Efficacy

While all analyses will be performed at each protocol-scheduled time point (i.e., Days 14, 28, 56, and 91), conclusions regarding the primary and key secondary endpoints will be based on analysis of Day 91 data. It is possible the effect of LYT-100 may increase over time, and thus the effect (benefit) could be greater at Day 91 than earlier time points. The effect-time profile for each endpoint is also of interest and will be tabulated as below as well as plotted accordingly.

15.7.1. Primary and Key Secondary Efficacy Endpoints

The primary method of analysis for continuous endpoints is consistent with the sample size methodology and will thus utilize mixed models for repeated measures (MMRM), assuming a Gaussian distribution, an unstructured covariance matrix, and the Kenward-Roger approximation for denominator degrees of freedom. Fixed effects will include treatment, visit, the treatment by visit interaction, the baseline value of the endpoint as a covariate, and study center; however, the SAP may specify additional covariates to be added to the model. By-visit pairwise comparisons will be assessed. with primary conclusions based on the Day 91 timepoint. Missing data will be imputed according to the 'type' of missingness, ie, data missing at random will be imputed differently than data that are missing NOT at random (eg, missing due to death, hospitalization, discontinuation due to TEAE); the specific imputation strategy for the primary and key secondary endpoints will be described in detail in the SAP.

A sensitivity analysis of the primary and key secondary endpoints will be performed using a nonparametric Wilcoxon rank sum test to test the active vs. placebo comparison at each time point. Analysis of the key secondary efficacy endpoint, dyspnoea-12,will be performed in a similar manner. Primary conclusion regarding efficacy of these endpoints will be based on the ITT population, with sensitivity support based on the FAS and PP populations.

15.7.2. Other Secondary Efficacy Endpoints

Analysis of other secondary and exploratory efficacy endpoints will be performed similarly to the primary efficacy endpoint.

Categorical endpoints will be assessed at each time point using a Cochran-Mantel-Haenszel (CMH) test, stratified by center. For ordinal and other categorical endpoints, a CMH row means scores test (CMH-RMS) (which used modified ridit scores) will be used, stratified by center. Specifically, for the WHO Ordinal Scale for Clinical Improvement, response definitions will include patients with at least 1-point improvement and at least 2-point improvement. WHO outcomes will also be assessed on a continuum using similar MMRM as for the primary efficacy endpoint. Bar charts of the distribution of outcomes will be provided for each visit to allow for visual inspection of any treatment differences.

Analysis of the incidence of pulmonary exacerbations (severe and non-severe will be assessed as separate endpoints. The primary assessment will be the time-to-first severe exacerbation via a Kaplan-Meier plot and logrank test statistic. If there are multiple exacerbations per subject, other methods of analysis may be considered.

The SF-36 (v2) will be assessed via analysis of each of the 8 domains as well as the 2 component scores. The outcomes will be used to allow for a more thorough understanding of the treatment benefit and may be explored via correlation analyses with the 6MWT and other endpoints, as the data warrant.

Kaplan-Meier plot and log-rank tests may assess time to all-cause mortality (if sufficient mortality data exist to allow for meaningful comparisons). The number (%) of patients dying (all-cause mortality) through Day 91 will be tabulated. The time to discharge of hospitalization (in days) and other time-to-event parameters, as the data permit. The number and percent of patients requiring re-hospitalizations will be tabulated.

A correlational analysis may also be undertaken to identify patient factors e.g., age, gender, BMI, etc. and potential biomarkers that are associated with overall survival and successful resolution of all signs and symptoms of the disease. Further, response definitions of select endpoints will be explored to better understand the benefit of LYT-100.

Statistical analyses will be performed using SAS, version 9.4. (SAS, Cary, NC).

15.8. Safety and Tolerability

Safety analyses will be performed using the Safety Population. Adverse events, concomitant medications, clinical laboratory findings, physical examinations, ECGs, and vital signs for each participant will be tabulated or summarized descriptively, where appropriate, as described in the following sections.

15.8.1. Adverse Events

Adverse events will be coded using MedDRA® Version 23.0; this version has the most up-to-date COVID-19 coding terms. Analysis will focus on treatment-emergent AEs (TEAEs). The number of patients experiencing TEAEs and the number of individual TEAEs will be provided, as well as by SOC and PT. The severity and the relationship to study drug of TEAEs will be summarized. Pre-treatment AEs will be tabulated separately from TEAEs. SAEs, TEAEs leading to discontinuation, and TEAEs leading to death will be tabulated.

15.8.2. Laboratory Evaluations

Laboratory evaluations (including hematology, biochemistry, coagulation and urinalysis) will be listed and summarized by protocol specified collection time point. This will be done both for actual observed laboratory values and for changes from baseline. Shift tables will also be provided for clinical laboratory results.

The abnormal urinalysis results, if applicable, will be listed only.

15.8.3. Vital Signs

Vital signs including SpO_2 will be listed and summarized by protocol specified collection time point. This will be done both for actual observed vital sign values and for changes from baseline.

15.8.4. ECG Values and Result

ECG values will be listed and summarized by protocol specified collection time point. 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. ECG results for QTcF will also be classified as <450 msec, 450-500 msec or >500 msec.

15.9. Population Pharmacokinetics- Part A Only

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.

15.10. Biomarkers- Part A Only

Exploratory analysis of biomarkers changes over time in C-reactive protein (CRP), lymphocyte count, d-dimer, cardiac troponin, ferritin, lactate dehydrogenase (LDH), IL-6, TGF-β1, TNF-α, IL-1β, PDGF- β, GCSF, and VEGF. Correlation of changes in biomarkers with clinical endpoints (e.g., 6MWT, mBDS) will be assessed where relevant in an exploratory fashion. Further details of this exploratory biomarker analysis will be provided in the Statistical Analysis Plan.

15.11. Statistical Method for the Open-Label Extension (Part B)

Part B is characterized by open-label treatment, and thus the analysis will be descriptive in nature. Where inferential methods are used, these will be used to better-inform as to the relative magnitudes of the longer-term effects from treatment with LYT-100, and not for hypothesis testing purposes.

The focus of the Part B analysis will be on the LYT-100 to LYT-100 group (as these patients will have been treated with up to 182 days with active treatment), but the Placebo to LYT-100 group will also be analyzed, with a focus on whether there are any meaningful differences in these exploratory efficacy endpoints from Part A compared to Part B.

OLE Safety Population: 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. Other analysis populations may be defined to help inform as to characteristics of the safety and exploratory efficacy profiles.

The primary objective of Part B is to assess safety and tolerability, and thus tabulations will be presented with this goal in mind. Analysis will include data from Part A, so that the slopes of changes over time from Study Day 1 through Study Day 182 can be described.

15.12. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by IEC / IRB / HREC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any participant into the study.

The Investigator is responsible for informing the IEC / IRB / HREC of any amendment to the protocol in accordance with local requirements. In addition, the IEC / IRB / HREC must approve

all advertising used to recruit patients for the study. The protocol must be re-approved by the IEC / IRB / HREC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IEC / IRB / HREC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug (active). The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IEC / IRB / HREC according to local regulations and guidelines.

15.13. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP applicable regulatory requirements and the Sponsor's policy on Bioethics.

15.14. Informed Consent

The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time without prejudice. The participant should be given the opportunity to ask questions and allowed time to consider the information provided before voluntarily signing the written ICF.

The participant's signed and dated informed consent (written, electronic, or oral) must be obtained before conducting any study procedures. The patients will be informed of their rights to privacy but will be made aware that the study data will be submitted to the Sponsor and possibly to drug regulatory authorities for review and evaluation. They will be informed also that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

The acquisition of informed consent should be documented in the participant's medical records, and the ICF will be signed and personally dated by the participant and by the person who conducted the informed consent discussion.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or legal representative. The date that informed consent was signed will be recorded on the CRF.

15.15. Data Protection

Patients will be informed that data will be held on file by the Sponsor and that these data may be viewed by staff including the study monitor and by external auditors on behalf of the Sponsor and appropriate regulatory authorities. Patients will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication. However, patients will be identified in such reports only by study identification number, gender and age. All participant data will be held in strict confidence.

16. REGULATORY REQUIREMENTS

The Contract Research Organization (CRO) will act as the legal Sponsor, when appropriate for the study and will fulfil the obligations that this role entails. The CRO shall, to the extent required by the applicable laws and regulations, interact when appropriate on behalf of the Sponsor in connection with this study. The planned regulatory pathway for this trial is through the appropriate regulatory agency's scheme. Aside from approval by the IEC / IRB / HREC and notification of the appropriate regulatory agency, no other regulatory approval will be required.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

All source data, clinical records and laboratory data relating to the study will be archived for 25 years after the completion of the study. All data will be available for retrospective review or audit.

Source documents are original documents, data, and records from which the participant's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, angiograms, study drug accountability logs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all study-related (essential) documentation. These include but are not limited to IEC / IRB / HREC correspondence, study drug accountability logs, and curricula vitae of all personnel participating in the study. These files must be suitable for inspection at any time by the Sponsor, monitor, and/or applicable regulatory authorities. All essential documentation should be retained by the institution for 15 years.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

17.3. Liability/Indemnity/Insurance

The Sponsor will ensure sufficient insurance is available to enable it to indemnify and hold the Investigator(s) and relevant staff as well as any hospital, institution, ethics committee or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the study drug but only to the extent that the claim is not caused by the fault or negligence of the patients or Investigator(s).

18. PUBLICATION POLICY

18.1. Publication of Results

The publication, presentation or other public disclosure of study results (each, a "Publication") will be accurate and honest, undertaken with integrity and transparency and in accordance with the Sponsor's approval.

Publication of results will be subjected to fair peer-review. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation.

All conflicts arising through disputes about authorship will be reviewed by the Sponsor.

Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organizations providing finance or facilities. Participant confidentiality will be maintained by referring to individual patients by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with the Sponsor's approval.

Study data that have not been published, presented or otherwise disclosed in accordance with the clinical trial agreement shall remain confidential information of the Sponsor, the Investigator may not disclose or permit the disclosure of such unpublished data to any third party, nor may they disclose or permit the disclosure of any study data to any third party in greater detail than the same have been disclosed in any permitted publication, presentation or other disclosure.

The clinical trial will be posted to a clinical trial registry as required by legal agreement, local law or regulation.

18.2. Disclosure and Confidentiality

By signing this protocol, the Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from his/her staff and the local IEC / IRB / HREC. Study documents provided by the Sponsor (Protocols, IBs, eCRFs, etc.) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the study.

The Investigator must ensure that the participant's anonymity is also maintained. Patients should only be identified by their initials and a participant study number on the CRFs and other source documents. Other study-related documents (e.g., signed ICFs) should be kept in strict confidence by the Investigator.

19. QUALITY CONTROL AND QUALITY ASSURANCE

19.1. Compliance with Good Clinical Practice

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 14.3 for more details regarding the audit process.

The study will be carried out in accordance with the current version of the Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects), Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2).

19.2. Archiving and Regulatory Inspection

All study-related documents and records are to be retained for a minimum of 15 years after trial completion. Written agreement from the Sponsor must precede destruction of the same.

In accordance with ICH GCP, this study may be selected for audit. Inspection of site facilities (e.g., pharmacy, medication storage areas, laboratories) and review of study-related records may occur by the Sponsor, the Sponsor's representative(s), or regulatory authority to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

20. CLINICAL STUDY REPORTS

A separate clinical study report (CSR) will be prepared for each Part of the study, A and B. They will reference ICH Guidance E3 and include:

- Details of where the study was carried out.
- Dates of the start and completion of each period of the study.
- Details of the study drug and a statement of production will be provided by the Sponsor.
- A statement confirming that the applicable IEC / IRB / HREC gave written approval for the study in accordance with local regulations.
- A demographic listing for all patients.
- A list of all AEs according to study drug.
- Details of any occurrences which may be of significance to the study outcome.
- Details of all operations, calculations and transformations performed on the reported data.
- The appropriate SAP report will be produced by the Sponsor, or their agents, and will be incorporated into each final report.
- A scientific interpretation of the results.
- A description of the study methods used.

Consideration will be given to any comments on a draft report. The report will incorporate the analytical and statistical results and methods produced by the Sponsor or their agents. A final report will be prepared to contain all those sections in the draft and a statement of compliance covering all the areas of the study conducted at the investigational site and the report, with GCP. The report will be issued under the Sponsor's responsibility.

Where required by the applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review complete study results. The Sponsor will also provide the Investigator with the full summary of study results.

21. SPONSOR AND INVESTIGATOR OBLIGATIONS

21.1. Protocol Amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IEC / IRB / HREC for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial patients. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

21.2. Protocol Deviations

Should any protocol deviation occur, it must be reported to the study monitor as soon as is reasonably practical. The deviation and the reason for its occurrence must be documented, reported to the relevant IEC / IRB / HREC (if required) and included in the CSR.

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APPENDIX 1. ENDPOINT SCALES

Table 10: WHO Ordinal Scale for Clinical Improvement (sample)

Ordinal Scale for Clinical Improvement		
Patient State	**Descriptor**	**Score**
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by ask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Mechanical Ventilation plus additional organ support (i.e. extracorporeal life support (ECLS), continuous renal replacement therapy (CRRT), vasopressors)	7
Dead	Death	8
World Health Organization 2020, February 19, 2020, Geneva Switzerland		

Table 11: 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

Table 12: Chest CT Scan Number of Involved Segments (sample)

Per lung	
Interstitial Change	Pleural effusion □ Right □ Left □ Bilateral □ Lymphadenopathy
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 □ NE
Consolidation	□ Central □ Peripheral □ Diffuse □ Absent □ NE
Reticular pattern	□ Central □ Peripheral □ Diffuse □ Absent □ NE
Mixed pattern	□ Central □ Peripheral □ Diffuse □ Absent □ NE
Honeycomb pattern	□ Central □ Peripheral □ Diffuse □ Absent □ NE
Interstitial Change	□ Septal thickening □ Crazy paving pattern □ Pleural thickening

Table 13: Modified Borg Dyspnoea Scale (sample)

The Modified Borg Dyspnoea Scale is collected on study days per schedule of events (Table 4) and at the beginning of the study visits and after resting for a minimum of 5 minutes.

"This is a scale that asks you to rate the difficulty of your breathing. It starts at number 0 where your breathing is causing you no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal. How much difficulty is your breathing causing you right now?"

0	**Nothing at all**
0.5	**Very, very slight (just noticeable)**
1	**Very slight**
2	**Slight**
3	**Moderate**
4	**Somewhat severe**
5	**Severe**
6	
7	**Very severe**
8	
9	**Very, very severe (almost maximal)**
10	**Maximal**

Table 14: The Borg Scale Used in 6-minute Walk test (sample)

0	**Nothing at all**
0.5	**Very, very slight (just noticeable)**
1	**Very slight**
2	**Slight (light)**
3	**Moderate**
4	**Somewhat severe**
5	**Severe (heavy)**
6	
7	**Very severe**
8	
9	
10	**Very, very severe (maximal)**

Shortness of breath and fatigue during 6MWT

Shortness of breath and *fatigue* are also measured with the 6MWT assessment using the same scale. At the beginning of the 6-minute walk test, the scale is shown to the patient who is asked:

1) "Please grade your level of shortness of breath using this scale." _____

2) Following the response to #1, the patient is then asked, "Please grade your level of fatigue using this scale." _____

3) At the end of the exercise, patient is reminded of the breathing number chosen before walking and then asked to grade their "breathing level" again. _____

4) The patient is then reminded of their grade before exercise and is asked to grade their level of fatigue. _____

Table 15: Charlson Comorbidity Index (sample)

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

Adapted from: Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis.1987; 40: 373-83.

Calculation: Add all items of the Comorbidity score: The total score is the Charlson Comorbidity Index.

COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease

Table 16: St. George's Respiratory Questionnaire-I (sample)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problem, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Name: …… Date: …….

ID Number: ……..

Age: …….. Sex: Male/Female

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

St. George's Respiratory Questionnaire-I (continued)

Part 1

Questions about how much chest trouble you currently have. Please tick in one box for each question.

	Almost every day	Only with chest infections	Not at all
1. I cough:	☐	☐	☐
2. I bring up phlegm (sputum):	☐	☐	☐
3. I have shortness of breath:	☐	☐	☐
4. I have attacks of wheezing:	☐	☐	☐

5. In a typical week how many attacks of chest trouble do you have? Please tick (✓) one:

More than 1 attack ☐

No attacks ☐

6. In a typical week how often do you have good days? Please tick (✓) one:

None ☐

A few days ☐

Every day is a good day ☐

Part 2

Section 1:

If you have ever had paid employment:

Please tick (✓) one:

My lung condition interferes or made me stop work ☐

My lung problem does not affect my job ☐

St. George's Respiratory Questionnaire-I (continued)

Section 2: Questions about what activities usually make you feel breathless. Please tick in each box that applies to you <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days:*

		True	False
1.	Getting washed or dressed	☐	☐
2.	Walking around the home	☐	☐
3.	Walking outside on the level	☐	☐
4.	Walking up a flight of stairs	☐	☐
5.	Playing sports or games	☐	☐

Section 3: Some more questions about your cough and breathlessness. Please tick in each box that applies to you <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days:*

		True	False
1.	My cough hurts	☐	☐
2.	My cough makes me tired	☐	☐
3.	I am breathless when I talk	☐	☐
4.	I am breathless when I bend over	☐	☐
5.	My cough or breathing disturbs my sleep	☐	☐
6.	I get exhausted easily	☐	☐

Section 4: Questions about other effects that your chest trouble may have on you. Please tick in each box that applies to you <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days:*

		True	False
1.	My cough or breathing is embarrassing in public	☐	☐
2.	My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
3.	I get afraid or panic when I cannot get my breath	☐	☐
4.	I feel that I am not in control of my chest problem	☐	☐
5.	Exercise is not safe for me	☐	☐
6.	Everything seems too much of an effort	☐	☐

St. George's Respiratory Questionnaire-I (continued)

Section 5: These are questions about how your activities might be affected by your breathing. Please tick in each box which you think applies to you because of your breathing

	True	False
1. Jobs such as housework take a long time, or I have to stop for rests	☐	☐
2. If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
3. If I hurry or walk fast, I have to stop or slow down	☐	☐
4. My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
5. My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 6: We would like to know how your chest usually affects your daily life. Please tick in each box that applies to you because of your chest trouble

	True	False
1. I cannot play sports or games	☐	☐
2. I cannot go out of the house to do the shopping	☐	☐
3. I cannot do housework	☐	☐
4. I cannot move far from my bed or chair	☐	☐

Now, would you tick in the box (one only) which you think best describes how your chest affects you:-

It does not stop me doing anything I would like to do	☐
It stops me doing one or two things I would like to do	☐
It stops me doing most of the things I would like to do	☐
It stops me doing everything I would like to do	☐

Table 17: Dyspnoea-12 (sample)

"This questionnaire is designed to help us learn more about how your breathing is troubling you.

Please read each item and then tick in the box that best matches your breathing **these days**. If you do not experience an item tick the 'none' box. Please respond to all items.

Name: _____ID: _____Date: ____/____/____

Item	None	Mild	Moderate	Severe
1. My breath does not go in all the way				
2. My breathing requires more work				
3. I feel short of breath				
4. I have difficulty catching my breath				
5. I cannot get enough air				
6. My breathing is uncomfortable				
7. My breathing is exhausting				
8. My breathing makes me feel depressed				
9. My breathing makes me feel miserable				
10. My breathing is distressing				
12. My breathing makes me feel agitated				
13. My breathing is irritating				

Table 18: SF-36 v2 (sample)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer each question by choosing just one answer. If you are unsure how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

□1 Excellent □2 Very good □3 Good □4 Fair □5 Poor

2. Compared to one year ago, how would you rate your health in general now?

□ 1 Much better now than one year ago

□ 2 Somewhat better now than one year ago

□ 3 About the same

□ 4 Somewhat worse now than one year ago

□ 5 Much worse now than one year ago

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	YES, limited a lot	YES, limited a little	NO, not limited at all
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	□1	□2	□3
4. Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	□1	□2	□3
5. Lifting or carrying groceries	□1	□2	□3
6. Climbing several flights of stairs	□1	□2	□3
7. Climbing one flight of stairs	□1	□2	□3
8. Bending, kneeling or stooping	□1	□2	□3
9. Walking more than a mile	□1	□2	□3
10. Walking several hundred yards.	□1	□2	□3
11. Walking one hundred yards	□1	□2	□3
12. Bathing or dressing yourself	□1	□2	□3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	YES	NO
13. Cut down the amount of time you spent on work or other activities	□1	□2
14. Accomplished less than you would like.	□1	□2
15. Were limited in the kind of work or other activities.	□1	□2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	□1	□2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	Yes,	No
17. Cut down the amount of time you spent on work or other activities	□1	□2
18. Accomplished less than you would like.	□1	□2
19. Did work or other activities less carefully than usual.	□1	□2

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

□ 1 Not at all

□ 2 Slightly

□ 3 Moderately

□ 4 Quite a bit

□ 5 Extremely

21. How much bodily pain have you had during the past 4 weeks?

□ 1 None

□ 2 Very mild

□ 3 Moderate

□ 4 Severe

□ 5 Very severe

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

□1 Not at all

□2 A little bit

□3 Moderately

□4 Quite a bit

□5 Extremely

These questions are about how you feel and how thing have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks….

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of life?	□1	□2	□3	□4	□5	□6
24. Have you been very nervous?	□1	□2	□3	□4	□5	□6
25. Have you felt so down in the dumps that nothing could cheer you up?	□1	□2	□3	□4	□5	□6
26. Have you felt calm & peaceful?	□1	□2	□3	□4	□5	□6

27. Did you have a lot of energy?	□1	□2	□3	□4	□5	□6
28. Have you felt down-hearted and depressed?	□1	□2	□3	□4	□5	□6
29. Did you feel worn out?	□1	□2	□3	□4	□5	□6
30. Have you been happy?	□1	□2	□3	□4	□5	□6
31. Did you feel tired?	□1	□2	□3	□4	□5	□6

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

□ 1 All of the time

□ 2 Most of the time

□ 3 Some of the time

□ 4 A little bit of the time

□ 5 None of the time

How TRUE or FALSE is each of the following statements for you.					
	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	□1	□2	□3	□4	□5
34. I am as healthy as anybody I know	□1	□2	□3	□4	□5
35. I expect my health to get worse	□1	□2	□3	□4	□5
36. My health is excellent	□1	□2	□3	□4	□5

APPENDIX 2. BLOOD VOLUMES

Estimates for the total volumes of blood drawn over the course of the study are presented below in Table 19 and will be confirmed by the central or local laboratory prior to commencement of the study. Further details will be provided in the Laboratory Manual and/or patient ICF.

Table 19. Estimated Blood Volumes- Part A

Test	Per Test Volume	Total Number of Samples	Total Volume
Hematology Panel with Reticulocytes	3 mL	6	18 mL
Chemistry	5 mL	6	30 mL
FSH X1	from above chemistry	-	-
Coagulation Panel (PT/INR, PTT)	4.5 mL	6	27 mL
Safety Biomarkers:			
• D-dimer	2.7 mL	6	16.2 mL
• C-reactive Protein • Ferritin	5 mL	6	30 mL
• Cardiac Troponin	3.5 mL	6	21 mL
• Lymphocyte Count	3 mL	6	18 mL
Inflammatory and Fibrotic Biomarkers: • IL-6 • TGF-β1 • TNF-α • PDGF • IL-1b • GCSF • VEGF	10 mL	6	60 mL
PK	4 mL	5	20 mL
Estimated Overall Blood Volume Collected Per Participant			241 mL

Table 20. Estimated Blood Volumes- Part B

Test	Per Test Volume	Total Number of Samples	Total Volume
Hematology Panel with Reticulocytes	3 mL	6	18 mL
Chemistry	5 mL	6	30 mL
FSH X1	from above chemistry	-	-
Coagulation Panel (PT/INR, PTT)	4.5 mL	6	27 mL
Estimated Overall Blood Volume Collected Per Participant			75 mL

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

Protocol Number: LYT-100-2020-02-US

A U.S. country-specific amendment to Protocol LYT-100-2020-02

Authors: PureTech LYT 100, Inc.

Development Phase: Phase 2
Document Version: Protocol Version 1.0 dated June 17, 2020
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Amendment #2: Protocol Version 3.1 dated October 20, 2020
Amendment #3: Protocol Version 4.0 dated December 22, 2020
Amendment #4: Protocol Version 5.0 dated March 12, 2021
Amendment #5: Protocol Version 6.0 April 27, 2021
Amendment #6: Protocol Version 7.0 U.S. September 29, 2021
Amendment #7: Protocol Version 8.0 January 26, 2022
Amendment #8: Version 8.1 U.S. January 26, 2022
Amendment #9: Version 8.2 U.S. March 17, 2022

Number of Pages: 142

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PROTOCOL AUTHORIZATION

Title: 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

As PureTech LYT 100, Inc. ("Sponsor") representative, I confirm that the study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (IP), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki and the International Council for Harmonization guidelines on Good Clinical Practice (GCP).

DocuSigned by:
Heather Paden
Signer Name: Heather Paden
Signing Reason: I am the author of this document
Signing Time: 21-Mar-2022 | 16:04 EDT
D010270479C741C2B9E3DDA8D026D4FF

21-Mar-2022 | 16:05 EDT

Heather Paden Date

INVESTIGATOR'S AGREEMENT

Title: 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

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s) (IB), electronic Case Report Forms (eCRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Human Research Ethics Committee (HREC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the appropriate Ethics Committee, except where necessary to avert an immediate hazard to the patients.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), in accordance with the current version of International Conference on Harmonization (ICH) guidelines for GCP, and in accordance with the current version of National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (updated 2018). The conduct of the study will also be in accordance with the Integrated Addendum to ICH E6 (R1), Guideline for GCP ICH E6 (R2).

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigational Site

Printed name of Investigator

Signature of Investigator

Date

PROTOCOL SYNOPSIS

Name of Sponsor/Company: PureTech LYT 100, Inc.	
Name of Investigational Product: Deupirfenidone Capsules	
Name of Active Ingredient: Deupirfenidone (LYT-100)	
Protocol Number: LYT-100-2020-02-U.S.	
Title of Study: 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	
Study Centre(s): Approximately 35 study centers in Europe, United States, Asia and South America.	
Studied Period (Years): Estimated date first Participant enrolled: Q4 2020 Estimated date last Participant completes double-blind treatment, Part A: Q1 2022 Estimated date last COA Development Sub-study Participant completed double-blind Treatment: Q3 2022 Estimated date first Participant enrolled to open-label extension, Part B: Q2 2021 Estimated date last Participant completes open-label extension, Part B: Q2 2022	**Phase of Study:** Phase 2

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. Other regions may be added as the pandemic mandates.

Clinical Outcome Assessment (COA) Development Sub-study

This protocol includes a Sub-study of COA Development (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 21-Jan-2022, and includes a total of N=177 patients), additional enrollment (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 subjects 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, they will 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 analyses.
- Sub-study patients enrolled after completion of the Part A enrolment will NOT be included in the primary analyses of Part A outcomes.

PART A:

After informed consent is obtained, patients will enter a screening phase for 5 days, to determine eligibility. The screening period may be extended up to a total of 10 days to allow for evaluation of all screening assessments required for study inclusion. Patients are required to have all screening assessments, including a training session for the 6-minute walk test (6MWT), and meet all inclusion/exclusion criteria for the trial prior to randomization. Approximately 168 eligible patients who previously hospitalized, but no longer require mechanical ventilation, extracorporeal membrane oxygenation, non-invasive ventilation (ie continuous positive airway pressure, high-flow nasal oxygen therapy or other high flow oxygen with FiO2 ≥35% and flow rate ≥ 8 lpm) for at least 72 hours prior to the screening visit, will be randomized to receive LYT-100 or placebo, in a ratio of 1:1, respectively, in conjunction with institutional standard of care for COVID-19. Enrollment in the United States (and other countries) may remain open in order for an additional approximately 20 subjects randomized to Part A to allow for evaluation of COVID Symptoms Assessments and Qualitative Interviews. Two 6MWT will be performed at baseline, with the longest distance recorded for the baseline measure. These tests can take place on Days -1 and/or Day 1, prior to dosing.

Patients randomized will be assigned to stratification levels as shown in Table 3. The primary analysis will be based on all data. Subgroup analysis may be performed as the data warrant, although the sample size for subgroups may not be sufficient for definitive conclusions to be drawn. Standard of care will be administered as per investigator's medical judgement, based on the severity of the disease, and according to local government and/or institutional guidelines. LYT-100 or placebo will be administered daily for up to 91 days, with an optional extension of open-label LYT-100 administration for up to an additional 91 days for those patients who qualify. Patients will start participation in the study while either hospitalized, or at time of hospital discharge / post-discharge from hospital for COVID-19 respiratory disease.

The timing of randomization into Part A is dependent on type of qualifying respiratory support and date of initial confirmed COVID-19 diagnosis, as described below in Table 1.

Table 1. Timing of Randomization Relative to COVID-19 Diagnosis and Qualifying Respiratory Support

Qualifying Respiratory Support	Initial Confirmed Diagnosis of COVID-19
Any form of supplementary oxygen treatment other than ECMO or MV	Within 90 days
ECMO or MV	Within 132 days

During Part A, treatment assignments will remain blinded to the patient, study staff, and sponsor. Patients will be seen either on the hospital ward and/or in the ICU during hospital stay or at discharge, or on a rehabilitation ward, an outpatient clinic or at the patient's home post-discharge. Note that for patients who were hospitalized and are discharged during the study, these patients will continue with study visits according to the Schedule of Events for Part A. For all patients, study follow-up visits will occur at Days 14, 28, 56, and 91. In Part A, patients who discontinue early or elect to not continue into Part B will also have a follow-up visit 14 days, post-completion of study treatment. (See Figure 1.)

For those patients who are eligible and who elect to continue into **Part B**, the open label extension, study visits will occur at Days 105, 119, 147 and Day 182. Part B patients who discontinue early will also have a follow-up visit 14 days, post-completion of Part B treatment. (See Figure 1.)

Study Objectives- Part A

COVID-19 respiratory disease is a multi-faceted indication, and thus this clinical study includes several objectives (and corresponding endpoints) to adequately describe the effects of study treatment. To that end, there are primary and key secondary objectives that form the basis for study success, while other secondary objectives will inform overall conclusions and allow for assessment of a preponderance of evidence as to the benefit of LYT-100 in this population.

Primary Objective:

To evaluate the effect of LYT-100 on the change in distance walked on the six-minute walk test performed in line with the American Thoracic Society/European Respiratory Society Guidelines.

Key Secondary Objective:

To evaluate the effect of 91 days of treatment with LYT-100 compared to placebo on 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 WHO Ordinal Scale for Clinical Improvement
4. Quality of Life 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 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 X-ray

12. Length of hospital stay
13. All-cause mortality
14. Use of supplemental oxygen from Baseline to end of treatment
15. COVID Symptom 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 Objectives:

To evaluate the plasma concentration vs. time data via population pharmacokinetic analysis of LYT-100 and its metabolite(s).

Study Objectives- Part B

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:

- Change in distance walked on the six-minute walk test performed in line with the American Thoracic Society/European Respiratory Society Guidelines.
- The Modified Borg Dyspnoea Scale (mBDS).
- Saint George Respiratory Questionnaire-I (SGRQ-I)
- Dyspnoea-12
- The WHO Ordinal Scale for Clinical Improvement
- Quality of Life assessment as collected using the SF-36 (v2), including 8 domains and 2 component scores.
- Number of lung segments involved using CT Scan and QLF assessment
- Pulmonary exacerbations, severe and non-severe
- All-cause rehospitalizations
- Severity of lung lobe(s) involvement, using CT Scan
- Pulse oximetry
- Chest X-ray
- Length of hospital stay
- All-cause mortality
- Use of supplemental oxygen from Baseline to end of treatment

Study Objectives COA Development Sub-study

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 Dyspnea-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.

Data Safety Monitoring Board (DSMB)

An independent, unblinded DSMB will assist with oversight of patient safety during both Parts A and B. A Charter will be written to describe the purpose, members, meeting frequency, and data to be reviewed by the DSMB.

Study Drug Dosage and Mode of Administration

Patients will receive LYT-100 (deupirfenidone) formulated as powder in 250 mg capsules or matching placebo. Dosing will be provided as shown in Table 2. In both Part A and Part B, an initial dosage of 500 mg BID will be given the first 3 days of dosing, followed by 750 mg BID thereafter. Patients will take LYT-100 study medication, or placebo (in Part A), orally and preferably with food (solid or nutritional supplements, whenever possible), with approximately 10 to 12 hours between the two daily doses.

Table 2: Dosing Regimens for Parts A and B

Part A: Double-Blind		**Part B: Open-Label Extension**	
Day 1 to Day 3	**Day 4 through Day 91**	**Day 91 through Day 93**	**Day 94 through Day 182**
[1]LYT-100 **500 mg BID** or matching Placebo[2] x 3 days	[1]LYT-100 **750 mg BID** or matching Placebo[2] x 88 days	[1]LYT-100 **500 mg BID**[2] x 3 days	[1]LYT-100 **750 mg BID**[2] x 88 days

[1]Patients will take study medication orally and preferably with food (solid or nutritional supplements, whenever possible), with approximately 10 to 12 hours between the two daily doses.

[2] Doses may be adjusted according to safety and tolerability to avoid toxicity by adjusting to lower doses in response to patient safety and tolerability issues, including: Skin reactions to sunlight; Significant changes to liver enzymes, and/or Gastrointestinal (GI) side effects. See protocol Section 5.2 and 11.1.3.1 for details.

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.

All patients will be monitored following screening for completion of clinical efficacy and safety assessments of LYT-100 at time points delineated in the Schedule of Events (Part A: Table 4; Part B: Table 5).

Number of Patients (Planned)

Approximately 168 patients with post-acute, documented COVID-19 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.

Additional patients may be randomized until an additional approximately 20 patients have been randomized into the SCOA.

COA Development Sub-study

Enrollment will remain open until and additional approximately 20 subjects are randomized as part of the SCOA.

Eligibility Criteria- Part A

The following Inclusion and Exclusion must be met before randomization into the study.

Inclusion Criteria- Part A

1. Positive result of a molecular RT-qPCR diagnostic test, RNA or antigen test for SARS-CoV-2 result from a clinical specimen deemed clinically associated with the current episode of illness, warranting hospital admission as per investigator's judgement, or previously hospitalized (central and/or local laboratory COVID-19 test results are accepted from any biological material source)
2. Hospitalization for COVID -19 respiratory disease and treated with supplemental oxygen (including MV, ECMO or any other means of oxygen administration) in hospital

   Note: Admission to a hospital Emergency Department, temporary hospital or any other hospital-affiliated facility used to treat acutely ill subjects in which the subject would otherwise be admitted to the hospital but due lack of bed space/ capacity in response to the COVID-19 pandemic, or otherwise treated by hospital staff, falls under the category of hospitalization.

   Also note: Hospitalization can be any length of time on at least one calendar day and does not need to be greater than or equal to 24 hours.
3. Written, electronic, or oral informed consent from the patient or Legally Authorized Representative prior to any study procedures in a manner approved by an IRB or Ethics Committee
4. Male or female, aged ≥18 to ≤80 years of age, inclusively at the time of informed consent
5. Able to perform and willing to comply with all study procedures and requirements
6. Able to bear weight and ambulate a minimum of 10 m distance (use of inhaled oxygen permitted)
7. Randomization day is dependent on type of qualifying respiratory support and date of initial confirmed COVID-19 diagnosis as described in Table 1
8. COVID-19 pneumonia findings on imaging (chest X-ray or CT Scan) with a minimum of two lung lobes involvement
9. Shortness of breath ≥ grade 3 on mBDS dyspnea scale
10. Laboratory parameters (CBC, biochemistry) deemed by the investigator as acceptable and/or not clinically significant to enroll the patient
11. Women of childbearing potential (WOCBP) must be non-pregnant and non-lactating, and must be abstinent from heterosexual intercourse for 90 days following last dose of study medication or agree to use one of the acceptable, highly effective double contraception:
    a. oral, intravaginal, or transdermal combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation
    b. oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
    c. intrauterine device (IUD)
12. Male patients must be surgically sterile (> 30 days since vasectomy with no viable sperm), abstinent, or if engaged in sexual relations with a WOCBP, the participant and his partner must be surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method from

screening until study completion, including the follow-up period and an additional 90 days after the last dose of study medication

13. Males will not donate sperm for at least 90 days after the last dose of study medication
14. Partners of male patients and female patients will report pregnancy occurring within 90 days from cessation of study medication
15. Patients can be on other medication (on and off label), apart from the ones specifically outlined in the Exclusion Criteria to treat COVID-19 respiratory disease that the investigator deems clinically relevant in combination with the study drug
16. Patients can concomitantly receive any standard of care as per investigators' clinical decision; standard of care may encompass any approved medication, on or off label apart from the ones specifically outlined in the exclusion criteria. Concomitant medication may be other medication(s) apart from the ones specifically outlined in the Exclusion Criteria

Exclusion Criteria- Part A

1. Patients who cannot follow-up with study participation requirements
2. Investigator considers patient is inappropriate to enroll in the trial
3. Pre-existing chronic respiratory condition(s), obstructive or restrictive, for which the patient is actively taking concomitant medication are excluded. Patients with history of Idiopathic Pulmonary Fibrosis (IPF), lung cancer, pulmonary arterial hypertension, other interstitial lung diseases, severe cardiac insufficiency (grade IV) are excluded irrespective of whether they are actively being medicated for those conditions or not
4. Pre-existing co-morbid conditions preventing outcome assessments, e.g., neurological, medical, orthopedic injury/disability, disease or condition that would prevent ability to transfer and walk for 6 minutes, prior to confirmed COVID-19 diagnosis
5. Co-morbid diagnosis of tuberculosis
6. Unstable angina or myocardial infarction in the last month prior to screening
7. Pre-existing co-morbidity associated with life expectancy less than 1 year
8. Present life expectancy less than 3 days and/or LDH > 360

   Note: If in the opinion of the Investigator an elevation of LDH > 360 at the time of screening is likely due to persistent effects from COVID-19 infection and expected to improve over time by ruling out all other potential causes or contributory factors for elevated LDH, the Investigator may use clinical judgement to enroll the patient and monitor LDH levels per protocol.
9. Body mass index ≥ 50 kg/m^2
10. Resting heart rate of ≥ 120 bpm, systolic blood pressure of > 180 mm Hg and a diastolic blood pressure of > 100 mm Hg and/or or a fall in pulse oximetry oxygen saturation (SpO_2) to <80% upon ambulation
11. Sepsis, septic/hypovolemic/cardiogenic/neurogenic shock
12. Patients on MV, ECMO, NIV, HFNO and/or other high flow oxygen FiO2 $\geq$35% and $\geq$ 8 lpm within the last 72 hours prior to screening. Low flow supplemental oxygen is allowed.
13. History of anaphylactic reaction (particularly reactions to general anesthetic agents); allergic reaction due to any drug which led to significant morbidity; prior allergic reaction to pirfenidone
14. Known symptoms of dysphagia or known difficulty in swallowing capsules and/or total gastrectomy
15. Patients undergoing dialysis or hemoperfusion, or with a history of dialysis or hemoperfusion,

or anticipated to require dialysis or hemoperfusion within 72 hours of screening or severe renal impairment (defined as creatinine clearance rate <30 mL/min) at the time of screening/ baseline

16. Use of any of the following drugs:
    a. Fluvoxamine, enoxacin, ciprofloxacin.
    b. Treatment with steroids under institutional protocols and guidelines to manage COVID-19 pneumonia/respiratory symptoms is allowed. Use of steroids off-label to treat non-COVID-19 related conditions is not allowed.
    c. Any Investigational Agents (i.e., non-approved or nonauthorized drugs), with the exception of those used for COVID-19 respiratory diseases that the investigator deems clinically relevant in combination with the study drug, as described below:

       i. Allowed agents
       - Patients who had received prior investigational agents for COVID-19 but are no longer taking those drugs are allowed.
       - Inhaled corticosteroids are allowed.
       - Patients that received prior convalescent plasma are allowed; however, concomitant convalescent plasma is excluded.

       ii. Excluded agents
       - Patients on concomitant experimental anti-viral, anti-fibrotic or anti-inflammatory therapies are excluded.
       - Any investigational agent not explicitly on this list should be reviewed by the medical monitor prior to initiating therapy or enrolling participant

    d. Other inhibitors of CYP1A2 (including but not limited to methoxsalen or mexiletine)
    e. Inducers of CYP1A2 (such as phenytoin), CYP2C9 or 2C19 (including but not limited to carbamazepine or rifampin)
    f. Drugs associated with ***substantial risk for prolongation of the QTc interval*** (including but not limited to moxifloxacin, quinidine, procainamide, amiodarone, sotalol). Note that QTc prolongation is not an all / nothing drug effect, and specifically the administration drugs such as hydroxychloroquine do not preclude participation in this trial but does mandate measurement of the QTc every 6 hours until deemed necessary in accordance with investigator judgement
    g. Vaccination with a live vaccine is not permitted during the period from 4 weeks prior to screening to 4 weeks after the last dose
    h. Tobacco and nicotine product and/ or a positive cotinine test at screening
    i. Pirfenidone or nintedanib
17. Any other reason that, in the opinion of the Investigator, might interfere with the evaluation required by the study
18. For baseline AST ≥2.5xULN, ALT ≥2.5xULN and/or total bilirubin >1.5xULN (in the absence of history of Gilbert syndrome and/or the absence of alkaline phosphatase ≥2xULN or clinical evidence of cholestasis), or severe hepatic impairment
19. Patients requiring surgery due to an acute onset condition prior to randomization
20. Patients experiencing tachypnea. For the purposes of this study, tachypnea is defined as a resting respiratory rate ≥ 25 per minute.

Eligibility Criteria- Part B

The following Inclusion and Exclusion must be met before the patient can continue into the Open Label Extension.

Inclusion Criteria- Part B

1. Patient must have completed Part A of the study, through Day 91 of treatment.
2. In the opinion of the Investigator, the patient is a good candidate for continued treatment.

Exclusion Criteria- Part B

Patients ***must not meet*** any exclusion criteria listed for Part A.

Duration of Study and Study Treatment

Part A- Double-Blind (including SCOA Development Sub-study)

Over five days (up to 10 days to allow for evaluation of all screening assessments), patients will be screened and complete baseline assessments. Randomization occurs on the day following the Baseline Visit/assessment, i.e., shortly prior to the first dose of double-blind study medication.

All patients will be treated up to 91 consecutive days. Follow-up of study assessments post-randomization are at Days 14, 28, 56 and Day 91. For hospitalized patients who are discharged during the study, these patients will continue with study visits according to the Schedule of Events for Part A (Table 4).

A follow-up post-treatment completion visit will occur within 14 days of last day of study treatment.

The total duration of the study for each participant in Part A is up to 118 days, including screening and baseline of 5 days (up to 10 days to allow for evaluation of all screening assessments), treatment period of 91 days and off-treatment safety follow-up of 14 days including a 3-day study window for last visit.

Part B- Open Label Extension

Following completion of treatment in study Part A all patients will be treated up to 91 consecutive days. Follow-up of study assessments post- randomization are at Days 105, 119, 147 and Day 182. For hospitalized patients who are discharged during the study, these patients will continue with study visits according to the Schedule of Events for Part B (Table 5).

A follow-up post-treatment completion visit will occur within 14 days of last day of study treatment.

The total duration of the study for each participant who completes both Parts A and B is up to 209 days, including screening and baseline of 5 days (up to 10 days to allow for evaluation of all screening assessments), treatment period of 91 days for Part A, treatment period of 91 days for Part B, and off-treatment safety follow-up of 14 days including a 3-day study window for last visit.

Endpoints - Part A

Efficacy Endpoints

The efficacy endpoints are consistent with the primary and secondary objectives of the study. 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:

- *6-minute walk test (6MWT)* is the primary efficacy endpoint. All patients will complete a 6MWT test according to the Schedule of Assessments and aligned with the American Thoracic Society/European Respiratory Society Guidelines with COVID-19 modifications provided in the 6MWT study procedural manual. 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. This is a self-

paced test. Patients choose their own intensity of exercise and may stop and rest during the test. Changes from baseline in the 6MWT distance will be assessed using covariates in a mixed model. Dyspnea and fatigue are also assessed prior to the 6MWT and end of the test (Table 14).

Key Secondary Efficacy Endpoints:

- *Dyspnoea-12 (D-12)* measures "breathlessness severity" without reference to current activity and was developed for use in interstitial lung disease and COPD current experience ("these days") and is assessed at baseline and at follow-up visits. The tool generates a total score using 12 descriptor items including seven physical and five affective items with response options none (0), mild (1), moderate (2) or severe (3). The total score ranges from 1 to 36 whereby the higher score correlates with greater breathlessness severity (Table 17).

Other Secondary and Exploratory Efficacy Endpoints:

- *Saint George Respiratory Questionnaire-I (SGRQ-I)* is an idiopathic pulmonary fibrosis disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with interstitial lung disease. There are 34 self-completed items with 3 domain component scores (Symptoms, Activities, and Impacts), with higher scores indicating more limitations. Changes from baseline in the component scores of the SGRQ-I will be assessed (Table 16).
- *Modified Borg Dyspnoea Scale (mBDS)* is a measure of dyspnea. The mBDS is a self-administered unidimensional assessment tool that analyzes breathlessness under exertion. Changes over time will be derived (Table 13).
- *WHO Ordinal Scale for Clinical Improvement* will be assessed for changes from baseline over time. The WHO ordinal scale has the following nine categories: (0) Uninfected (No clinical or virological evidence of infection); (1) Ambulatory (No limitation of activities); (3) Hospitalized Mild Disease (Hospitalized, no oxygen therapy); (4) Oxygen by mask or nasal prongs; (5) Hospitalized Severe Disease (Non-invasive ventilation or high-flow oxygen); (6) Intubation and mechanical ventilation; (7) Ventilation plus additional organ support (i.e. extracorporeal life support (ECLS), continuous renal replacement therapy (CRRT), vasopressors); (8) Dead (Death); (Table 10).
- The *SF-36* (v2) is a self-administered questionnaire containing 36 items that measures functional status, well-being and overall evaluation of health in 8 domains and 2 summary component scores. It requires approximately 5-10 minutes to complete and uses scaled, ordinal responses (e.g., All of the time, Most of the time, A good bit of the time, etc.) Changes in the standardized component scores and domain scores will be calculated (Table 18).
- The proportion of patients with "normal" CT scan images will be defined in a responder analysis. Patients with pre-existing chest pathology pre-COVID-19 should be considered "normal" for those pre-existing items/findings. Chest CT scans will be performed according to the CT Scan manual. Lung lobe involvement will be assessed for each of five lobes via central read with the terms defined by the Fleischner Society (Hansell et al 2018). CT scans may also be analyzed with semi-Quantitative Lung Fibrosis (QLF) and computer-Aided Diagnosis (CAD) QLF Scores (Kim et al, 2010). Table 11 shows how each lobe will be scored, the total score for each finding per lobe (range 0 to 5), each finding across the lung (range 0-25) and total score (range 0 to 100) will be derived accordingly. Changes from baseline in this total score will be assessed. A responder analyses will be performed, in which the proportion of patients showing ground glass

opacities, fibrosis, consolidation, reticulation/bronchiectasis, and other radiographic abnormality improvement(s) by determining at least a 2-point score improvement for each abnormality across the five lobes (range 0-25), will be derived. 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 12. Shifts in these characteristics over the course of treatment will be of interest.

- *Biomarker* changes in will be assessed, including C-reactive protein (CRP), lymphocyte count, d-dimer, cardiac troponin, ferritin, lactate dehydrogenase (LDH), IL-6, TGF-β1, TNF-α, IL-1β, PDGF- β, GCSF, and VEGF.
- The proportion of patients with *'normal' chest X-ray* will be defined in a responder analysis. Patients with pre-existing chest pathology pre-COVID-19 should be considered 'normal' for those pre-existing items/findings.
- *Pulse oximetry* will be performed at rest and changes over time will be determined.
- *Number of hospital stay days* and *time to all-cause mortality* will be assessed.
- Percentage of patients who develop *respiratory exacerbations, severe or non-severe*
- *All-cause rehospitalizations*. Patients who are hospitalized at the time of randomization would need to have been discharged and readmitted for inclusion in this assessment.
- *Use of supplemental oxygen* from Baseline to end of treatment
- Daily COVID Symptom Assessment--change from baseline in the total score will be assessed. The psychometric properties of this scale will be explored.

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.

Population PK

Using plasma concentration versus time data, population pharmacokinetic analysis will be performed to assess the exposure-response characteristics of LYT-100 and its metabolite(s).

COA Development Sub-study

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

Endpoints- Part B

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, and all are as described for Part A (see above).

- 6-minute walk test (6MWT)
- Dyspnoea-12 (D-12)
- Modified Borg Dyspnoea Scale (mBDS)
- Saint George Respiratory Questionnaire-I (SGRQ-I)
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2)
- The proportion of patients with “normal” CT scan images will be defined in a responder analysis.
- The proportion of patients with ‘normal’ chest X-ray will be defined in a responder analysis.
- Pulse oximetry
- Number of hospital stay days and time to all-cause mortality
- Percentage of patients who develop respiratory exacerbations, severe or non-severe
- All-cause rehospitalizations.
- Use of supplemental oxygen

Statistical Methods for Part A:

The primary focus of the statistical analysis is on the double-blind comparison of LYT-100 to placebo (Part A). The following methods describe those for Part A; Part B methods are provided at the end of this section. Note that a comprehensive SAP will be written, in which the methods of statistical analysis will be described separately for Part A from Part B.

Sample Size

The study will utilize a suite of endpoints to measure patient clinical function and health-related quality of life. The sample size was based on both the 6MWT (a measure of patient clinical function).).

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 patients 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., patients 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 estimation.

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 of 75 meters, estimated correlation between observations on the same subject of 0.50, and an alpha of 5%.

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.

The sample size for the SCOA was estimated based on the need to achieve saturation in the generation of COVID Symptoms in this target population. It is estimated that approximately 20 patients will be sufficient for these purposes.

Randomization Stratification:

It was originally planned that approximately 168 patients will be randomized to Part A to receive LYT-100 or placebo in a 1:1 ratio; the actual number of patients randomized will be based on recruitment into the SCOA

The randomization will be stratified by the longest distance measured from two 6MWT at baseline and risk factors (

An additional approximately 20 patients will be randomized accordingly as part of the SCOA, using the same methods as for Part A patients.

Table 3). The intent of the use of these strata in the randomization is to ensure similar distribution of disease severity to the two treatment arms.

An additional approximately 20 patients will be randomized accordingly as part of the SCOA, using the same methods as for Part A patients.

Table 3. Randomization Stratification Levels (Study LYT-100-2020-02)

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**

Study Populations

- The Safety Population is defined as all patients who received at least one dose of study

treatment. All safety endpoints will be assessed using this population. Patients will be analyzed according to the treatment they actually received, regardless of which treatment they were randomized to.

- The Intent to Treat (ITT) population is defined as all randomized patients. All efficacy endpoints will be assessed using this population, with primary conclusions regarding study drug effect to be based on the ITT population outcomes (with the FAS and PP populations assessed for sensitivity and to support the ITT conclusions). Patients will be analyzed according to the treatment group they were randomized to, regardless of which treatment they actually received.
- 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 6-minute walk test. 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.
- The Per-Protocol (PP) population is 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 have no major protocol deviations that could affect interpretability of the efficacy outcome. Subjects who died or discontinued due to TEAE will be included in this population.
- The Pharmacokinetic (PK) Population is defined as all patients who receive study treatment and provide at least one plasma concentration measure. This population will be determined by the study pharmacokineticist.
- 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 symptoms diary. This population includes subjects who have also participated in the qualitative research interviews.

General Statistical Plan

A comprehensive statistical analysis plan will be written that will include details regarding the statistical analysis. The methods described below summarize the general approach.

Demographic information and patient disposition outcomes will be tabulated (including the number and percent of patients who are enrolled, who receive treatment, who prematurely discontinue and reasons for discontinuation, and who complete the study). Summary statistics for days of exposure and concentration of exposure will be provided.

The baseline for each variable (except the 6MWT) will be the last measurement obtained prior to first dose of study treatment. For the 6MWT distance, the longest distance of the two Day -1/ Day 1 distances will be used as baseline for purposes of analysis.

All efficacy analyses will be based on the ITT population unless otherwise specified. Baseline patient / clinical data, and all secondary endpoints will be presented descriptively as means, medians, or proportions with appropriate measures of variance, e.g., range, 95% CI).

The primary method of analysis for continuous endpoints is consistent with the sample size methodology and will thus utilize mixed models for repeated measures (MMRM), assuming a Gaussian distribution, an unstructured covariance matrix, and the Kenward-Roger approximation for denominator degrees of freedom. Fixed effects will include treatment, visit, the treatment by visit interaction, the baseline value of the endpoint as a covariate, and study center; however, the SAP may specify additional covariates to be added to the model. By-visit pairwise comparisons will be assessed.

A sensitivity analysis of the primary and key secondary endpoints will be performed using a nonparametric Wilcoxon rank sum test to test the active vs. placebo comparison at each time point.

Categorical endpoints will be assessed at each time point using a Cochran-Mantel-Haenszel (CMH) test, stratified by center. For ordinal and other categorical endpoints, analysis using a Cochran-Mantel-Haenszel test with modified ridit scores to assess the differences in row mean scores between the treatment groups (referred to as a CMH-RMS) test statistic from the SAS PROC FREQ procedure will be used,

Kaplan-Meier plot and log-rank tests may assess time to all-cause mortality (if sufficient mortality data exist) as well as time to discharge from hospital (in days) and other time-to-event parameters, as the data permit. The proportion of all-cause mortality (deaths) through Day 91 will be tabulated.

Correlational analysis may also be undertaken to identify patient factors and potential biomarkers that are associated with overall survival and successful resolution of all signs and symptoms of the disease. Statistical analyses will be performed using SAS, version 9.4. (SAS, Cary, NC).

Inferential Testing and Multiplicity Considerations

The significance level of all tests will be a 2-tailed alpha level of 0.05. There is one key secondary efficacy endpoint. Efficacy 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.

Safety Analysis

Safety analyses will be performed using the Safety Population. Adverse events, concomitant medications, clinical laboratory findings, physical examinations, ECGs, and vital signs for each participant will be tabulated or summarized descriptively, where appropriate.

Treatment-emergent adverse events and changes in laboratory, vital signs, and ECG parameters will be summarized. Shift tables will also be provided for clinical laboratory results. ECG results will be classified as normal and abnormal and summarized. ECG results for QTcF will also be classified as <450 msec, 450-500 msec or >500 msec.

Population PK (Part A only)

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.

Part B Methods

Part B is characterized by open-label treatment, and thus the analysis will be descriptive in nature. Where inferential methods are used, these will be used to better-inform as to the relative magnitudes of the longer-term effects from treatment with LYT-100, and not for hypothesis testing purposes.

The focus of the Part B analysis will be on the LYT-100 to LYT-100 group (as these patients will have been treated with up to 182 days with active treatment), but the Placebo to LYT-100 group will also be analyzed, with a focus on whether there are any meaningful differences in these exploratory efficacy endpoints from Part A compared to Part B.

OLE Safety Population: 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 will be assessed. Other analysis populations may be defined to help inform as to characteristics of the safety and exploratory efficacy profiles.

The primary objective of Part B is to assess safety and tolerability, and thus tabulations will be presented with this goal in mind. Analysis will include data from Part A, so that the slopes of changes over time from Study Day 1 through Study Day 182 can be described.

COA Development Sub-study Methods

A supplemental SAP will be written to define the methods to be used for the SCOA to evaluate the COA measures used in this study. As part of this sub-study analysis, and to further inform the basis for any observed treatment benefit from LYT-100 as well as to refine the precision of such estimate, it is possible that an exploratory analysis of the pooled data from both Part A and the COA Development Sub-study could be used in an analysis of exposure, safety, and efficacy outcomes.

Table 4: Study Schedule of Assessments for Part A: Double-Blind Placebo-Controlled

	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								
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
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.
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.

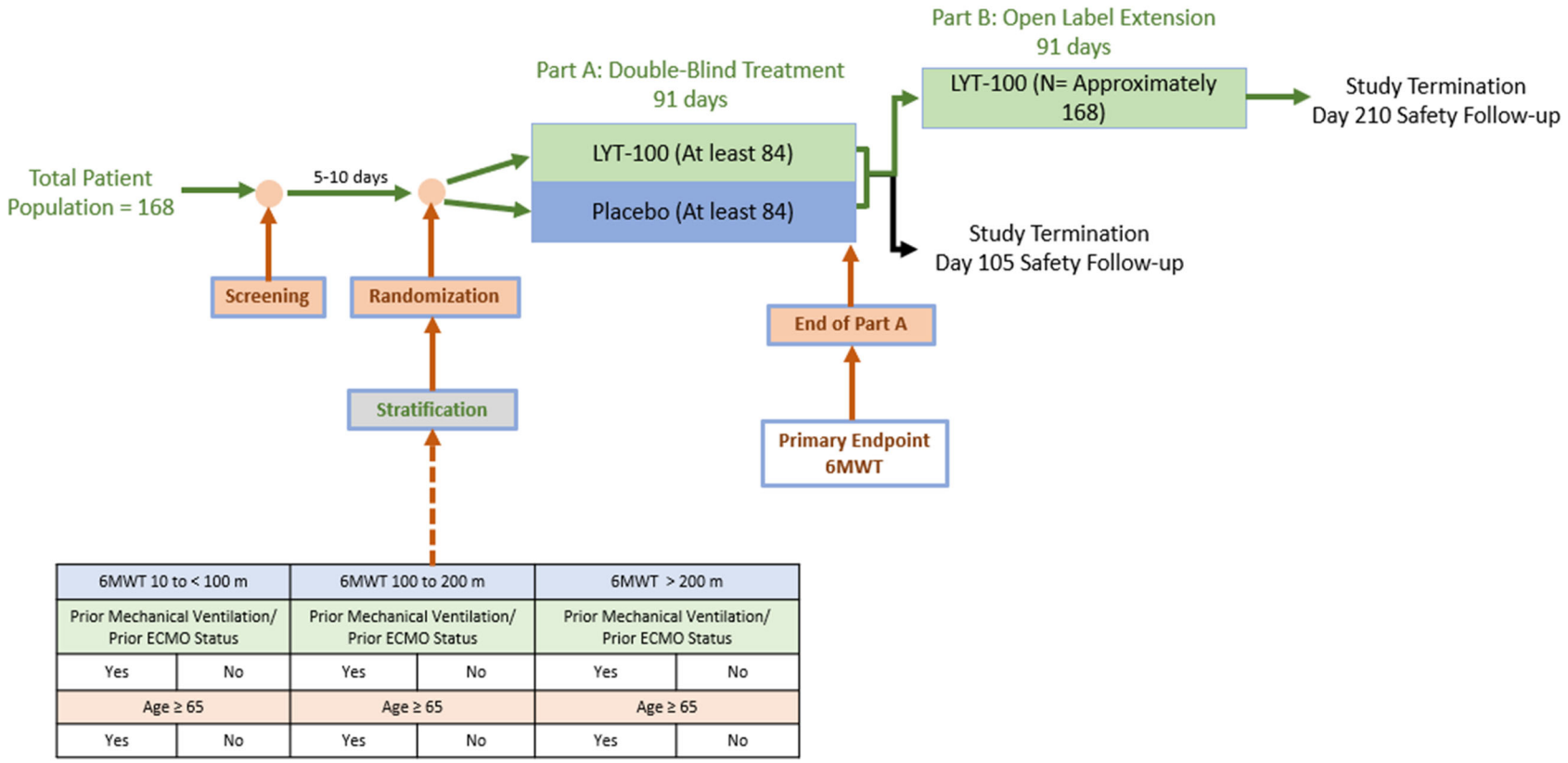
Table 5: Study Schedule of Assessments for Part B: Open Label Extension

	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 and/or rehabilitation, and hospitalization status		X	X	X	X	X	X
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
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. Abbreviated symptom directed physical examination will be performed.
3. 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,
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.

Figure 1: Study Design (Study LYT-100-2020-02)



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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
AUC	Area under the curve
AE	Adverse Event
ALB	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BASO	Basophils
BICARB	Bicarbonate
BID	Twice daily
BILI	Total Bilirubin
BILIDIR	Direct Bilirubin
BIPAP	Bilevel positive airway pressure
BMI	Body Mass Index
BP	Blood pressure
bpm	Beats per minute
CA	Calcium
cGMP	Current good manufacturing practice
CI	Confidence interval
CL	Chloride
COVID-19	Coronavirus 2019
CoV	Coronavirus
CPK	Creatine phosphokinase
CPAP	Continuous Positive Airway Pressure
CREAT	Creatinine
CRO	Clinical Research Organization
CRP	C-reactive protein
CRU	Clinical research unit
CSR	Clinical study report
DLCO	Diffusing capacity of the lungs for carbon monoxide
DLCOpp	Diffusing capacity of the lungs for carbon monoxide, percent predicted
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case Report Form
EOS	End of study
ESN	Eosinophils
EMA	European Medicines Agency
FDA	Food and Drug Administration
FEV	Forced Expiratory Capacity
FEV1	Forced Expiratory Capacity inf the first second
FEV1/FVC	Ratio between FEV1 and FVC
FiO2	Fraction of inspired oxygen

Abbreviation or Specialist Term	Explanation
FSH	Follicle-stimulating hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GI	Gastrointestinal
GLOBUL	Globulin
GLU	Glucose
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HCV	Hepatitis C virus
HGB	Hemoglobin
HFNO	High-Flow Nasal Oxygen
HR	Heart rate
HREC	Human Research Ethics Committee
HRQol	Health related quality of life
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
INR	International normalized ratio
IP	Investigational product
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IV	Intravenous
K	Potassium
LDH	Lactate dehydrogenase
LFT	Liver function test
LYM	Lymphocytes
MedDRA®	Medical Dictionary for Regulatory Activities
mBDS	Modified Borg Dyspnoea scale
MERS	Middle east respiratory syndrome coronavirus
MM	Medical Monitor
MV	Mechanical ventilation
n	Number
NA	Sodium
NEUT	Neutrophils
NHMRC	National Health and Medical Research Council
NIV	Non-invasive ventilation
NSAID	Nonsteroidal anti-inflammatory drug
OCCBLD	Occult Blood
OCP	Oral contraceptive pill
OLE	Open label extension
OTC	Over the counter
PD	Pharmacodynamics

Abbreviation or Specialist Term	Explanation
PDGF-β	Platelet-derived growth factor beta
PE	Physical examination
PEF	Peak Exploratory Volume
PFT	Pulmonary Function Test
PHOS	Phosphate
PI	Principal Investigator
PK	Pharmacokinetics
PLAT	Platelets
PO2	Partial pressure of oxygen
PP	Pharmacokinetic population
PR	Pulse rate
PROT	Protein
PT	Preferred term
RT-PCR	Reverse transcription polymerase chain reaction
QoL	Quality of life
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cells
RETI	Reticulocytes
RPSD	Randomization plan and specifications document
RR	Respiration rate
RV	Residual Volume
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe acute respiratory syndrome
SCOA	Clinical Outcome Assessments Development Sub-Study
SD	Standard deviation
SF-36 v2	36-item quality of life questionnaire; version 2
SGRQ-1	Saint George Respiratory Questionnaire - IPF version
SOC	System organ class
SpO2	Oxygen Saturation
SPGRAV	Specific Gravity
STST	Sit-to Stand test
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TGF-β1	Transforming growth factor beta 1
TID	Three times a day
TLC	Total lung capacity
TNF-α	Tumor necrosis factor alpha
TROP1	Troponin 1
VT	Tidal Volume
U	Urea
UROBIL	Urobilinogen
VEGF	Vascular endothelial growth factor
WBC	Leukocytes (white blood cells)
WHO	World Health Organization
WOCBP	Woman of childbearing potential
6MWT	Six-minute walk test

1. BACKGROUND AND INTRODUCTION

1.1. Introduction

SARS-CoV-2 virus and the resulting respiratory disease, coronavirus disease 2019 (COVID-19), is rapidly spreading around the globe, with an overall case fatality rate of approximately 5% (Wu 2020, Baud 2020, Zhu 2020). As of June 12, 2020, more than seven million and four hundred thousand deaths have been confirmed around the world (Baud 2020). These have been increasing in many countries in an exponential fashion with new regions recently reporting new outbreaks.

The most common presenting symptoms of COVID-19 are cough, fever, and malaise (Guan 2020, Huang 2020, Jiang 2020). In moderate to severe cases worsening pulmonary function, pneumonia, lung damage, and death can ensue (Chen 2020a). Chest radiographs may show evidence of pneumonia which is typically bilateral, while CT scans show ground glass opacity, smooth or irregular, interlobular septal thickening, ill-defined margins, air bronchograms, crazy paving pattern, thickening of the adjacent pleura, nodules, cystic changes, bronchiolectasis, pleural effusion, or lymphadenopathy (Zhao 2020). The presence of significant radiologic abnormalities in the lung are indicative of progression and poor prognosis. COVID-19 survivors have lung fibrosis and reduced pulmonary function. Data from other relevant causes of lung injury informs the potential long-term consequences of COVID-19 (Chesnutt 1997; Ichikado 2012). ARDS and mechanical ventilation—both of which can occur in COVID-19—cause persistent lung fibrosis, pulmonary dysfunction, and diminished of quality of life (Cabrera-Benitez 2014). Similarly, previous viral pneumonias related to SARS-CoV-2 have also caused lung fibrosis and pulmonary dysfunction that continues after the acute infection has resolved. In the case of SARS, these issues have persisted for nearly 15 years (Zhang 2020). COVID-19 post-discharge studies suggest a similar phenomenon, further reinforcing the need for early intervention to prevent lung fibrosis.

While the epidemiology of COVID-19 disease is influenced in part by test sampling practices and demography in different countries, a wide range of severity of illness has been recognized. Cases frequently occur with minimal symptomatology and detection in asymptomatic individuals has been well documented (Wang 2020). On the other hand, severe cases with fulminant multisystem involvement may occur (Hu 2020, Greenland 2020). Among cases admitted to ICUs requiring mechanical ventilation, ARDS occurs in one-third to one-half, and ten percent or more of ICU patients will have complicating acute renal failure (Yang 2020). The median time from ICU admission to death in an early series of 52 patients in China was 7 days (Yang 2020). While older age and the presence of comorbidities portends a worse prognosis, fatal cases have occurred in otherwise young and/or healthy individuals. While too soon to know the long-term effects among survivors, based on experience with other severe viral infections delayed morbidity and mortality, including development of pulmonary fibrosis, is expected (Venkataraman 2017).

The understanding of the pathophysiology of COVID-19 related lung damage is rapidly evolving. Post-mortem samples from patients with COVID-19 show diffuse alveolar damage suggestive of acute respiratory distress syndrome (ARDS), which has previously been identified in patients of related coronaviral infections like SARS and MERS (Xu 2020). ARDS in coronaviral infection likely results from inflammation, fluid accumulation in the lungs, and progressive fibrotic changes that interfere with gas exchange necessary for respiration.

Specifically, the initial viral replication generates an immune response, including increases in pro-inflammatory cytokines like IL-6, TNFα, and IL-1β, which recruit immune cells that cause local tissue damage and fibrosis (Gralinski 2018, Sun 2020). Ultimately, progressive lung damage from this inflammation and tissue re-modelling contributes to respiratory failure and is thought to be the ultimate cause of death in most patients. Preliminary reports from COVID-19 suggest a similar process, with striking increases in pro-inflammatory cytokines like IL-6 and TNF and development of radiological signs of inflammatory and fibrotic lesions in the lungs (Shi 2020).

1.2. Therapeutic Options for COVID-19 (Supportive, Antiviral, and Adjunctive)

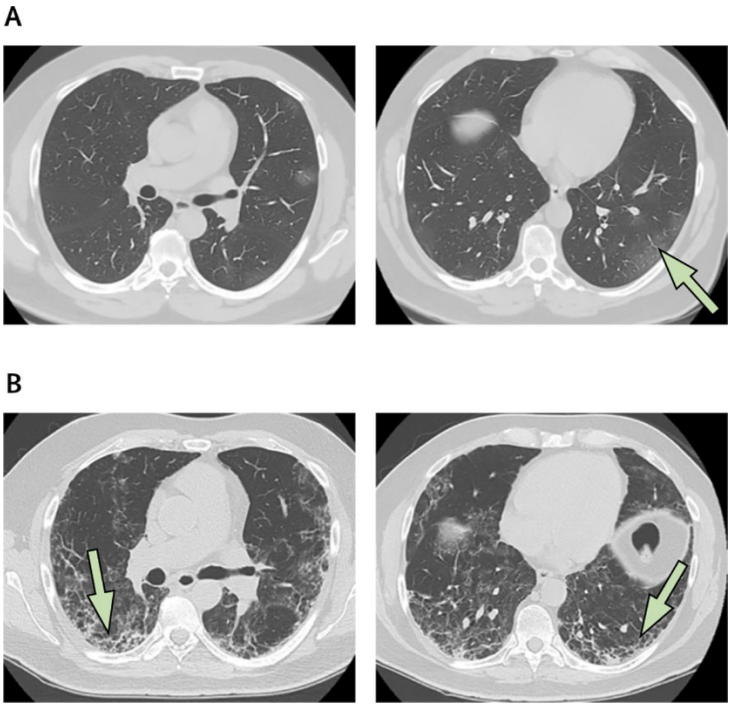
No effective specific treatment for COVID-19 has yet been identified. Although rapidly evolving as clinical experience is gained, principles of therapy are extrapolated from other life-threatening lung disease and include supportive respiratory therapies, anti-viral drugs, and adjunctive treatments. A vast array of anti-viral agents has been proposed and these are under investigation in more than 200 registered clinical trials. These agents include ritonavir boosted lopinavir, arbidol, remdesivir, and favipiravir among others (Cao 2020, Gautret 2020, Dong 2020). However, in general there is limited data for these agents to date with regards to clinically important outcomes. Adjuvant agents are those that do not have direct anti-viral effects per se but manage the complicating immune and other host inflammatory processes. These agents include immunomodulators such as tocilizumab, corticosteroids, convalescent plasma, and immune globulins, all of which are under current investigation (Mehta 2020, Wu 2020, Zhou 2020). The focus of most of these research efforts is early-phase disease, with the hope of preventing progression to critical illness. Few trials are focusing on patients who have progressed to requiring critical care, and even fewer on preventing progression to the fibrotic phase of ARDS, which appears to be when the number of deaths begins to peak.

Coronavirus Disease 2019 (COVID-19) is an acute respiratory disease caused by the coronavirus SARS-CoV-2. In some patients, COVID-19 is marked by rapid respiratory and systemic decline which can lead to death or lasting disabilities in survivors. 20-30% of hospitalized COVID-19 patients presenting with pneumonia will require intensive respiratory support (Chen 2020b; Guan and Zhong 2020). COVID-19 disease severity and mortality are largely driven by inflammatory and vascular destruction of tissue (Conti 2020). The early immune response to SARS-CoV-2 infection can progress to inflammation in both lungs, resulting in consolidation lesions and fibrosis (Li 2020b; Shi 2020). The initial SARS-CoV2 viral replication elicits an increase in pro-inflammatory cytokines like IL-6, TNF-α, TGF-β, and others. In some patients, an uncontrolled inflammatory response (Mehta 2020) results in acute respiratory distress syndrome (ARDS), which can necessitate mechanical ventilation (Wang 2020a).

In survivors, disease and invasive treatment both create fibrotic scarring and the risk of persistently diminished lung function (Chung 2020). Lung scarring can reduce the function of the lung, as reflected by changes in pulmonary function tests. These in turn reflect a patient's difficulties in everyday situations. For example, in interstitial lung disease, reduction in the diffusion capacity predicts oxygen desaturation during exercise (Rizzi 2015). In COVID-19, clinicians are already documenting rapid progression to lung fibrosis (Figure 2). The potential for fibrosis-mediated lung damage and the unprecedented scale of the current pandemic creates an enormous public health challenge: patients who have recovered from the acute symptoms of

COVID-19 yet have persistent pulmonary dysfunction. New therapeutic options are needed to address the underlying inflammation and fibrotic mechanisms that lead to lung scarring and long-term respiratory complications in COVID-19 survivors. Here we propose an approach using LYT-100, a clinical-stage, antifibrotic and anti-inflammatory drug for the treatment of COVID-19 related respiratory complications.

Figure 2: Lung CT of a patient with coronavirus disease 2019.



(A) Images of peripheral mild ground glass opacities in the left lower lobe (arrow). (B) Three weeks later, at the same lung zones, the disease has rapidly progressed, and fibrotic changes are now evident (arrows). Source: 10.1016/S2213-2600(20)30222-8

In COVID-19, acute disease course can be modeled in three stages: 1) an initial response mounted by the immune system to the virus, 2) a potential secondary interferon-driven immune response leading to tissue damage, and 3) a final hyperinflammation in which an inflammatory macrophage response leads to aberrant tissue repair and ultimately fibrosis (Merad and Martin 2020; Siddiqi and Mehra 2020). In earlier stages, the presence of serum cytokines and other inflammatory markers are predictors of disease severity and death (Chen 2020a; Ruan 2020; Zhou 2020) and can be used to predict patients at critical risk (Yan 2020). As the disease progresses, more severe patients have an imbalanced macrophage population in lung tissue tilted toward inflammation (Liao 2020). These infiltrating macrophages carry a gene signature associated with tissue repair and fibrosis. The immune system transitions from repelling the initial insult to repair, but inflammation can lead instead to fibrosis or scarring. A similar phenomenon has been observed in patients with ARDS undergoing mechanical ventilation (Cabrera-Benitez 2014).

The transition from inflammation to fibrosis can be visualized in COVID-19 patients with pneumonia. Early imaging shows inflammation-related opacification, while later tests reveal a characteristic pattern of lung damage due to interstitial lung remodeling, likely alveolar epithelial cell injury (Shi 2020). Chest X-rays show evidence of pneumonia, while CT scans show ground glass opacity, smooth or irregular, interlobular septal thickening, ill-defined margins, air bronchogram, "crazy-paving" pattern, thickening of the adjacent pleura, nodules, cystic changes, bronchiolectasis, pleural effusion, or lymphadenopathy. In more severe cases of COVID-19, the process of lung fibrosis likely begins early, and histological changes including fibrotic organizing pneumonia are present (Polak 2020). Antemortem and postmortem studies have revealed diffuse alveolar damage (Barton 2020) and microvascular thrombosis that add to the risk of lung fibrosis, if not already present (Polak 2020).

The COVID-19 pandemic has been underway for less than a year, and post-discharge data are rapidly emerging. A high proportion of mild, moderate and severe COVID-19 patients (17-53%) show signs of lung fibrosis already at three weeks post symptom onset (Li 2020a; Ye 2020). Clinician investigators are also reporting lung fibrosis that persists beyond the acute infection, and follow-up CT scans are being considered to evaluate permanent lung scarring (Hosseiny 2020). Of COVID-19 patients with pneumonia, 44% of patients had fibrosis on CT imaging at 9 days post-discharge (Yu 2020). The group of patients with fibrosis had higher CRP and IL-6 during their hospitalization, supporting the link between inflammation in the acute phase and fibrosis during the transition to recovery. Compared to the worst CT scan, the follow-up CT scan fewer involved segments and more intense ground glass opacification. While features like interstitial thickening and crazy paving pattern mostly resolved, other more fibrotic patterns like irregular interface and parenchymal band emerged or persisted.

Fibrosis in the lungs can impair lung capacity, pulmonary function, and gas exchange. COVID-19 patients with lung fibrosis had higher rates of shortness of breath, or dyspnea, than those without (Yu 2020). Emerging data from pulmonary function testing also suggest quantitative changes in COVID-19 survivors who were hospitalized. After discharge, COVID-19 patients had reduced diffusing capacity of the lung for carbon monoxide percent predicted, DLCO%, as well as an abnormal ratio of first forced expiratory volume (FEV1) to forced vital capacity (FVC), FEV1/FVC%. These deficits can improve somewhat with respiratory rehabilitation but do not return to normal (Liu 2020). Another study in COVID-19 that included mild and severe cases found that nearly half (47%) of all patients had impairments in gas exchange, including 30% of mild patients (Mo 2020). These deficits in DLCO were accompanied by less common abnormalities in spirometry, including changes in FVC, FEV1, and FEV1/FVC. The DLCO% reflects the ability of the lungs to conduct gas exchange, and impairment in gas exchange results from reducing the available pulmonary vascular surface and thickening of the alveolar wall. Fibrosis in the alveolar wall can impair the diffusion of oxygen. This can lead to impaired respiratory function and serve as a predictor for deleterious outcomes. For example, in SARS, changes in DLCO% were thought to be more sensitive than high-resolution CT scans, as radiologic changes might lag behind functional changes (Xie 2005).

COVID-19 patients with post-acute impairment in lung function from fibrosis or residual inflammation can have dyspnea and deficits in pulmonary function testing. These deficits can translate into problems with physical functioning, similar to those observed after ARDS or SARS. The 6-minute walk test (6MWT) is a simple to administer and interpret test of functional capacity, including exercise endurance and cardiopulmonary function. The 6MWT

has been used to test pulmonary function in fibrotic pneumonias, including IPF interstitial pneumonia (Eaton et al., 2004). The 6MWT has also been used to characterize physical functioning after viral pneumonias or ARDS, where the expected course is a recovery from an acute event. For example, a meta-analysis of post-SARS complications found a reduced 6MWT distance, which had the ability to improve some improvements up to 3-6 months but plateauing recovery after 6-12 months (Ahmed et al., 2020). Critical illness in general is associated with 6-minute walk test distance (6MWD) decline, but ARDS in particular results in lower 6MWD across a year of follow-up (Parry et al., 2019). Although ARDS patients recover over this year, the recovery is blunted compared to other critically ill patients, and patients with mechanical ventilation have even lower 6MWD values initially and through recovery (Li et al., 2006).

1.2.1. Pirfenidone

Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone; Deskar; Esbriet; AMR-69; S-7701) is an orally active small molecule and the first treatment that has been shown in clinical trials to slow the progression of idiopathic pulmonary fibrosis (IPF), a chronic, progressive, fibrosing interstitial lung disease with unknown etiology (Nathan 2017, King 2014a, King 2014b). It is approved for the treatment of IPF in many countries in Europe, North America, Latin America and Australasia. Pirfenidone has been shown to be generally well tolerated; the most common adverse events (AEs) are gastrointestinal symptoms (nausea, diarrhea, dyspepsia, vomiting), fatigue, rash, and photosensitivity reactions. This novel pyridine compound has anti-inflammatory, antioxidant, and antifibrotic properties. Among many other demonstrated effects, pirfenidone attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as TGF β and platelet-derived growth factor, or PDGF (Schaefer 2011). Pirfenidone has demonstrated activity in nonclinical models for multiple other fibrotic conditions, including those of the lung, kidney and liver (Schaefer 2011, Scriabine 2009).

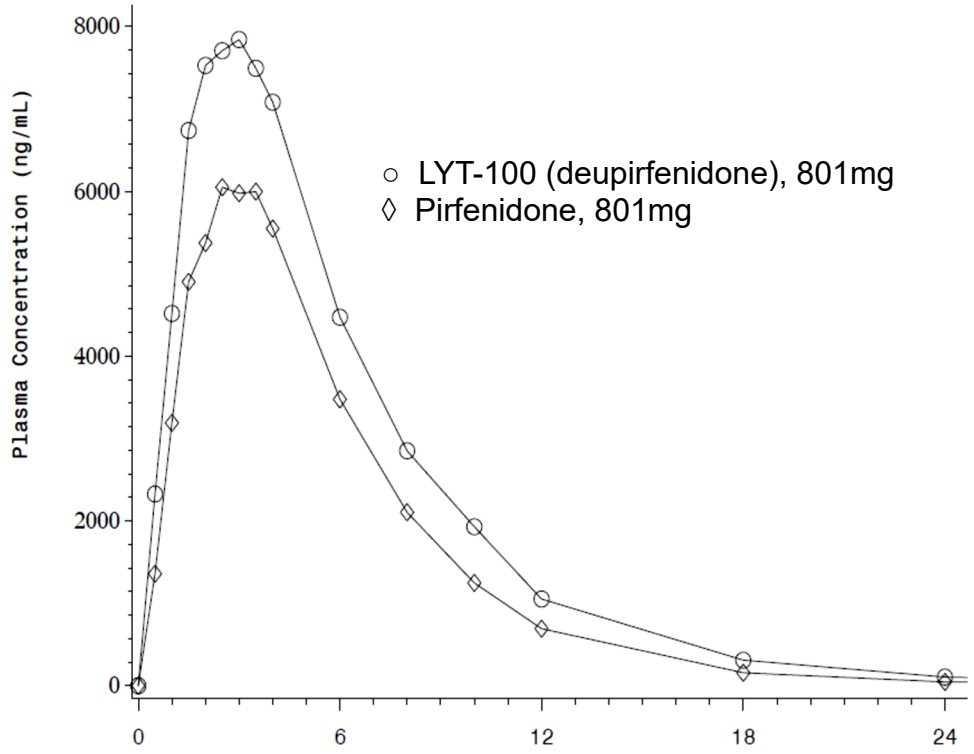
1.2.2. LYT-100 (Deupirfenidone)

LYT-100 (deupirfenidone) is a selectively deuterated form of pirfenidone. While pirfenidone has established efficacy in treating fibrotic conditions such as IPF, the short half-life of the drug requires that it be dosed at least three times per day. In addition, metabolism of pirfenidone, primarily by CYP1A2, has the potential to lead to interpatient variability in pharmacokinetics, safety, and efficacy. To address the possible limitations of pirfenidone, a selectively deuterated form of pirfenidone (LYT-100) has been developed, which is expected to be metabolized more slowly and with less variability between patients, compared with non-deuterated pirfenidone. LYT-100 therapy may therefore result in improved tolerability and efficacy compared with pirfenidone.

Both animal models and preclinical toxicology studies have been completed with LYT-100 that demonstrate its biologic activity and safety. These were followed by a phase I randomized, double-blind, single-dose crossover study to compare the pharmacokinetics, safety, and tolerability of LYT-100 with pirfenidone in healthy volunteers. Twenty-four subjects received a comparable single 801 mg oral dose of either LYT-100 or pirfenidone in Period 1 and, following washout, crossed over to receive the other treatment in Period 2.

Pharmacokinetic results demonstrated that deuteration of pirfenidone in LYT-100 resulted in an approximately 25% higher C_{max} and 35% higher overall exposure relative to the non-deuterated form, pirfenidone, as shown in Figure 3. Note that, in humans, approximately 80% of an oral pirfenidone dose is excreted in urine, with the majority of recovered drug material (>95%) excreted as the 5-carboxy-pirfenidone metabolite and less than 1% as unchanged pirfenidone.

Figure 3: LYT-100 increases C_{max} and AUC compared to pirfenidone when administered at an equal dose in healthy volunteers (Study SD-560-C-22)



1.2.3. Pirfenidone and LYT-100 as candidate adjunct therapies for severe COVID-19 disease

Pirfenidone has been suggested for the treatment or prevention of ARDS because of its multiple effects on the underlying inflammatory and fibrotic mechanisms. In rodent models of ARDS, pirfenidone ameliorates pulmonary inflammation and fibrosis induced by LPS, reducing cytokines like IL-1β and fibrotic regulators like TGF-β in the lungs (Corbel 2001). Pre-treatment with pirfenidone also reduces immune cell activation and levels of cytokines and TGF-β (30). Other potential mechanisms include the role of pirfenidone as a scavenger molecule protective against reactive oxygen species in the progression of lung damage. In an oleic-acid induced acute lung injury model, early treatment with pirfenidone reduced the severity of lung damage by physiology and histology (Mei 2005).

Clinicians have reported experiences with pirfenidone in non-viral acute respiratory distress, both in a pre-treatment and treatment regimen. IPF patients who are already receiving pirfenidone treatment have better outcomes measured by survival when admitted into respiratory

intensive care units with progression to ARDS, and this pre-treatment with pirfenidone may prevent inflammatory and fibrotic processes and lead to chronic lung damage (Vianello 2019). Anecdotal case reports and series in patients with post viral pneumonia raise the further possibility of a therapeutic effect.

The known effectiveness of pirfenidone in treatment of pulmonary fibrosis as well as the putative mechanism of action and clinical observations suggest that either pirfenidone or LYT-100 holds significant promise as adjuvant therapies for severe COVID-19 disease. The more favorable PK characteristics of LYT-100 suggest this is the better candidate to take forward into clinical trials in COVID-19 patients.

1.3. Summary of Nonclinical and Clinical Studies with LYT-100

1.3.1. Nonclinical Studies

LYT-100 has been evaluated in limited pharmacology, PK, metabolism and toxicity studies via the oral route (along with a pirfenidone comparator arm), since extensive nonclinical and clinical data are available for pirfenidone (CDER, 2014) including pharmacology; safety pharmacology; absorption, distribution, metabolism and excretion; toxicology studies with durations up to 6 months in rats and 9 months in dogs; reproductive toxicity; genotoxicity; carcinogenicity in mice and rats; and photosafety.

A brief summary of the non-clinical pharmacology, pharmacokinetics and toxicology of LYT-100 is provided in the following sections. More detailed information is provided in the LYT-100 Investigator's Brochure.

1.3.1.1. Pharmacology

In vitro and *in vivo* pharmacology studies conducted with LYT-100 have verified that deuteration does not alter the pharmacodynamics (PD) of pirfenidone with respect to its anti-fibrotic and anti-inflammatory mechanisms of action.

Safety pharmacology studies have not been conducted with LYT-100, as data on a full battery of safety pharmacology studies are available for pirfenidone including assessments of neurological, cardiovascular, respiratory, and gastrointestinal effects.

1.3.1.2. Pharmacokinetics

Single dose absorption and PK of LYT-100 and pirfenidone and the resulting metabolites have been studied in rats, dogs and chimpanzees, as summarized in the Investigator Brochure.

In brief, studies of the *in vitro* hepatic microsomal stability of pirfenidone and LYT-100 in human, monkey, dog, rat, and mouse liver microsomes demonstrated that deuteration improved the metabolic stability of pirfenidone in all species. An *in vitro* comparative mass balance study of pirfenidone and LYT-100 in human and rat liver microsomes and a comparative study of pirfenidone and LYT-100 metabolites in rat, dog, mouse and monkey liver microsomes revealed that metabolism of both compounds was qualitatively similar and showed that deuteration did not introduce novel metabolites, although metabolism of LYT-100 occurred more slowly. No studies have been carried out examining the potential for LYT-100 to interact with human transporter proteins, although pirfenidone does not appear to be a substrate for multiple transporters tested. The major human metabolite of pirfenidone, 5-carboxy pirfenidone, did not

inhibit transporters except for OAT1 and OAT3. Metabolite 5-carboxy pirfenidone is a substrate of human breast cancer resistance protein and P-glycoprotein.

1.3.1.3. Toxicology

A comparative dose range finding study of a single dose (male and female rats) or two daily oral doses (female rats) of LYT-100 and pirfenidone demonstrated findings consistent with previous reports on pirfenidone, and supported dose selection for a subsequent 4-/13-week oral toxicity study in rats, as described briefly below.

The objective of the sub-chronic, repeat-dose study was to evaluate the toxicity of LYT-100 (250, 500, and 750 mg/kg/day) or pirfenidone (750 mg/kg and 875 mg/kg) when administered orally once daily for 91 consecutive days to Sprague Dawley rats and to evaluate the potential reversibility of any findings following a 4-week recovery period. In addition, the toxicokinetic characteristics of LYT-100 and pirfenidone were determined.

There were no LYT-100- or pirfenidone-related ophthalmic, group mean body weight changes, clinical pathology or gross pathology findings. Non-adverse LYT-100- and pirfenidone-related changes were observed in clinical observations, body weight gain, feed consumption, organ weights and histopathology. Test article-related organ weight changes included increased mean liver weights in males and females for both drugs. Increased liver weight was correlated histopathologically with centrilobular hepatocyte hypertrophy (believed to be an adaptive change associated with drug metabolizing enzyme induction). These findings were not considered adverse and were correlated with LYT-100 C_{max} of up to 187,476 ng/mL (female) and 135,080 ng/mL (male) on Day 1.

Toxicokinetic analysis revealed that exposure to LYT-100 at a dose of 750 mg/kg was similar to the exposure to the same dose of pirfenidone.

1.3.2. Clinical Studies

The pharmacokinetics, safety, tolerability and food effect of LYT-100 has been tested in two studies in healthy volunteers:

- A Phase 1, randomized, double-blind, single-dose crossover study to compare the PK, safety, and tolerability of LYT-100 with pirfenidone in 24 healthy volunteers.
- A Phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose design to assess the safety, tolerability, PK and food effect profile of multiple doses of LYT-100 in healthy volunteers.

Single 801 mg oral doses of LYT-100 and pirfenidone were well tolerated and had a comparable safety profile. A total of 44 treatment-emergent adverse events (TEAEs) were reported during the study by 14 (58%) of the 24 participants enrolled. Most of these events were mild in severity and there were no events rated as severe. There were no deaths, serious adverse events (SAEs), or AEs leading to withdrawal of study drug reported during the study. The most common AE following either treatment was headache, reported by 21% of participants during each treatment. No significant changes in laboratory parameters, vital signs, or ECGs were observed following either treatment.

The pharmacokinetics of the single 801 mg dose of LYT-100 demonstrated an approximately 25% higher C_{max} and 35% higher overall exposure relative to pirfenidone. The C_{max} and overall

exposure were not associated with an appreciable difference in elimination $t_{½}$. Increased systemic exposure of LYT-100 was associated with a corresponding decrease in C_{max} and overall exposure of the most abundant circulating metabolite (5-carboxy metabolite). (See Figure 3 above).

Five dose levels of LYT-100 ranging from 100 mg BID to 1000 mg BID were assessed in the multiple ascending dose study. While the data remains blinded at this time, the TEAE profile demonstrates that LYT-100 is well tolerated over five days of BID dosing up to 1000 mg (2000 mg daily dose). There were no clinically relevant findings in vital signs, electrocardiograms, biochemistry, hematology, urinalysis, or coagulation parameters. In total, 33 subjects experienced a total of 72 AEs. All AE's were graded as mild, and less than half of these AEs (33 of 72) were considered possibly related to treatment. The most common TEAE was headache (25% of subjects). There have been no SAEs

Pharmacokinetic data for the five dose levels of LYT-100 showed a dose proportional increase in AUC and Cmax for both LYT-100 and the major metabolite, 5-carboxy-pirfenidone. C_{trough} was similar between subjects at each dose level, and no obvious durg accumulation was observed.

In a subsequent cohort, a food effect for LYT-100 was noted on C_{max}, with a 23% lower C_{max} in the presence of food. The AUC0-∞ was similarly decreased by 19% in the presence of food. It should be noted that the food effect for pirfenidone is even more pronounced, with a 49% decrease in the C_{max} in the presence of food. The decrease in the pirfenidone AUC0-∞ is similar to that of LYT-100 in the presence of food (16% and 19%, respectively).

No food effect was observed on either Cmax or AUC0-∞ for the three metabolites measured, and there was no food effect on T_{max} for any analyte. This is different from the effect observed on pirfenidone, where food slows the absorption of the drug, with a median Tmax shift from 0.5 to 3.0 hours.

Additional details for both studies are provided in the Investigator's Brochure.

1.4. Summary of Clinical Studies of Pirfenidone

The safety of pirfenidone has been evaluated in over 1500 healthy volunteers and patients with IPF, including four Phase 3 multicenter, double-blind, placebo-controlled, randomized studies. Three multinational studies (CAPACITY 004 and CAPACITY 006, N=779 patients; ASCEND, N=555 patients) included a total of 1,334 patients (King 2014b, Noble 2011). A study conducted in Japan included 275 patients (Taniguchi 2010).

Following treatment for up to 72 weeks with either pirfenidone 801 mg TID (three times a day), 399 mg TID, or placebo, the majority of patients (98%) in both the CAPACITY 004 and 006 studies (Nobel 2011), experienced at least one treatment-emergent AE. The most common AEs in the pooled pirfenidone 801 mg TID group, with at least a 1.5-times increased incidence relative to placebo, were GI events (nausea, dyspepsia, vomiting, and anorexia), skin-related events (rash, photosensitivity), and dizziness; a dose-response in frequency was noted. Most AEs were assessed as mild to moderate in severity. Serious AEs were reported in 33% of the pooled pirfenidone group and 31% of the pooled placebo group. The incidence of patients discontinuing pirfenidone due to adverse events was low (15% of pooled pirfenidone group; 9% of pooled placebo group).

In the ASCEND study (King 2014b), gastrointestinal and skin-related events were more common in the pirfenidone group than in the placebo group; most AEs were assessed as mild to moderate in severity. The incidence of patients discontinuing pirfenidone due to adverse events was low (14% of pirfenidone group; 11% of placebo group). Excluding patients with worsening fibrosis, serious AEs were reported in 18.7% of patients in the pirfenidone group and 20.2% of patients in the placebo group.

In the Japanese study (Taniguchi 2010), photosensitivity, anorexia, dizziness and elevated γ-glutamyl-transpeptidase were significantly more common (≥5%; $p<0.05$) in the high-dose (600 mg TID) group than in the placebo group. Skin-related (photosensitivity, asteatotic eczema) and gastrointestinal AEs (abdominal discomfort) as well as decrease in white blood cells were more common in the low-dose (400 mg TID) group than in the placebo group. Photosensitivity was the major AE observed in 51% of the patients in the high-dose group and 53% in low-dose group. Of the patients who developed photosensitivity, most had mild events (70% in the high-dose group and 80% in the low-dose group), and the remainder had moderate events. Most of the AEs resolved after decreasing the pirfenidone dose or temporarily withholding the pirfenidone. The incidence of participants discontinuing pirfenidone due to adverse events was low in both dose groups (18% of high-dose pirfenidone group, 20% of low-dose pirfenidone group, 13% of placebo group).

Overall, pirfenidone was well tolerated in the Phase 3 studies. The most common AEs were gastrointestinal AEs (e.g., nausea, dyspepsia, diarrhea, vomiting), fatigue, anorexia, dizziness, rash and photosensitivity reactions. Serious AEs occurred infrequently and with similar incidence for pirfenidone and placebo participants. AEs leading to discontinuation of study treatment were infrequent and included nausea, rash and photosensitivity reactions.

Further information on clinical experience with LYT-100 and pirfenidone is provided in the Investigator's Brochure.

1.5. Summary of Potential Risks and Benefits of LYT-100

In nonclinical studies to date, no meaningful differences have been observed in the *in vivo* pharmacology and toxicology profiles of LYT-100 when compared with pirfenidone. In humans, LYT-100 is expected to have an AE profile similar to that of pirfenidone when participants achieve comparable systemic exposure. Therefore, AEs associated with the use of pirfenidone are considered expected with use of LYT-100 and prescribing recommendations for pirfenidone are expected to be applicable for LYT-100.

1.6. Study Rationale

Given the high case-fatality, incidence, and therefore expected mortality burden associated with COVID-19 disease, new therapeutic agents are emergently needed. Deupirfenidone is a promising candidate adjunctive therapy that may offer potential survival benefit when added to supportive care and anti-viral therapies. Additionally, while it may attenuate the severe complications acutely, by means of its anti-fibrotic properties it may also hold significant potential for long term functional and survival benefits. A clinical trial is needed before this agent can be added to the therapeutic armamentarium. In addition, critically ill patients have substantially different dosing requirements to patients with normal organ function due to abnormalities in volumes of distribution, fluid shifts, altered metabolism, and risk of adverse

reactions (Roberts 2016). While evaluating the effect of deuterated pirfenidone (LYT-100) in pulmonary complications related to COVID-19, the safety and tolerability effects of LYT-100 at a lowered dose and twice per day dosing regimen will also be monitored closely in this post-acute adult patient population.

This study will be conducted in patients who test positive for COVID-19 and will aim to address issues in post-acute patients with COVID-19 infection. The study will be conducted at multiple study centers in Asia, the United States and Europe. Other regions may be added as the pandemic mandates (i.e., South America). Screening period will not exceed 10 days. Only patients who meet all the applicable inclusion and none of the applicable exclusion criteria per study part will be enrolled.

1.7. Treatment Periods

This study includes screening, study treatment, and post-treatment periods. The treatment periods will be conducted in two parts, A and B.

- Patients will be screened and complete baseline assessments.Randomization (Day 1) occurs on the day following the Baseline Visit/assessment.
- Part A: 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.
- For patients who choose to terminate early, or who complete Part A but do not elect to continue in Part B, a follow-up post-treatment completion visit will occur within 14 days of last day of study treatment ± 3 days.
- Part B: Patients who complete 91 days of treatment in Part A and who are eligible may elect to participate in Part B. All patients will be treated in Part B up to 91 consecutive days, with study assessments on Days 91, 105, 119, 147 and 182.
- For patients who terminate early from Part B, or after completion of Part B, a follow-up post-treatment completion visit will occur within 14 days of last day of study treatment ± 3 days.

The total duration of the study for each participant in Part A is up to 118 days, including screening and baseline of 5 days (up to 10 days to allow for evaluation of all screening assessments), treatment period of 91 days and off-treatment safety follow-up of 14 days including 3-day study window for last visit.

The total duration of the study for each participant who completes both Parts A and B is up to 209 days, including screening and baseline of 5 days (up to 10 days to allow for evaluation of all screening assessments), treatment period of 91 days for Part A, treatment period of 91 days for Part B, and off-treatment safety follow-up of 14 days including a 3-day study window for last visit.

1.8. Participant Population

This study will enroll adults age 18 to 80 diagnosed as post-acute, COVID-19 patients, warranting hospital admission as per investigator's judgement, or previously hospitalized.

For the purposes of this study, "post-acute" is defined as patients who require ***none*** of the following:

- mechanical ventilation (MV);
- extracorporeal membrane oxygenation (ECMO);
- non-invasive ventilation (NIV); (i.e. continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP));
- high-flow nasal oxygen therapy (HFNO); and/or
- other high flow oxygen with FiO2 ≥35% and flow rate ≥ 8 lpm.

Diagnosis of COVID-19 may be done at a central or local laboratory test from any biological material source. The accepted tests include positive result of a validated molecular RT-PCR diagnostic test or SARS-CoV-2 RNA result from a clinical specimen deemed clinically associated with the current episode of illness.

Women of childbearing potential will be included and are subject to contraceptive requirements during the study from Screening until study completion, including the follow up period (see Section 4.6.1). Women of childbearing potential must demonstrate negative pregnancy testing at Screening and prior to study drug administration on Day 1 and be willing to have additional pregnancy tests as required throughout the study. This is in line with regulatory Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, FDA 2006.

1.9. Ethical Principles

This study will be conducted in accordance with the principles of the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and with the NHMRC National Statement on Ethical Conduct in Human Research (updated 2018). The conduct of the study will be in accordance with the ICH Integrated Addendum to E6(R1): Guideline for Good Clinical Practice ICH E6(R2).

This study will be conducted under a protocol reviewed and approved by an IEC / IRB / HREC and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

2. TRIAL OBJECTIVES AND PURPOSE

2.1. Objectives- Part A

This study 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. The objectives are consistent with the study design. Efficacy endpoints are defined in Section 15.6.

COVID-19 respiratory disease is a multi-faceted indication, and thus this clinical study includes a number of objectives (and corresponding endpoints) to adequately describe the effects of study treatment. To that end, there are primary and key secondary objectives that form the basis for study success, while other secondary objectives and exploratory objectives will inform overall conclusions and allow for assessment of a preponderance of evidence as to the benefit of LYT-100 in this population.

2.1.1. Primary Objective

To evaluate the effect of LYT-100 on the change in distance walked on six-minute walk test (6MWT) performed and must conform to the American Thoracic Society/European Respiratory Society Guidelines (Crapo et al 2002).

2.1.2. Key Secondary Objective

To evaluate the effect of 91 days of treatment with LYT-100 compared to placebo on dyspnoea-12

2.1.3. 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 WHO Ordinal Scale for Clinical Improvement
4. Quality of Life 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 QLF assessment
6. Inflammatory, fibrosis and other biomarkers
7. Pulmonary exacerbations, severe and non-severe
8. All-cause rehospitalizations. (Patients who are hospitalized at the time of randomization would need to have been discharged and readmitted for inclusion in this assessment.)
9. Severity of lung lobe(s) involvement, using CT Scan
10. Pulse oximetry
11. Chest X-ray
12. Length of hospital stay
13. All-cause mortality
14. Use of supplemental oxygen from Baseline to end of treatment

15. COVID Symptom Assessment

2.1.4. 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.

2.1.5. Pharmacokinetic Objective

To evaluate the plasma concentration vs. time data via population pharmacokinetic analysis of LYT-100, and its metabolite(s)

2.2. Objectives- Part B

2.2.1. Primary Objective

To assess the longer-term safety, tolerability, and efficacy of LYT-100 through up to 182 days of treatment.

2.2.2. 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:

- Change in distance walked on six-minute walk test (6MWT) performed and must conform to the American Thoracic Society/European Respiratory Guidelines (Crapo et al 2002)
- Dyspnoea-12
- Saint George Respiratory Questionnaire-I (SGRQ-I)
- The Modified Borg Dyspnoea Scale (mBDS)
- The WHO Ordinal Scale for Clinical Improvement
- Quality of Life assessment as collected using the SF-36 v2, including 8 domains and 2 component scores
- Number of lung segments involved using CT Scan and QLF assessment
- Pulmonary exacerbations, severe and non-severe
- All-cause rehospitalizations
- Severity of lung lobe(s) involvement, using CT Scan
- Pulse oximetry
- Chest X-ray

- Length of hospital stay
- All-cause mortality
- Use of supplemental oxygen from Baseline to end of treatment

2.3. Study Objectives COA Development Sub-study

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 Dyspnea-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 COA Development Sub-study, patients will remain blinded to treatment.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This study is 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-100 750 mg, twice per day (BID) compared to placebo. Part B is an open label extension study for patients who complete Part A.

This study will enroll adults age 18 to 80 diagnosed as post-acute, COVID-19 patients, warranting hospital admission as per investigator's judgement, or previously hospitalized.

For the purposes of this study, "post-acute" is defined as patients who require ***none*** of the following:

- mechanical ventilation (MV);
- extracorporeal membrane oxygenation (ECMO);
- non-invasive ventilation (NIV); (i.e. continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP));
- high-flow nasal oxygen therapy (HFNO)[1]; and/or
- other high flow oxygen with FiO2 ≥35% and flow rates ≥ 8 lpm (i.e. venturi or non-rebreather masks).

Diagnosis of COVID-19 may be done at a central or local laboratory test from any biological material source. The accepted tests include positive result of a validated molecular RT-PCR diagnostic test, RNA or antigen test for or SARS-CoV-2 result from a clinical specimen deemed clinically associated with the current episode of illness.

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

After informed consent is obtained, patients will enter a screening phase for 5 days (up to 10 days to allow for evaluation of screening assessments), to determine eligibility. Patients are required to have all screening assessments, including training for the 6-minute walk test, and meet all inclusion/exclusion criteria for the trial prior to randomization. Eligible patients will be randomized to receive LYT-100 or placebo in Part A, in a ratio of 1:1, in conjunction with current standard of care for COVID-19. The randomization will be stratified by 6MWT baseline and other risk factors (see Table 7, below).

Standard of care will be administered as per investigator's medical judgement, based on the severity of the disease, and according to local government and/or institutional guidelines. LYT-

[1] High Flow Nasal Oxygen (HFNO) consists of nasal cannula connected to an oxygen flow meter with an air–oxygen gas blender and gas analyzer allowing FIO2 delivery of up to 100%. HFNO with **maximum** gas flow rates typically set between 40 and 60 liter per min, depending on the device, and provides an anatomical oxygen reservoir within the nasopharynx and oropharynx which is transmitted to the lower airways to generate positive end expiratory pressure (PEEP).

100 or placebo will be administered daily for up to 91 days. Patients will start participation in the study while either hospitalized, or at time of hospital discharge or post-discharge from hospital for COVID-19 respiratory disease.

The timing of randomization is dependent on type of qualifying respiratory support and date of initial confirmed COVID-19 diagnosis.

- Patients who have received any form of supplemental oxygen (except ECMO or MV) must initiate treatment within 90 days of initially confirmed COVID-19 diagnosis by molecular RT-qPCR
- Patients who were previously treated with ECMO or MV must initiate treatment within 132 days from initial confirmed diagnosis of COVID-19. See Table 6, below.

Table 6. Timing of Randomization Relative to COVID-19 Diagnosis and Qualifying Respiratory Support

Qualifying Respiratory Support	Initial Confirmed Diagnosis of COVID-19
Any form of supplementary oxygen other than ECMO or MV	Within 90 days
ECMO or MV	Within 132 days

Treatment assignments will remain blinded to the patient, study staff, and sponsor.

Patients will be seen either on the hospital ward and/or in the ICU during hospital stay or at discharge, or on a rehabilitation ward, an outpatient clinic or at the patient's home post-discharge. Note that for patients who were hospitalized and are discharged during the study, these patients will continue with study visits according to the Schedule of Events for Part A. For all patients, study follow-up visits will occur at Days 14, 28, 56, and 91. Patients in Part A who terminate early or elect to not continue will also have a follow-up visit 14 days, post-completion of study treatment in Part A. (See Figure 1.)

For those patients who qualify for Part B and enter the open label extension, study visits will occur at Days 91, 105, 119, 147 and Day 182. Patients in Part B who terminate early or elect to not continue will also have a follow-up visit 14 days, post-completion of study treatment in Part B. (See Figure 1.)

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

This protocol includes a COA Development Sub-study (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 21-Jan-2022, and includes a total of N=177 patients), additional enrollment (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 subjects 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, they will 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 analyses.
- Sub-study patients enrolled after completion of the Part A enrolment will NOT be included in the primary analyses of Part A outcomes.

3.2. Number of Patients

Approximately 168 eligible patients who no longer require mechanical ventilation, extracorporeal membrane oxygenation, non-invasive ventilation, continuous positive airway pressure, high-flow nasal oxygen therapy or other high flow oxygen (with FiO2 ≥35% and flow rate ≥ 8 lpm) at the time of randomization, will be randomized in Part A to receive LYT-100 or placebo, in a ratio of 1:1, with at least 84 patients randomized to LYT-100 and at

SCOA enrollment will remain open until an additional approximately 20 subjects are randomized as part of the SCOA.

Only patients who complete 91 days of treatment in Part A will be eligible for participation in Part B.

3.3. Treatment Assignment and Randomization

The randomization for Part A will be stratified by 6MWT baseline and other risk factors (Table 7).

Table 7: Randomization Stratification Levels (Study LYT-100-2020-02)

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**

Patients who elect to continue in Part B will not be re-randomized. Their original stratification for Part A will carry over into Part B.

3.4. Criteria for Study Termination

The study will be completed as planned unless:

- New information or other evaluation regarding the safety of the study medication indicates a change in the known risk/benefit profile for the compound, such that the

risk/benefit is no longer acceptable for patients participating in the study. This may be determined by the Sponsor in conjunction with the Medical Monitor, Investigator, DSMB, and/or regulatory authorities.

- The study is terminated by the Sponsor for administrative reasons.

If the Sponsor elects to terminate or suspend the study or the participation of the investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor. The procedure will be followed by the investigational site during the course of termination or study suspension.

3.5. Data Safety Monitoring Board (DSMB)

An independent, unblinded DSMB will assist with oversight of patient safety during both Parts A and B of this study. A Charter will be written to describe the purpose, members, meeting frequency, and data to be reviewed by the DSMB.

The DSMB will meet approximately monthly during enrollment and treatment to review unblinded safety and efficacy data of all patients.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Participant Inclusion Criteria-Part A

To be eligible for this study, patients must meet ***all*** of the following inclusion criteria:

1. Positive result of a molecular RT-qPCR diagnostic test, RNA or antigen test SARS-CoV-2 result from a clinical specimen deemed clinically associated with the current episode of illness, warranting hospital admission as per investigator's judgement, or previously hospitalized (central and/or local laboratory COVID-19 tests are accepted from any biological material source)
2. Hospitalization for COVID -19 respiratory disease and treated with supplemental oxygen (including MV, ECMO or any other means of oxygen administration) in hospital.

   Please note that admission to a hospital Emergency Department, temporary hospital or any other facilities used to treat acutely ill subjects which would otherwise be admitted to the hospital due to the total number of patients admitted to the facility exceeding capacity and response to the COVID-19 pandemic, or otherwise treated by hospital staff, falls under the category of hospitalization.

   Please also note that hospitalization can be any length of time on at least one calendar day and does not need to be ≥ 24 hours
3. Signed (written, electronic, or oral) consent on an IRB or Ethics Committee approved informed consent from the patient or Legally Authorized Representative prior to any study procedures
4. Male or female, aged ≥18 to ≤80 years of age, inclusively at the time of informed consent
5. Able to perform and willing to comply with all study procedures and requirements
6. Able to bear weight and ambulate a minimum of 10 m distance (use of inhaled oxygen permitted)
7. Randomization day is dependent on type of qualifying respiratory support and date of initial confirmed COVID-19 diagnosis as described in Table 6, above.
8. COVID-19 pneumonia findings on imaging (chest X-ray or CT Scan) with a minimum of two lung lobe involvement
9. Shortness of breath ≥ grade 3 on mBDS dyspnea scale
10. Laboratory parameters (CBC, biochemistry) deemed by the investigator as acceptable and/or not clinically significant to enroll the patient
11. Women of childbearing potential (WOCBP) must be non-pregnant and non-lactating, and must be abstinent from heterosexual intercourse for 90 days following last dose of study medication or agree to use one of the acceptable, highly effective double contraception:
    a. oral, intravaginal, or transdermal combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation
    b. oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
    c. intrauterine device (IUD)

12. Male patients must be surgically sterile (> 30 days since vasectomy with no viable sperm), abstinent, or if engaged in sexual relations with a WOCBP, the participant and his partner must be surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method from screening until study completion, including the follow-up period and an additional 90 days after the last dose of study medication
13. Males will not donate sperm for at least 90 days after the last dose of study medication
14. Partners of male patients and female patients should report pregnancy occurring within 90 days from cessation of study medication
15. Patients can be on other medication (on and off label), apart from the ones specifically outline in the Exclusion Criteria, to treat COVID-19 respiratory disease, that the investigator deems clinically relevant in combination with the study drug
16. Patients can concomitantly receive any standard of care as per investigators' clinical decision; standard of care may encompass any approved medication, on or off label apart from the ones specifically outlined in the exclusion criteria. Concomitant medication may be other medication(s) apart from the ones specifically outlined in the Exclusion Criteria.

4.2. Participant Exclusion Criteria-Part A

To be eligible for this study, patients ***must not meet any*** of the following exclusion criteria:

1. Patients who cannot follow-up with study participation requirements
2. Investigator considers patient is inappropriate to enroll in the trial
3. Pre-existing chronic respiratory condition(s), obstructive or restrictive, for which the patient is actively taking concomitant medication are excluded. Patients with history of Idiopathic Pulmonary Fibrosis (IPF), lung cancer, pulmonary arterial hypertension, other interstitial lung diseases, severe cardiac insufficiency (grade IV) are excluded irrespective of whether they are actively being medicated for those conditions or not.
4. Pre-existing co-morbid conditions preventing outcome assessments, e.g., neurological, medical, orthopedic injury/disability, disease or condition that would prevent ability to transfer and walk for 6 minutes, prior to confirmed COVID-19 diagnosis
5. Co-morbid diagnosis of tuberculosis
6. Unstable angina or myocardial infarction in the last month prior to screening
7. Pre-existing co-morbidity associated with life expectancy less than 1 year
8. Present life expectancy less than 3 days and/or LDH > 360

   Note: *If in the opinion of the Investigator an elevation of LDH > 360 at the time of screening is likely due to persistent effects from COVID-19 infection and expected to improve over time by ruling out all other potential causes or contributory factors for elevated LDH, the Investigator may use clinical judgement to enroll the patient and monitor LDH levels per protocol.
9. Body mass index ≥ 50kg/m^2
10. Resting heart rate of ≥ 120 bpm, systolic blood pressure of > 180 mm Hg and a diastolic blood pressure of > 100 mm Hg and/or or a fall in pulse oximetry oxygen saturation (SpO_2) to <80% upon ambulation

11. Sepsis, septic/hypovolemic/cardiogenic/neurogenic shock
12. Patients on MV, ECMO, NIV, HFNO or other high flow oxygen (FiO2 ≥35% and flow rate ≥ 8 lpm) within the last 72 hours prior to screening
13. History of anaphylactic reaction (particularly reactions to general anesthetic agents); allergic reaction due to any drug which led to significant morbidity; prior allergic reaction to pirfenidone.
14. Known symptoms of dysphagia or known difficulty in swallowing capsules and/or total gastrectomy
15. Patients undergoing dialysis or hemoperfusion, or with a history of dialysis or hemoperfusion, or anticipated to require dialysis or hemoperfusion within 72 hours of screening or severe renal impairment (defined as creatinine clearance rate <30 mL/min) at the time of screening/baseline.
16. Use of any of the following drugs:
    a. Fluvoxamine, enoxacin, ciprofloxacin
    b. Treatment with steroids under institutional protocols and guidelines to manage COVID-19 pneumonia/respiratory symptoms is allowed. Use of steroids off-label to treat non-COVID-19 related conditions is not allowed.
    c. Any Investigational Agents (i.e., non-approved or nonauthorized drugs), with the exception of those used for COVID-19 respiratory diseases that the investigator deems clinically relevant in combination with the study drug, as described below:

       i. Allowed agents
          - Patients who had received prior investigational agents for COVID-19 but are no longer taking those drugs are allowed.
          - Inhaled corticosteroids are allowed.
          - Patients that received prior convalescent plasma are allowed; however, concomitant convalescent plasma is excluded.

       ii. Excluded agents
          - Patients on concomitant experimental anti-viral, anti-fibrotic or anti-inflammatory therapies are excluded.
          - Any investigational agent not explicitly on this list should be reviewed by the medical monitor prior to initiating therapy or enrolling participant.
    d. Other inhibitors of CYP1A2 (including but not limited to methoxsalen or mexiletine)
    e. Inducers of CYP1A2 (such as phenytoin), CYP2C9 or 2C19 (including but not limited to carbamazepine or rifampin)
    f. Drugs associated with ***substantial risk for prolongation of the QTc interval*** (including but not limited to moxifloxacin, quinidine, procainamide, amiodarone, sotalol). Note that QTc prolongation is not an all / nothing drug effect, and specifically the administration drugs such as hydroxychloroquine do not preclude participation in this trial but does mandate measurement of the QTc every 6 hours until deemed necessary in accordance with investigator judgement

g. Vaccination with a live vaccine is not permitted during the period from 4 weeks prior to screening to 4 weeks after the last dose
h. Tobacco and nicotine products and/ or a positive a cotinine test at screening
i. Pirfenidone or nintedanib

17. Any other reason that, in the opinion of the Investigator, might interfere with the evaluation required by the study
18. For AST ≥2.5xULN, ALT ≥2.5xULN and/or total bilirubin >1.5xULN (in the absence of history of Gilbert syndrome and/or the absence of alkaline phosphatase ≥2xULN or clinical evidence of cholestasis), or severe hepatic impairment
19. Patients requiring surgery due to an acute onset condition prior to randomization.
20. Patients experiencing tachypnea. For the purposes of this study, tachypnea is defined as resting respiratory rate ≥ 25 per minute.

4.3. Participant Inclusion Criteria-Part B

1. Patients must have completed Part A of the study, through Day 91 of treatment.
2. In the opinion of the Investigator, the patient is a good candidate for continued treatment with LYT-100.

4.4. Participant Exclusion Criteria- Part B

Patients ***must not meet any*** of the exclusion criteria as listed for Part A.

4.5. Participant Withdrawal Criteria

Patients may withdraw their consent to participate in the study at any time. If a participant withdraws consent, the date and reason for consent withdrawal should be documented. Participant data will be included in the analysis up to the date of the withdrawal of consent.

Apart from withdrawal of consent, reasons for early termination of individual patients can include:

- Protocol deviations or participant non-compliance (must be specified on the appropriate electronic Case Report Form [eCRF]);
- Related serious or severe AEs;
- Administrative decision by the Investigator or the Sponsor;
- Death;
- Other (must be specified).

Patients will be encouraged to return to the clinical research unit to complete all necessary assessments and until the Investigator deems that it is safe to be discharged. Wherever possible, the tests and evaluations, including those listed for the final visit, should be performed for all patients who discontinue treatment prior to the completion of the study. For patients who discontinue treatment due to a related adverse event per investigator's decision, these patients should remain in the study after being discontinued from treatment and be followed for all

scheduled assessments. Subjects will only be removed from the study due to withdrawal of consent or loss of follow up.

4.6. Concomitant Medications and Other Therapies

The following drugs are not permitted during the study, and they must be discontinued at least 28 days or 10 half-lives (whichever is the longer) prior to study drug dosing:

- Fluvoxamine, enoxacin, ciprofloxacin;
- Other inhibitors of CYP1A2 (including but not limited to methoxsalen or mexiletine);
- Inducers of CYP1A2 (such as phenytoin), CYP2C9 or 2C19 (including but not limited to carbamazepine or rifampin);
- Any drug associated with prolongation of the QTc interval (including but not limited to moxifloxacin, quinidine, procainamide, amiodarone, sotalol). Note that QTc prolongation is not an all / nothing drug effect, and specifically the administration drugs such as hydroxychloroquine do not preclude participation in this trial but does mandate measurement of the QTc every 6 hours until deemed necessary in accordance with investigator judgement.

Vaccination with a live vaccine is not permitted during the period from 4 weeks prior to screening to 4 weeks after the last dose.

Immunosuppressants or other immune-modifying drugs are not permitted, except for corticosteroids at the discretion of the Investigator as part of standard of care for COVID-19 respiratory pathology, and remdesivir where it is provided as part of standard of care for the treatment of COVID-19. Dexamethasone or other corticosteroids may be administered under institutional SOC to manage COVID-19 pneumonia/respiratory symptoms. If no institutional protocols or guidelines are in place, dexamethasone may be administered up to a total daily dose of 6 mg either by oral or intravenous routes for up to 10 days, as supported by the recent RECOVERY trial (Horby et al 2020), or until hospital discharge, whichever comes first. If the use of corticosteroids is extended, then they may be used for up to 3 weeks concomitantly with LYT-100. In that period use of corticosteroids should be limited to prednisone (up to 1 mg/kg/day), methylprednisolone (up to 1/mg/kg/day), or hydrocortisone (up to 160 mg). Inhaled corticosteroids are allowed. Any significantly immune-suppressing or anti-inflammatory drug used off-label, including experimental therapies as part of a clinical trial must be discontinued at least 3 months prior to screening or 5 half- lives, whichever is longer.

Use of concomitant pirfenidone and/or nintedanib is excluded.

Prior and/ or concurrent physical and/ or pulmonary rehabilitation is allowed and will be documented in the eCRF.

4.6.1. Contraception

Estrogen preparations (e.g., oestradiol, ethinyloestradiol or gestodene) may be used throughout the trial for contraception, hormone replacement therapy, or menopausal replacement therapy.

Acceptable, highly effective double contraception is defined as a condom AND one other form of the following:

- Established hormonal contraception (oral contraceptive pills [OCPs], long-acting implantable hormones, injectable hormones);
- A vaginal ring or an intrauterine device (IUD);
- Documented evidence of surgical sterilization at least 6 months prior to Screening (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy for women or vasectomy for men [with appropriate post -vasectomy documentation of the absence of sperm in semen] provided the male partner is a sole partner).

Women not of childbearing potential must be postmenopausal for ≥12 months. Postmenopausal status will be confirmed through testing of follicle-stimulating hormone levels (FSH) ≥ 40 IU/mL at Screening for amenorrhoeic female participants. Females who are abstinent from heterosexual intercourse will also be eligible.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered highly effective methods of birth control. Participant complete abstinence for the duration of the study and for 1 month after the last study treatment is acceptable.

Female patients who are in same sex relationships are not required to use contraception.

Males must be surgically sterile (>30 days since vasectomy with no viable sperm), abstinent, or if engaged in sexual relations with a WOCBP, the participant and his partner must be surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method from Screening until study completion, including the follow-up period and an additional 90 days after the last dose of study medication. Acceptable methods of contraception include the use of condoms and the use of an effective contraceptive for the female partner that includes: OCPs, long-acting implantable hormones, injectable -hormones, a vaginal ring or an IUD. Patients with same sex partners (abstinence from penile-vaginal intercourse) are eligible when this is their preferred and usual lifestyle.

5. TREATMENT OF PATIENTS

5.1. Description of Study Drug

The LYT-100 drug product and matching placebo are presented as follows:

- LYT-100, 250 mg and matching placebo – Size 1, Swedish orange opaque, hard-gelatin capsules.

The capsules are packaged in high-density polyethylene (HDPE) bottles and a white, polypropylene screw cap with an induction sealed aluminum inner seal. The IPs should be stored at a controlled room temperature of 15°C -25°C [59°F to 77°F]. Capsule count *per bottle* is 102 capsules, which is equivalent to a 14-day supply + 3 additional days of 750 mg twice per day. Three additional days of drug are provided in each bottle in the event of lost capsules or use of allowable 3-day study window extension. Two bottles will be provided *per single kit* to supply study medication for 28 days and includes a total of 6 extra days.

Patients will take LYT-100 study medication, or placebo, orally and preferably with food (solid or nutritional supplements, whenever possible), with approximately 10 to 12 hours between the two daily doses. Doses may be adjusted according to safety and tolerability to avoid toxicity.

Note that, for the first 3 days of treatment, the dose of LYT-100 will be 500 mg BID (or 2 capsules of matching placebo). Day 4 through Day 91 the dose of LYT-100 will be 750 mg BID (or 3 capsules of matching placebo). If dosing titration is not well tolerated, doses may be adjusted according to safety and tolerability to avoid toxicity by adjusting to lower doses in response to patient safety and tolerability issues. Adjustments may be made as follows: reduction to 1 capsule, BID X 2 days (may be longer if needed), 2 capsules, BID X 2 days (may be longer if needed), 3 capsules, BID, thereafter.

Table 8 provides the dosing regimens to be used during the 91-day treatment period.

Table 8: Dosing Regimens for Days 1 through 3 and Thereafter (Study LYT-100-2020-02)

Part A: Double-Blind		**Part B: Open Label Extension**	
Days 1 through 3	**Days 4 through 91**	**Days 91 through 93**	**Days 94 through 182**
[1]LYT-100 **500 mg BID** or matching Placebo[2] x 3 days	[1]LYT-100 **750 mg BID** or matching Placebo[2] x 88 days	[1]LYT-100 **500 mg BID**[2] x 3 days	[1]LYT-100 **750 mg BID**[2] x 88 days

[1] Patients will take study medication orally and preferably with food (solid or nutritional supplements, whenever possible), with approximately 10 to 12 hours between the two daily doses.
[2] Doses may be adjusted according to safety and tolerability to avoid toxicity by adjusting to lower doses in response to patient safety and tolerability issues, including: Skin reactions to sunlight; significant changes to liver enzymes, and/or gastrointestinal (GI) side effects. See Section 5.2 for details.

In Part B, in order to maintain the study blind in Part A, all patients will be treated with the same dosing regimen shown in Table 8. All patients entering Part B will receive LYT-100 500 mg BID for three days, followed by LYT-100 750 mg BID thereafter.

5.2. Dose Adjustment

5.2.1. Gastrointestinal Events

Patients who experience intolerance to therapy due to gastrointestinal side effects should be reminded to take LYT-100 with food. If gastrointestinal events do not improve, or worsen in severity, dose reduction may be considered per Investigator judgment.

5.2.2. Photosensitivity Reaction or Rash

Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded to avoid exposure to the sun and to use a sunblock daily when going outdoors even if they will not be exposed to direct sunlight. Dose reduction may be considered per Investigator judgment.

5.2.3. Other

If dosing titration is not well tolerated or the dose needs to be reduced due to toxicity, adjustments to dosing may be made as follows:

- Days 1-3: reduction from 2 capsules, BID, to 1 capsule, BID, x 2 days (may be longer if needed);Days 4-91: reduction from 3 capsules, BID, to 2 capsules, BID x 2 days (may be longer if needed); and if reduction from 750 mg to 500 mg of Investigational Product BID is not sufficient to address difficulties with tolerability or toxicity, further reduction to 250 mg BID is allowed.
- Days 4-91: following dose reduction return to 3 capsules, BID, at Investigator's discretion.

5.3. Prior and Concomitant Medications

5.3.1. Prior Medications

All medications, including OTC medications, vitamins, and herbal supplements, taken during the 30 days prior to the first study drug administration will be recorded and reviewed by the Investigator to determine whether the participant is suitable for inclusion in the study.

Please note: For any subject who receives a COVID-19 vaccination, the type (e.g., Pfizer, Moderna, Janssen/ J&J) of vaccine and date(s) of administration must be reported as a prior medication.

5.3.2. Concomitant Medications

All medications, including OTC medications, vitamins, and herbal supplements, taken by patients during the course of the study will be recorded in the eCRF and coded using the most current World Health Organization (WHO) drug dictionary. Prior and concomitant medications will be listed by participant and summarized by anatomical therapeutic chemical (ATC) and Preferred Term (PT).

Please note: For any subject who receives a COVID-19 vaccination, the type (e.g., Pfizer, Moderna, Janssen/ J&J) of vaccine and date(s) of administration must be reported as a concomitant medication.

5.4. Treatment Compliance

Patients will be provided with enough LYT-100 study medication bottles to cover the prescribed daily dose until their next study visit. The number of capsules dispensed at each study visit will be recorded in the patient's source documents. Patients will be instructed to retain and return all emptied and non-emptied bottles to each study visit. Study drug capsule counts returned at each visit will be totaled and recorded in the patient's source document record. The difference in the number of capsules dispensed and number of capsules returned will be reconciled against the anticipated number capsules administered to account for all dosing intervals since the last study visit to determine study drug medication compliance.

A phone application to provide medication reminders will be used to assist the patient with medication adherence during the study treatment phase of the trial.

5.5. Blinding- Part A and SCOA

Blinding procedures for Part A of the study will be described in detail in a separate randomization plan and specifications document.

The Sponsor, Investigator, Medical Monitor, study personnel, and patients are not to make any effort to determine which study drug therapy is being received.

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 participant'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 may break the study code for that participant only using the Interactive Web Response 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 adverse event), must be documented in the participant's medical records. The study monitor should be promptly informed of premature unblinding.

As soon as possible, and without revealing the participant's study treatment assignment (unless important to the safety of patients remaining in the study), the Investigator must notify the Sponsor by telephone and then in writing if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to unblinding.

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

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Supplies

The Sponsor will supply the study drug to the investigational site. The study drug provided for this study was manufactured under current Good Manufacturing Practices (cGMP) and will be suitable for human use.

6.2. Study Drug Packaging and Labelling

The Sponsor is responsible for the preparation and labelling and providing details of batch numbers, safety, and stability data.

The study drug is labelled in accordance with local regulatory requirements and will be shipped at a temperature of 15°C-25°C [59°F to 77°F].

6.3. Study Drug Storage

Upon receipt, the study drug must be stored at 15°C-25°C [59°F to 77°F].

The Investigator will be fully responsible for the security, accessibility, and storage of the study drug while it is at the investigational facility.

6.4. Study Drug Preparation

Procedures relating to study drug preparation and dispensing are outlined in the Pharmacy Manual.

6.5. Administration

The Investigator is responsible for the education of study staff and patients as to the correct administration of the study drug.

6.6. Study Drug Accountability

A record will be maintained by the investigational site that will account for all dispensing and return of any used and unused study drug. At the end of the study, the study drug will be reconciled, and a copy of the record given to the study monitor.

6.7. Study Drug Handling and Disposal

On completion of the study, any surplus study drug supplies will be destroyed upon receipt of written approval from the Sponsor and evidence of destruction supplied to the study monitor. If no supplies remain, this will be documented in the dispensing record.

7. STUDY SCHEDULE

Please see Table 4 for Schedule of Assessments-Part A and Table 5 for Schedule of Assessments- Part B. Where possible, assessments should be conducted in order of least invasive to most invasive. Study manuals will be described for certain endpoints (e.g., 6MWT, Chest x-ray, CT Scans) that will define how procedures will be performed. The sections below describe the general procedures to be performed each day.

In general, patient-reported quality of life scales (e.g., SF-36 v2, mBDS, SGRQ-I) should be performed at the beginning of each visit, with the remaining procedures (e.g., blood collections, 6-minute walk tests) performed after.

Throughout patient participation, patients should be warned to avoid exposure to sunlight and avoid sunlamps. They should be encouraged to wear sunscreen and protective clothing on a daily basis to avoid potential for skin reactions.

Throughout the conduct of the study, patients and study staff should take appropriate precautions to mitigate or minimize infection risks. This includes the use of personal protective equipment (masks, gowns, gloves) and hand washing, as appropriate for the situation.

7.1. Screening and Baseline

7.1.1. Screening- Visit 1 (Day -10 to Day -2)

Over five days (up to 10 days to allow for evaluation of all screening assessments), patients will be screened and complete baseline assessments. Patients are required to have all screening assessments, including training for the 6-minute walk test, and meet all inclusion/exclusion criteria for the trial prior to randomization.

At Screening, patients will be provided with full information concerning details of the study assessments and procedures. They will also be provided with an informed consent form (ICF). Prior to being asked to sign the consent form, patients will be given time to review study information and ask any questions.

After the Informed Consent Form is obtained (written, electronic, or oral), screening assessments will be carried out as follows:

- Confirmation of a positive RT-PCR diagnostic test / RNA or antigen SARS-CoV-2
  Note: COVID positive diagnostic test results of tests conducted prior to ICF should be used even if this date predates the screening period and does not need to be repeated as part of screening.
- Eligibility - inclusion/exclusion criteria
- Recording of demographic information
- Pertinent Medical History
- Modified Borg Dyspnoea Scale (mBDS) - conduct this at beginning of visit
- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral,

contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)

- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Chest x-ray
- Confirmation of prior requirement for NIV, ECMO, MV, HFNO, and/or other supplemental oxygen during hospitalization, with current need for NIV, ECMO, MV, HFNO, and/or other high flow oxygen (FiO2 ≥ 35% and flow rate ≥ 8 lpm) excluding the subject
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis, urine cotinine, and FSH for post-menopausal females only)
- Urine pregnancy test (WOCBP only). (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
- Brief training for the 6 Minute Walk Test at the end of the screening visit. Following verbal instructions from a qualified staff member, the patient will practice the 6 MWT for approximately 2 minutes
- Pre-treatment adverse events
- Prior and concomitant medications - include medications 30 days prior to screening
- Daily Covid Symptoms Diary (to be performed by the subject before bedtime throughout the screening period)
- Up to approximately 50 US participants will be asked to participate in qualitative interviews to help further long COVID research. Subjects will either be asked to participate in interviews as part of screening or as part of the post-blinded treatment follow-up Visit (approximately between Days 91 and 105). Early termination patients may also be interviewed at the sponsor's discretion.

Note: AEs and changes in concomitant medications will be recorded from the time of informed consent. They will be recorded, and 'pre-treatment' will be noted for AEs and concomitant medications taken prior to first dose of study medication.

Please also note the following clarifications with regards to screening activities

- When evaluating eligibility, if screening lab values are exclusionary, and the Investigator's judgement believes the values are likely due to persistent effects from the COVID infection and are expected to improve over time (e.g., liver function tests), these labs may be re-drawn during the screening period.
- Rescreening of subjects is allowed with prior approval from the Sponsor.
- Screening labs collected as part of standard of care are acceptable to be used for eligibility assessments and do not need to be repeated as long as they are collected within the screening window.

- The protocol allowed screening window, of up to 10 days, is to allow for all study procedures to be performed and evaluated prior to baseline

7.1.2. Baseline-Visit 2 (Day -1 to Day 1)

The following assessments will be carried out over the course of 1 to 2 calendar days:

- Modified Borg Dyspnoea Scale – collect this at beginning of visit
- Abbreviated symptom-directed physical examination
- Measurement of height and weight, and calculation of Body Mass Index
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- Charlson Comorbidity Index
- Chest CT Scan (If a CT scan without contrast was obtained within 7 days of Baseline, and there have been no significant changes in signs and symptoms of respiratory complications in those 7 days, then an additional CT scan will not need to be collected. However, the prior CT scan must have been done without contrast.)
- Dyspnoea-12 – collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) – collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2) – collect this at beginning of visit
- Daily Covid Symptoms Diary (to be performed by the subject from Day 1 through Day 91) before bedtime
- Patient Global Item of Severity (PGIS)- asking patients to recall the week prior to the assessment.
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Biomarkers – time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)
- Pre-treatment adverse events
- Concomitant medications.
- 6-minute Walk Test – Two tests must be conducted between Day -1 and Day 1, and the longest distance recorded for the baseline measure. There should be a minimum of 30 minutes between the two tests if both are conducted on Day -1. The second test can also be performed on Day 1.
  - Patients who complete both baseline 6MWTs on Day -1 may be randomized on the same day using the study EDC system, following completion of all Day -1 assessments and confirmation that the patient meets all eligibility criteria. Following randomization, the subject should take their first dose of study

medication while onsite (preferably with food, solid or nutritional supplements, whenever possible). Vital signs (BP, HR, RR, SpO2, Temperature) and Modified Borg (Dyspnea) Scale are repeated post study medication administration and recorded in the Study Treatment Day 1 eCRF.

– Patients who complete the first baseline 6MWT on Day -1 and the second 6MWT on Day 1 will be randomized on Day 1 using the study EDC system following confirmation that the patient meets all eligibility criteria. Following randomization, the subject should take their first dose of study medication while onsite (preferably with food, solid or nutritional supplements, whenever possible).

7.2. Study Treatment Period – Part A: The study treatment period includes visits at Day 1, 14, 28, 56, and 91.

7.2.1. Day 1-Visit 3 (First Dose of Study Medication)

- Patients will be randomized prior to dosing on Day 1 (see Section 3.3). Daily Covid Symptoms Diary (to be performed by the subject from Day 1 through Day 91) before bedtime
- Weekly Patient Global Item of Severity (PGIS) is captured in the ePRO and is to be performed at baseline (Day 1)
- 6-minute walk test for baseline measure (only if a second test was not conducted on Day -1; see above); prior to study medication administration
- Study Drug Administration/Accountability – doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- After dosing, the following should be performed:
- Post-treatment vital signs (blood pressure, heart rate, respiratory rate, SpO_2 after participant has been resting in a supine position for at least 5 minutes and prior to blood draws), oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- Post-treatment Modified Borg Dyspnoea Scale
- Post-treatment Adverse Events
- Post-treatment Concomitant medications

7.2.2. Day 14- Visit 4

Assessments will be conducted as follows:

- Modified Borg Dyspnoea Scale – collect this at beginning of visit
- Abbreviated symptom-directed physical examination
- Weight and Body Mass Index calculation
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)

- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Dyspnoea-12
- WHO Ordinal Scale for Clinical Improvement
- Daily Covid Symptoms Diary (to be performed by the subject from Day 1 through Day 91) before bedtime
- Weekly Patient Global Item of Severity (PGIS) to be performed on the first day of each week.
- Patent Global Item of Change (PGIC)
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Biomarkers – time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)
- Study Drug Administration/Accountability – doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- PK blood sample- collect the time of the last dose taken prior to blood collection; one PK sample is collected at visit and the corresponding time interval must be recorded as one of the following: 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 interval within the same patient at future visits.
- Adverse Events / Mortality
- Concomitant medications.
- 6-minute Walk Test – conduct this at end of visit

7.2.3. Day 28- Visit 5

Assessments will be conducted as follows:

- Modified Borg Dyspnoea Scale – collect this at beginning of visit
- Weight and calculation of Body Mass Index
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- Dyspnoea-12 – collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) – collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2) – collect this at beginning of visit

- Daily Covid Symptoms Diary (to be performed by the subject from Day 1 through Day 91) before bedtime
- Weekly Patient Global Item of Severity (PGIS) to be performed on the first day of each week.
- Patent Global Item of Change (PGIC)
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Urine Cotinine
- Biomarkers – time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)
- Study Drug Administration/Accountability – doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- PK blood sample- collect the time of the last dose taken prior to blood collection; one PK sample is collected at visit and the corresponding time interval must be recorded as one of the following: 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 interval within the same patient at future visits.
- Adverse Events / Mortality
- Concomitant medications.
- 6-minute Walk Test – conduct this at end of visit

7.2.4. Day 56- Visit 6

Assessments will be conducted as follows:

- Modified Borg Dyspnoea Scale – collect this at beginning of visit
- Weight and calculation of Body Mass Index
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- Dyspnoea-12 – collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) – collect this at beginning of visit
- SF-36 (v2) – collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- Daily Covid Symptoms Diary (to be performed by the subject from Day 1 through Day 91) before bedtime
- Weekly Patient Global Item of Severity (PGIS) to be performed on the first dayday of each week.
- Patent Global Item of Change (PGIC)

- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Biomarkers – time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)
- Study Drug Administration/Accountability – doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- PK blood sample- collect the time of the last dose taken prior to blood collection; one PK sample is collected at visit and the corresponding time interval must be recorded as one of the following: 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 interval within the same patient at future visits.
- Adverse Events / Mortality
- Concomitant medications.
- 6-minute Walk Test – conduct this at end of visit

7.2.5. Day 91- Visit 7A

Assessments will be conducted as follows:

- Modified Borg Dyspnoea Scale – collect this at beginning of visit
- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Charlson Comorbidity Index
- Chest CT scan
- Chest x-ray
- Dyspnoea-12 – collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) – collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2) – collect this at beginning of visit
- Daily Covid Symptoms Diary (to be performed by the subject from Day 1 through Day 91) before bedtime
- Weekly Patient Global Item of Severity (PGIS) to be performed on the first day of each week.
- Patent Global Item of Change (PGIC)

- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis, urine cotinine)
- Urine pregnancy test (WOCBP only)
- Biomarkers – time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)
- Study Drug Administration/Accountability – Collect any remaining study medication from Part A.
- PK blood sample- collect the time of the last dose taken prior to blood collection; one PK sample is collected at visit and the corresponding time interval must be recorded as one of the following: 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 interval within the same patient at future visits.
- Adverse Event / Mortality
- Concomitant medications.
- 6-minute Walk Test – conduct this at end of visit
- Schedule post-treatment patient interview approximately between Days 91 and 105

7.2.6. Early Termination (Visit ET)

An early termination visit must be conducted if the patients discontinues study medication for any reason. It should be conducted within 2 weeks of the last dose of study medication. All patients should be strongly encouraged to continue with all remaining study visits even though they are no longer on study medication.

- Modified Borg Dyspnoea Scale – collect this at beginning of visit
- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Chest x-ray
- Dyspnoea-12 – collect this at beginning of visit
- SF-36 (v2) – collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Biomarkers – time of biomarker sample collection should be consistent across study days, occurring always either before noontime (morning) or after noontime (afternoon)

- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- PK blood sample-collect the time of the last dose taken prior to blood collection; one PK sample is collected at visit and the corresponding time interval must be recorded as one of the following: 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 interval within the same patient.
- Study Drug Administration/Accountability – Collect any remaining study medication from Part A.
- Adverse Events / Mortality
- Concomitant medications.
- 6-minute Walk Test – conduct this at end of visit

Please note: Vital status, overall survival status should be collected at day 91 days (91 days from the first dosing date) for any subjects that prematurely discontinue from the study.

7.3. Post-Treatment- Day 105 End of Study- Part A (Visit 8A)

End of study is when the last visit and last assessment(s) are conducted. Assessments will be conducted as follows:

- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Chest x-ray
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Adverse Events / Mortality
- Concomitant medications
- Up to approximately 50 US participants will be asked to participate in qualitative interviews to help further long COVID. Subjects will either be asked to participate in interviews as part of screening or as part of the post-blinded treatment follow-up Visit (approximately between Days 91 and 105). Early termination patients may also be interviewed at the sponsor's discretion.

Note: While "a follow-up post-treatment visit will occur within 14-day of last day of study treatment", if a patient discontinues study drug prematurely but continues to follow study

procedures the 14-day post treatment visit is not required as long as they have been off study medication for at least 14 days at the time of their last in-clinic visit.

7.4. Study Treatment Period- Part B

The study treatment period includes visits at Day 91, 105, 119, 147, and 182.

7.4.1. Day 91; Visit 7B (First Day of Open Label Study Period)

Day 91 (Visit 7A) of Part A is the same day as the Day 91 (Visit 7B) of Part B; i.e. both visits are conducted on the same day. Dosing for Part B should be performed AFTER all assessments below are performed.

- After completion of all procedures for Visit 7A of Part A, Visit 7B is used to confirm eligibility for participating in Part B. A new ICF will be signed by each patient participating in Part B.
- Study Drug Administration/Accountability – Distribute Open Label study drug to patients. All patients entering Part B will take LYT-100 500 mg BID for three Days, and then LYT-100 750 mg BID thereafter. Doses are intended to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals.
  - All patients who are continuing into Part B should take their final dose of Part A medication in the morning, prior to returning any remaining supplies from Part A.
  - The evening dose for all patients should be taken from Part B supplies.

7.4.2. Day 105- Visit 8B

This visit corresponds to the 14-day post-treatment safety follow-up visit (Visit 8A) for patients from Part A who do NOT choose to continue in Part B. Assessments will be conducted as follows:

- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Dyspnoea-12 - collect this at beginning of visit
- Study Drug Administration/Accountability - doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- Adverse Events / Mortality

- Concomitant medications.
- 6-minute Walk Test - conduct this at end of visit

7.4.3. Day 119- Visit 9

Assessments will be conducted as follows:

- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 6-minute Walk Test - conduct this at end of visit
- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Dyspnoea-12 - collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2) - collect this at beginning of visit
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Urine Cotinine
- Study Drug Administration/Accountability - doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- Adverse Events / Mortality
- Concomitant medications.

7.4.4. Day 147- Visit 10

Assessments will be conducted as follows:

- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 6-minute Walk Test - conduct this at end of visit
- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Dyspnoea-12 - collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) - collect this at beginning of visit
- SF-36 (v2) - collect this at beginning of visit

- WHO Ordinal Scale for Clinical Improvement
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Study Drug Administration/Accountability - doses are to be taken twice per day, approximately 10 to 12 hours apart and preferably with meals
- Adverse Events / Mortality
- Concomitant medications.

7.4.5. Day 182- Visit 11

Assessments will be conducted as follows:

- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Charlson Comorbidity Index
- Chest CT scan
- Chest x-ray
- 6-minute Walk Test - conduct this at end of visit
- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Dyspnoea-12 - collect this at beginning of visit
- St. George's Respiratory Questionnaire-I (SGRQ-I) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- SF-36 (v2) - collect this at beginning of visit
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis, urine cotinine)
- Urine pregnancy test (WOCBP only)
- Study Drug Administration/Accountability – Collect any remaining study medication from Part B
- Adverse Event / Mortality
- Concomitant medications

7.4.6. Early Termination (Visit ET)

An early termination visit must be conducted if a patient discontinues study medication for any reason. It should be conducted within 2 weeks of the last dose of study medication. All patients who terminate early should be strongly encouraged to continue with all remaining study visits even though they are no longer on study medication.

- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Chest x-ray
- 6-minute Walk Test - conduct this at end of visit
- Modified Borg Dyspnoea Scale - collect this at beginning of visit
- Dyspnoea-12 - collect this at beginning of visit
- SF-36 (v2) - collect this at beginning of visit
- WHO Ordinal Scale for Clinical Improvement
- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Adverse Events / Mortality
- Concomitant medications.

7.5. Post-Treatment: Day 196 End of Study- Part B (Visit 12)

End of study is when the last visit and last assessment(s) is conducted. Assessments will be conducted as follows:

- Abbreviated symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiratory rate, SpO_2) after participant has been resting in a supine position for at least 5 minutes and prior to blood draws; oral, contactless, or tympanic body temperature (same temperature measurement should be used throughout the study)
- 12-lead ECG (after participant has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Chest x-ray

- Supplemental oxygen use, pulmonary exacerbation and/or rehabilitation, and hospitalization status
- Laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Urine pregnancy test (WOCBP only)
- Adverse Events / Mortality
- Concomitant medications

Note: While "a follow-up post-treatment visit will occur within 14-day of last day of study treatment", if a patient discontinues study drug prematurely but continues to follow study procedures the 14-day post treatment visit is not required as long as they have been off study medication for at least 14 days at the time of their last in-clinic visit.

8. EFFICACY ASSESSMENTS AND ENDPOINTS

All efficacy endpoints will be derived at each protocol-schedule time point for which they are collected, with analysis performed (e.g., change from baseline) for each time point. A detailed description of the collection of assessments will be documented in an assessment collection and specification manual.

8.1. 6-Minute Walk Test (6MWT)

The 6-minute walk test (6MWT) is the primary efficacy endpoint. All patients will complete a 6MWT test according to the Schedule of Assessments and aligned with the American Thoracic Society/European Respiratory Society Guidelines (Crapo et al 2002) and according to the 6MWT study procedural manual. 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. The 6MWT has been used to measure physical functioning following ARDS in the setting of post-mechanical ventilation as well as recovery from other viral pneumonias (Hsieh et al., 2018).

This is a self-paced test. Patients choose their own intensity of exercise and may stop and rest during the test (Crapo et al 2002). This test should be scheduled as the last assessment collected at study visits, e.g., after vital signs, daily pulse oximetry reading, dyspnea scales, QOL and other blood collection assessments. Oxygen supplementation is allowed during the test; however, the subject must use the same device and oxygen flow rate at each 6MWT assessment. The patient's dyspnea and fatigue are also assessed prior to the 6MWT and end of test. Patients who are unable to complete (or walk) due to disease severity will be assigned a distance of 0 (zero). (Table 14).

Reproducibility and reliability of the 6MWT is critically important to the study. While not specified in the ATS guidelines as a relative contraindication, if a subject is feeling acutely ill for any reason, including after receiving a COVID-19 vaccine, visit should be rescheduled to ensure that they are not performing the 6MWT during an acute illness.
Changes from baseline in the 6MWT distance will of primary interest.

8.2. Dyspnoea-12 (D-12)

D-12 measures "breathlessness severity" without reference to current activity and was developed for use of dyspnea in interstitial lung disease and COPD current experience ("these days") and is assessed at baseline and at follow-up visits. One of the primary complaints of post-acute respiratory complications of COVID-19 is dyspnea (Carfi et al., 2020) The tool generates a total score using 12 descriptor items including seven physical and five affective items with response options none (0), mild (1), moderate (2) or severe (3). Table 17 provides a sample of the scale. The total score ranges from 1 to 36 whereby the higher score correlates with greater breathlessness severity.

8.3. Other Secondary or Exploratory Efficacy

Other secondary efficacy endpoints are intended to be supportive to the primary and key secondary efficacy endpoints.

8.3.1. St. George Respiratory Questionnaire-I (SGRQ-I)

The SGRQ-I is an idiopathic pulmonary fibrosis disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with interstitial lung disease. There are 34 self-completed items with 3 domain component scores (Symptoms, Activities, and Impacts). Higher scores indicate more limitations. Table 16 provides a sample of the scale.

Changes from baseline in the component scores of the SGRQ-I will be assessed as secondary efficacy endpoint. Further, a responder analysis will be performed in which the proportion of patients experiencing an increase of ≥4 units (vs < 4 units) will be assessed.

8.3.2. Modified Borg Dyspnoea Scale (mBDS)

The mBDS is a measure of dyspnea. The mBDS is a self-administered unidimensional assessment tool that analyzes breathlessness under exertion. Table 13 provides a sample of the scale. One of the primary complaints of post-acute respiratory complications of COVID-19 is dyspnea (Carfi et al., 2020). The primary assessment will be the changes from baseline.

8.3.3. WHO Ordinal Scale for Clinical Improvement

The WHO Ordinal Scale for Clinical Improvement (Table 10) will be assessed for changes over time of ≥ 1 point as well as a responder analysis (improvement by at least 1 point and also for at least 2 points) . 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); (3) Hospitalized Mild Disease (Hospitalized, no oxygen therapy); (4) Oxygen by mask or nasal prongs; (5) Hospitalized Severe Disease (Non-invasive ventilation or high-flow oxygen); (6) Intubation and mechanical ventilation; (7) Mechanical Ventilation plus additional organ support (i.e. extracorporeal life support (ECLS), continuous renal replacement therapy (CRRT), vasopressors); (8) Dead (Death)

8.3.4. SF-36 (v2)

The SF-36 v2 (Table 18) is a self-administered questionnaire containing 36 items that measures health on functional status, well-being, and overall evaluation of health in 8 domains. It requires 5-10 minutes to complete and uses scaled, ordinal responses (e.g., All of the time, Most of the time, A good bit of the time, etc.) (Brazier 1992). The domain scores and component summaries are as follows:

- SF-36 v2 scaled domains
    - Vitality
    - Physical functioning
    - Bodily pain
    - General health perception
    - Physical role functioning
    - Emotional role functioning
    - Social role functioning

- Mental health

- SF-36 v2 Mental Component Summary
- SF-36 v2 Physical Component Summary

Changes in the standardized component scores and domain scores will be calculated.

8.3.5. COVID Symptoms Assessments (Table 21)

8.3.5.1 Daily COVID Symptoms Scale (Table 21.1) is a self-administered questionnaire containing 7 daily symptoms known to be associated with post-acute COVID-19 infections (headache, fatigue, shortness of breath, loss of taste and loss of smell on a scale from 0 (no symptom) to 10 (worst imaginable symptom)).

8.3.5.2 Weekly Patient Global Item of Severity (PGIS) (Table 21.2) is a self-administered questionnaire on a 5-point scale (from none to severe) to be performed at Baseline (Day 1) and weekly thereafter from Day 1 to Day 922 (on the first dayday of each week) asking subjects to rate their overall severity of their Covid Symptoms, or your symptoms related to having had COVID-19 overall over the past week.

8.3.5.3 Patient Global Item of Change (PGIC) (Table 21.3) is a self-administered questionnaire on a 7-point scale (from much worse to much better) to be completed on Days 14, 28, 56 and 91 asking subjects to rate how their overall COVID symptoms, or your symptoms related to having had COVID-19 have changed since you began taking study medication.

8.3.6. Participant 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. Early termination patients may also be interviewed at the discretion of the sponsor. The sample size was elected to be in line with evidenced-based recommendations for the estimate of sample sizes for qualitative interviews. This research has demonstrated that, across a wide range of diseases, 84% of all relevant symptom concepts will emerge by the tenth interview and 97% of relevant symptom concepts will emerge by the twentieth interview.

Every effort will be made to address demographic representativeness in the sample, including recruiting participants across education, race/ethnicity, gender, and age range. In addition, to the extent possible, participants recruited during screening will match the main inclusion and exclusion criteria found in protocol LYT-100-2020-02 (COVID-19 pneumonia findings on imaging (chest X-ray or CT Scan) with a minimum of two lung lobe involvement and shortness of breath ≥ grade 3 (on mBDS dyspnea scale) with the exception of specific exclusion criteria (i.e. abnormal safety labs such as elevated LFTs, BMI or logistical constraints to enrollment).

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. For example, the interview guide will include non-leading questions such as “What is a bad day like with long COVID?”

The interview guide will include topics, questions, and probes designed to understand long COVID recovery from the participant's perspective. The interview guide will begin with an overall introduction about the interview and then move into a general discussion about the participant's experience. During this concept elicitation phase of the interview, the interviewer will listen for terms and wording that are spontaneously voiced by the participants when describing any problems they may have experienced (with particular reference to respiratory problems). A mix of open-ended and closed-ended questions will be used to ensure that the participants are not unduly biased in their responses. Probing questions will also be used to determine how much change on specific questions are required to be meaningful. Participating patients may be recontacted to debrief as additional questions are added to the interview guide. Participating patients may be recontacted to debrief as additional questions are added to the interview guide.

After the open-ended portion of the interviews are completed, interviewers will test several questionnaires (focused on respiratory, COVID symptoms, and leg fatigue) that have been included in a current trial protocol. These questionnaires are:

- Dyspnoea-12
- Patient Global Impression (PGI) of Symptoms (i.e. breathing trouble, leg fatigue, shortness of breath) and Change (i.e. change in breathing trouble, leg fatigue, shortness of breath)
- mBDS for dyspnea and leg fatigue as conducted during the 6MWTfor dyspnea and leg fatigue (as conducted during the 6MWT
- SGRQ-I
- Daily COVID Symptoms Assessment

The questionnaires will undergo a standard cognitive debriefing exercise where participants are asked to comment on the relevant sections of each questionnaire including, understandability and clarity of the instructions, items and response options.

8.3.7. Chest CT Scan

Qualitative assessments will be collected from chest CT Scans without contrast. The proportion of patients with "normal" CT scan images will be defined in a responder analysis. Patients with pre-existing chest pathology pre-COVID-19 should be considered "normal" for those pre-existing items/findings. Chest CT scans will be performed according to the CT Scan manual. Lung lobe involvement will be assessed for each of five lobes via central read with the terms defined by the Fleischner Society (Hansell et al 2018).

The CT images will be assessed for the presence of ground-glass opacity (hazy areas of increased attenuation without obscuration of the underlying vasculature), consolidation (homogeneous opacification with obscuration of the underlying vasculature), reticular pattern (consisting of either coarse linear or curvilinear opacity or fine subpleural reticulation without substantial ground-glass opacity), mixed pattern (combination of consolidation, ground-glass opacity, and reticular opacity in the presence of architectural distortion), and honeycomb pattern (clustered cystic air spaces). The distribution of abnormalities will be classified as predominantly subpleural (involving mainly the peripheral one-third of the lung), central (involving mainly the central two-third of the lung), or diffuse.

CT scans may also be analyzed with semi-Quantitative Lung Fibrosis (QLF) and computer-Aided Diagnosis (CAD) QLF Scores (Kim et al, 2010). Table 11 shows how each of the five lobes will be scored; the total score for each of the four 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 in this total score will be assessed.

A responder analyses will be performed, in which the proportion of patients showing ground glass opacities, fibrosis, consolidation, reticulation/bronchiectasis, and other radiographic abnormality improvement(s) by determining at least a 2-point score improvement for each abnormality across the five lobes (range 0-25) will be derived. 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 12. Shifts in these characteristics over the course of treatment will be of interest.

8.3.8. Biomarkers (Part A only)

Changes in biomarkers will be assessed, including C-reactive protein (CRP), lymphocyte count, d-dimer, cardiac troponin, ferritin, lactate dehydrogenase (LDH), IL-6, TGF-β1, TNF-α, IL-1β, PDGF- β, GCSF, and VEGF (see Section 9.1.2).

8.3.9. Chest X-Ray

Qualitative assessments will be collected from chest X-rays. The proportion of patients with "normal" chest X-ray will be defined in a responder analysis. Patients with pre-existing chest pathology pre-COVID-19 should be considered "normal" for those pre-existing items/findings.

8.3.10. Pulse Oximetry (SpO_2)

In patients requiring oxygen supplementation, ensure oxygen is administered at the prescribed rate for a minimum of 15 minutes prior to SpO_2 assessment. Changes over time in SpO2 will be assessed.

8.3.11. Length of Hospital Stay and Mortality

Total number of days of hospital stay will be assessed. Date of (original) admission, date of (original) discharge and rehospitalization(s) and subsequent discharge(s) will be collected. Methods for handling hospitalization days and patients who die or discontinue treatment prematurely will be addressed in the SAP. Time to all-cause mortality will be assessed if the data permit.

8.3.12. Other clinical outcomes

Other clinical outcomes will be assessed, as follows:

- The percentage of patients who develop severe pulmonary exacerbations
- The percentage of patients who develop non-severe pulmonary exacerbations
- Percentage of patients who experience rehospitalization for any cause, while on treatment.
- Use of supplemental oxygen from Baseline to end of treatment.

8.3.13. COA Development Sub-study

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

9. PHARMACOKINETIC AND BIOMARKER ASSESSMENTS- Part A Only

9.1. Blood Collection

Blood samples (for PK and biomarker analysis) and urine samples (for screening and safety evaluations) will be obtained at the time points delineated in the Schedule of Assessments (see Table 4).

The actual collection time of each sample must be recorded in the source data documentation, on the collection tube, and in the eCRF. Please see footnotes to Schedules of Assessments for permitted time windows for sample collection.

All blood samples will be collected in accordance with the site's standard operating procedures and will be processed according to instructions provided in the Laboratory Manual at the time points delineated in the Schedule of Assessments.

The total volumes of blood to be taken from each participant are detailed in Appendix 2, Table 19.

The Sponsor will supply complete written instructions for handling, processing, storage, and shipping of samples prior to study initiation.

9.1.1. Pharmacokinetics

Blood samples for population pharmacokinetics will be collected on Study Days 14, 28, 56, and 91. When pharmacokinetic levels are collected, the last dose of study medication taken prior to blood collection will be recorded, including the date and the time. Each participant will provide up to a minimum of 1 sample at each timepoint in reference to dosing: Pre-dose (Hour 0), 1 to <2 h, 2 to <4 h, 4 to <8 h, 8 to 12 h. Sites should avoid on-treatment duplications of the same timepoint interval within the same patient. The following is an example of blood collection options:

- Day 14 (**4 to <8 h** sample collected)
- Day 28 (**Pre-dose** (Hour 0) sample collected; *patient should bring medication with them to the visit*)
- Day 56 (**1 to <2 h**, **2 to <4 h sample**, *can collect two timepoints at a visit if patient plans to be at the site for extended time*)
- Day 91 (**8 to 12 h**, *again patient should bring medication with them to the visit if next dose is due shortly after the blood collection*).

For trough or later timepoint intervals such as 8 to 12 hours, the patient should be instructed to hold their next study medication dose and bring it with them to their study visit(s) to accommodate the longer time intervals required from their last dose taken.

9.1.2. Biomarkers

Blood samples for biomarkers will be collected at Baseline and on Study Days 14, 28, 56, 91 and at Day 105/Early Termination/End of Study. 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.

The following biomarkers will be assessed: C-reactive protein (CRP), lymphocyte count, d- dimer, cardiac troponin, ferritin, lactate dehydrogenase (LDH), IL-6, TGF-β1, TNF-α, IL-1β, PDGF- β, GCSF and VEGF. Additional biomarkers may be explored at a future time following the completion of this study.

Analyses of biomarkers will include changes from baseline.

9.2. Sample Analysis

Plasma PK and biomarker sample analysis will be performed using appropriately validated procedures and methods as outlined in the Laboratory Manual.

10. ASSESSMENT OF SAFETY

This study includes many efficacy parameters that can sometimes be considered safety outcomes. Because these parameters (e.g., chest x-ray and CT scan) are included as efficacy objectives, these assessments are described in the Efficacy Assessments and Endpoints (Section 8). Further, 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. An independent, unblinded DSMB will assist with oversight of patient safety during this study by reviewing unblinded safety data on a monthly basis during enrollment and treatment (Section 3.5).

10.1. Safety Parameters

Study procedures should be completed as delineated in the Schedule of Assessments (Table 4). However, if a participant is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the Sponsor's Medical Monitor or appropriate designee. Any unscheduled procedures required for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures.

10.1.1. Demographic/Pertinent Medical History

Pertinent medical history (including alcohol, smoking status, and prior requirement for MV, ECMO, NIV, HFNO or other high flow oxygen (FiO2 ≥35% and flow rate ≥ 8 lpm), age (calculated), sex, ethnicity, and race will be recorded at Screening.

The Charlson Comorbidity Index (CCI) predicts 10-year survival in patients with multiple comorbidities (Charlson et al 1987).

10.1.2. Vital Signs

Vital signs (tympanic, contactless, or oral temperature, blood pressure, heart rate, respiratory rate, SpO2) will be measured at the time points specified in the study schedules with patients resting for at least 5 minutes in a supine position prior to assessment. When the time of vital signs measurement coincides with a blood draw, the vital signs will be taken before the scheduled blood draw where possible while ensuring the blood draw is within the window specified in the protocol.

Additional vital signs may be performed at other times if deemed necessary.

10.1.3. Weight and Height

Body height (centimeters) and body weight (kilograms) will be measured at the time points delineated in the study schedule and will be used to calculate BMI by dividing the participant's body weight in kilograms by the participant's height in meters squared (kg/m^2). Body weight and height will be obtained with the participant's shoes and jacket or coat removed.

10.1.4. Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician, qualified nurse practitioner or physician's assistant as per the PI at the time points specified in the study schedules.

- Complete physical examinations include general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes.
- Symptom-directed physical examinations include head, ears, eyes, nose, throat, chest (heart, lungs), abdomen, skin, musculoskeletal, and lymph nodes and any pertinent system based on any prior findings.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

10.1.5. Electrocardiogram

A 12-lead ECG will be taken at the time points delineated in the study schedules. Additional ECG monitoring may be performed at other times if deemed necessary.

ECGs will be performed prior to vital signs with patients in a supine position. Patients must be in this position for at least 5 minutes before the ECG is taken.

All ECG tracings will be reviewed by the PI or designee.

When the time of ECG monitoring coincides with a blood draw, the ECG will be taken before the scheduled blood draw while ensuring the blood draw is within the window specified in the protocol.

10.1.6. Laboratory Assessments

Safety laboratory tests (hematology, biochemistry, coagulation, urinalysis and urine cotinine) will be performed at the time points specified in the study schedules. Additional clinical laboratory tests may be performed at other times if deemed necessary based on the participant's clinical condition.

Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory.

A blood sample will be taken from each participant for hematology, coagulation and biochemistry analyses at the time points delineated in the study schedules.

10.1.6.1. Hematology

Hematology parameters to be tested are:

- Hemoglobin (HGB)
- Hematocrit (HCT)
- Erythrocytes (RBC)
- Platelets (PLAT)
- Leukocytes with differential (including Eosinophils (ESN), Neutrophils (NEUT), Basophils (BASO), Lymphocytes (LYM - collected with biomarkers and at screening) and Reticulocytes (RETI)

10.1.6.2. Biochemistry

Biochemistry parameters to be tested are:

- C-reactive protein (CRP - collected with biomarkers and at screening)
- Urea (U)
- Creatinine (CREAT)
- Total Bilirubin (BILI) and Direct Bilirubin (BILIDIR)
- BUN (blood urea nitrogen)
- 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 – collection with biomarkers and at screening in PartA; collected and tested as part of blood chemistries in Part B)
- Ferritin (collected with biomarkers and at screening)
- Transforming Growth Factor Beta 1 (TGF-β1)
- Tumor necrosis factor alpha (TNF-α)
- Interleukin 6 (IL-6)
- Interleukin 1 beta (IL-1β)
- Platelet-derived growth factor- β (PDGF- β)
- Granulocyte colony-stimulating factor (GCSF)
- Vascular endothelial growth factor (VEGF)

10.1.6.3. Coagulation

Coagulation parameters to be tested are:

- INR
- Prothrombin time
- APTT
- d-dimer (collected with biomarkers)

10.1.6.4. Urinalysis

A urinalysis test (dipstick) will be performed for each participant. Urinary analysis will be performed at Screening and other times according to the study schedule. If abnormality is noted for protein, blood, nitrite or leukocyte esterase (and at the discretion of the Investigator) a microscopic examination of RBC, WBC, bacteria and casts will be performed.

Dipstick urinalysis (chemical) parameters to be tested are:

- pH (PH)
- Specific Gravity (SPGRAV)
- Protein (PROT)
- Glucose (GLUC)
- Ketones (KETONES)
- Total Bilirubin (BILI)
- Occult Blood (OCCBLD)
- Nitrite (NITRITE)
- Urobilinogen (UROBIL)
- Leukocytes (WBC)

10.1.6.5. Urine Cotinine

A urine cotinine test will be performed at screening, Days 28 and 91 (Visits 5 and 7A) in Part A, and Days 119 and 182 (Visits 9 and 11) in Part B, to measure the amount of cotinine in urine for patients exposed to nicotine.

10.1.6.6. Pregnancy and Follicle-Stimulating Testing

A pregnancy test will be performed at the screening visit and periodically during the trial in WOCBP only. 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.

Postmenopausal status will be confirmed through testing of follicle-stimulating hormone levels (FSH) ≥ 40 IU/mL at Screening for amenorrhoeic female patients. Females who are abstinent from heterosexual intercourse will also be eligible.

11. ADVERSE AND SERIOUS ADVERSE EVENTS

Safety and tolerability will be assessed throughout the study by monitoring AEs, physical examination, vital signs, 12-lead ECGs, clinical laboratory values (hematology panel, multiphasic chemistry panel and urinalysis), and concomitant treatments.

In this study, AEs will be reported for all patients from the time of consent until the completion of the Follow-up/EOS visit. AEs reported prior to the first dose will be denoted as pre-treatment. SAEs will be reported for all patients (enrolled and not enrolled) from the time of consent. AEs reported from the time of consent to confinement on Day -1 will be recorded as pre-treatment AEs.

Treatment emergent- AEs are defined as an AE that occurs following first dose of study medication and will be evaluated from the first administration of study drug until the EOS visit. AEs that are ongoing at the final onsite visit will be marked as Not Recovered/Not Resolved on the AE eCRF page (see Section 11.1.4).

All spontaneously volunteered and enquired for, as well as observed AEs, will be recorded in the participant's medical records and the eCRF.

11.1. Definition of Adverse Events

An AE is any event, side-effect, or other untoward medical occurrence that occurs in conjunction with the use of a medicinal product in humans, whether or not considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavorable 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 or not considered related to the medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition;
- New conditions detected or diagnosed after study drug administration that occur during the reporting periods, even though it may have been present prior to the start of the study;
- Signs, symptoms, or the clinical sequelae of a suspected interaction;
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or concomitant medications (overdose per se will not be reported as an AE/SAE).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure should be reported as an AE if it meets the criteria of an AE;
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital);
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

If there is evidence of an AE through report or observation, the Investigator or designee will evaluate further and record the following information:

- Time of onset and resolution
- Severity
- Causality/relation to study treatment
- Action taken regarding study drug
- Outcome

11.1.1. Severity of an Adverse Event

Severity (intensity) of AEs will be graded by the Investigator as one of:

- **Mild (Grade 1):** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate (Grade 2):** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe (Grade 3):** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- **Life-threatening (Grade 4):** A type of AE that places the participant at immediate risk of death.
- **Death (Grade 5):** Events that result in death.

11.1.2. Causal Relationship of an Adverse Event

The Investigator will assess the relationship between study drug and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to study drug will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug should be considered and investigated, if appropriate. The following definitions are general guidelines to help assign grade of attribution:

- **Not related:** The event is clearly related to other factors such as the participant's environment or clinical state, therapeutic interventions or concomitant drugs administered to the participant. This is especially so when an event occurs prior to the commencement of treatment with the study drug.
- **Possible:** The event follows a reasonable temporal sequence from the time of study drug administration or follows a known response to the study drug but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.

- **Probable:** The event follows a reasonable temporal sequence from the time of study drug administration and follows a known response to the study drug and cannot be reasonably explained by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.

11.1.3. Action Taken with Investigational Products

Should the Investigator need to alter the administration of the study drug from the procedure described in the protocol due to the well-being and safety of the participant then the action taken will be recorded on the AE eCRF page, as one of the following options:

- Dose Reduced
- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Other

11.1.3.1. Action Taken with Investigational Product: Liver Function Testing

When ALT and/ or AST are elevated, discontinuation of confounding concomitant medications should be considered. Please see Table 9 for a list of such medications.

Table 9. Medications to be Used with Caution in Combination with LYT-100

Amiodarone	Disulfiram	Levofloxacin	Probenecid
Amitriptyline	Duloxetine	Ketoconazole	Propafenone
Aprepitant	Entacapone	Methoxsalen	Quinidine
Bupropion	Ethylestradiol	Metronidazole	Sertraline
Chloramphenicol	Fenofibrate	Mexiletine	Sildenafil
Cinacalcet	Fluconazole	Modafinil	Terbinafine
Citalopram	Fluoxetine	Moxifloxacin	Topiramate
Clozapine	Fluvastatin	Nicotine	Voriconazole
Diclofenac	Insulin	Omeprazole Paroxetine	Zafirlukast
Diltiazem	Lansoprazole		

Note: Table 9 is not an exhaustive list but rather a list of commonly known concomitant medications that are known to cause elevations in Liver Function Tests and as such clinical judgment should be used to consider discontinuation of a concomitant medication in the event of LFT elevation.

When ALT and/or AST are elevated >3 x ULN with elevation of bilirubin: Study drug should be discontinued and not restarted.

When ALT and/or AST are elevated ≤3 x ULN without elevation of bilirubin (Grade 1) and in the absence of symptoms: Study drug may be continued at current dose with monitoring of LFTs weekly.

When ALT and/or AST are elevated >3 - ≤5 x ULN without elevation of bilirubin (Grade 2) and in the absence of symptoms: Study drug should be held, LFTs should be checked weekly until resolution of elevations, and then patient can be re-started on study drug at 250 mg BID

with at least weekly monitoring of LFTs for an appropriate period of time. If LFTs are within normal limits within 2 weeks of holding study medication, restarting study drug at full dose can be considered.

When ALT and/or AST are elevated >5 x ULN without elevation of bilirubin and in the absence of symptoms: Study drug should be discontinued and not restarted.

11.1.4. Outcome

Outcome of an AE will be recorded on the AE eCRF as follows:

- Recovered/Resolved
- Recovering/Resolving
- Recovered/Resolved with Sequelae
- Not Recovered/Not Resolving/Ongoing, up to a 30-day follow-up period for treatment-related AEs
- Fatal
- Unknown (or participant lost to follow-up after 4 attempts at contact over a period of 30 days).

11.2. Definition of Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up-), and at any dose of the study drug (active or placebo), that fulfils one or more of the following:

- Results in death.
- It is immediately life-threatening.
- It requires in-patient hospitalization or prolongation of existing hospitalization.
- It results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or birth defect.
- It is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above.

Important medical events that may not be one of the above may be considered an SAE by the Investigator when, based upon appropriate medical judgment, they are considered clinically significant and may jeopardize the participant, or may require medical or surgical intervention to prevent one of the outcomes listed above.

An AE is considered “life-threatening” if, in the opinion of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

11.2.1. Notification of a Serious Adverse Event

All SAEs regardless of relationship to the IP during the period starting from the time of informed consent through the Follow-up Visit, will be recorded in the eCRF. Once the Investigator becomes aware of an SAE, he/she must report the SAE to the Clinical Research Organization (CRO) Safety Department within 24 h of knowledge of the event.

A SAE report must include a full description of the event including the below parameters (include any protocol specific requirements):

- Diagnosis or description of event
- Onset date
- Severity assessment
- Causal relationship to the IP
- Assessment of seriousness of the event
- Corrective treatment administered for the SAE
- Action taken related to IP include the following: dose interruption, dose delay, dose reduction, or IP discontinuation
- Outcome of event and end date

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to CRO Safety Department as soon as information is available.

As further information regarding the SAE becomes available, such follow-up information should be documented on a new SAE report form, marked as a follow-up report, and sent electronically. Paper reporting will be used as back-up for reporting if EDC is unavailable.

Withdrawal from the study in the event of an SAE and therapeutic measures taken shall be at the discretion of the Investigator. A full explanation for the discontinuation from the study should be made in the participant's medical records and in the eCRF. All patients who discontinue study medication should be strongly encouraged to continue with all remaining study visits for follow-up on key safety and efficacy assessments.

All SAEs that occur within 30 days after the last dose of study drug should be recorded and reported as noted previously.

11.3. Clinical Laboratory Abnormalities and other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., biochemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECG and vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed **clinically significant** or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (and recorded as an SAE if they meet the criteria of being serious) as previously described. Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are included as AEs (and SAEs if serious).

The Investigator should exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the participant and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions yet be of a magnitude to require glucose administration to prevent such sequelae.

11.4. Recording Adverse Events

AEs spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded in accordance with the Investigator's normal clinical practice and on the AE page of the eCRF during the study at the investigational site.

However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs and SAEs will be collected from the time of consent until the end of the study. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the participant to discontinue the study. AEs that occur during the study must be documented in the participant's medical record, on the AE CRF and on the SAE report form. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE form, preferably with baseline values and copies of laboratory reports.

In addition, if the abnormal assessment meets the criteria for being serious, the SAE form must also be completed. A diagnosis, if known, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE/SAE page. If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded. Additional information of reporting SAEs will be provided in the Safety Management Plan.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2. An AE of severe intensity may not be considered serious.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the participant was discontinued from the study. All pregnancies should be reported within 24 hours of awareness (including pregnancies of female partners of male patients). Paper reporting will be used for documenting pregnancies and should be followed until outcome is known. Outcome of pregnancy should also be reported on a follow-up pregnancy report form.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

11.5. Reporting Serious Adverse Events

Any SAEs considered possibly or probably related to the study drug and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to the Sponsor and/or the CRO Safety Department within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE eCRF forms/pages, verify the accuracy of the information recorded on the SAE eCRF forms/pages with the corresponding source documents, and send a copy to the Sponsor and/or CRO Safety Department. Paper SAE reporting may be used as a back-up for electronic SAE reporting system when the system is not available.

Additional follow-up information, if required or available, should all be emailed to the Sponsor and/or CRO Safety Department within 24 hours of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IEC / IRB / HREC of all SAEs that occur at their site in accordance with the IEC / IRB / HREC SAE reporting policy. The Investigator will also be notified of all unexpected, serious, drug-related events that occur during the clinical trial. The investigational site is responsible for notifying its IEC / IRB / HREC of these additional SAEs.

11.6. Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs that are deemed related, possibly related or probably related to the study drug must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant dies or is lost to follow-up. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a participant dies during participation in the study or during a recognized follow-up period, the Sponsor should be provided with a copy of any post-mortem findings, including histopathology.

12. STUDY COMPLETION AND DISCONTINUATION

12.1. Participant Discontinuation

In accordance with applicable regulations, a participant has the right to discontinue participation in the study, at any time and for any reason, without prejudice to his future medical care.

If a participant discontinues study medication because of an AE, the Investigator must arrange for the participant to have appropriate follow-up care until the AE is resolved or has stabilized. Unresolved AEs will be followed until the last scheduled Follow-up visit or until the PI and Medical Monitor determine that further follow-up is no longer indicated. In addition to AEs, other reasons for removal of patients from the study might include, but are not limited to, withdrawal of consent, administrative decision by the Investigator or the Sponsor, protocol deviation, or participant noncompliance.

If a participant asks or decides to discontinue participation in the study, all efforts will be made to complete and report the observations, especially the listed primary and secondary objectives, as thoroughly as possible up to the date of withdrawal. The primary reason for withdrawal will be identified and recorded on the appropriate eCRF, along with the date of withdrawal. For patients who discontinue treatment due to a related adverse event per investigator's decision, these patients should remain in the study after being discontinued from treatment and be followed for all scheduled assessments. Subjects will only be removed from the study due to withdrawal of consent or loss of follow up.

12.2. Definition of the End of the Trial

The end of study for each participant is defined as the date of the last subject's last visit.

13. TERMINATION OR SUSPENSION OF THE STUDY

The Sponsor, Investigator and the IEC / IRB / HREC reserve the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in the eCRFs. The Investigator should notify the relevant IEC / IRB / HREC in writing of the study's completion or early discontinuation.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Monitoring will include both remote and on-site visits when this is permitted in line with national and local guidelines during the COVID-19 pandemic. An initiation visit will be performed at each site before the first subject is included. Initiation visits may be conducted remotely. Monitoring visits and contact will occur at regular intervals thereafter. A close-out visit will be performed after the database lock for Part B and resolution of all pending queries and follow-up of ongoing AEs/SAEs. Full details of the study monitoring procedures to be employed in this trial will be detailed in the Monitoring Plan.

Before an investigational site can enter a participant into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

The Sponsor will appoint a Contract Research Organization to manage and monitor the study so as to assure them of the adequate conduct of the study and to act as the contact with the investigational site. A study monitor will be identified and will be responsible for liaison with, and support of, the investigational site.

The study monitors and the regulatory authority inspectors are responsible for contacting and visiting the investigative site for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs, essential documentation, and other pertinent data) provided that participant confidentiality is respected

During the study, the monitor will have regular contacts with the investigational site for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study drug accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the CRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IEC / IRB / HREC.

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

14.2. Data Management

All data will be recorded in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF information is to be filled in by site staff as per the eCRF Completion Guidelines. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be subject to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

All eCRFs should be maintained on the system with details of any changes logged accordingly.

Two independent database locks are planned for this study: the first for the double-blind, randomized treatment portion (Part A) and the second for the open label extension (Part B).

14.3. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IEC / IRB / HREC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

15. STATISTICAL METHODS

This is a Phase 2 study in patients with active COVID-19 disease and thus has potential to be an important treatment during the current pandemic. The study is rigorously designed to collect a wide range of endpoints to assess the benefits (and risks) of treatment with LYT-100 in this population. Thus, there are several endpoints identified. Testing of primary and key secondary efficacy endpoints will be performed and will not be controlled for multiplicity. Other secondary efficacy endpoints will be tested and used to provide support as to the preponderance of evidence of the benefit/risk profile of LYT-100, with magnitude of effects, consistency of direction of effect (i.e., beneficial or harmful), and significance of inferential tests all taken into account to draw final conclusions regarding the study outcomes. Primary efficacy conclusions will be based on Day 91 (end of double-blind treatment), with supporting data from earlier timepoints included to describe the time-profile of any treatment benefits. A comprehensive statistical analysis plan will be written that will include details regarding the statistical analysis. The methods described below summarize the general approach.

Further, note that the primary focus of the statistical analysis is on the double-blind comparison of LYT-100 to placebo (Part A). The following methods describe those for Part A; Part B methods are provided at the end of the Statistical Methods section. A comprehensive SAP will be written, in which the methods of statistical analysis will be described separately for Part A from Part B.

15.1. Sample Size

The study will utilize a suite of endpoints to measure patient clinical function and health-related quality of life. The sample size was based on the 6MWT (a measure of patient clinical function).

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 patients 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., patients 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 approximately 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 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.

- The sample size for the SCOA was estimated based on the need to achieve saturation in the generation of COVID Symptoms in this target population. It is estimated that approximately 20 patients will be sufficient for these purposes.

15.2. General Statistical Plan

The baseline value for all variables will be the last measurement obtained prior to the participant receiving the first dose of study treatment.

In general, descriptive statistics (arithmetic mean, standard deviation [SD], median, minimum and maximum) will be calculated for continuous valued safety data by specified assessment time point. Frequency summaries (i.e., number and percentage of each observed category) will be provided for categorical and ordinal safety data by time point.

Primary efficacy conclusions will be on the, Intent to Treat population, with supporting analyses performed for population definitions. Subgroup analysis for the randomization strata (or other subgroup definitions) may be performed where applicable. Safety conclusions will be based on the Safety Population.

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

Statistical methods will be further outlined in a statistical analysis plan (SAP) and approved by the Sponsor prior to any analysis. Procedures outlined in the SAP will supersede protocol specified statistical methods in the event of divergence. Part A and B will be described separately in the SAP.

A Supplemental SAP will be written to define the methods to be used for the SCOA to evaluate the COA measures used in this study. As part of this sub-study analysis, and to further inform the basis for any observed treatment benefit from LYT-100 as well as to refine the precision of such estimate, it is possible that an exploratory analysis of the pooled data from both Part A and the SCOA could be used in an analysis of exposure, safety, and efficacy outcomes.

15.3. Handling of Missing Data

This study is being performed in patients with active COVID-19 diagnosis. There may be restrictions beyond the patient's control that may limit the collection of study visit assessments. Attempts should be made to collect assessments at the hospital, rehab, out-patient clinic and/or patient'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 patients 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 (including topic such as imputation methods for data missing at random vs missing NOT at random) will be described in the SAP prior to unblinding.

15.4. Analysis Populations

Participant inclusion into each analysis population will be determined prior to unblinding, except the PK Population.

- The Safety Population is defined as all patients who received at least one dose of study treatment. All safety endpoints will be assessed using this population. Patients will be analyzed according to the treatment they actually receive, regardless of which treatment they were randomized to.
- The Intent to Treat (ITT) population is defined as all randomized patients. All efficacy endpoints will be assessed using this population, with primary conclusions regarding study drug effect be based on the ITT population outcomes. Patients will be analyzed according to the treatment group they were randomized to, regardless of which treatment they actually receive.
- 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.
- The Per-Protocol (PP) population is 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 have no major protocol deviations that could affect interpretability of the efficacy outcomes. Subjects who died or discontinued due to TEAE will be included in this population.

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

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

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, as well as the development stage of this study, 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).

15.5. Baseline Characteristics, Patient Disposition, and Medications

The baseline for each variable (except the 6MWT) will be the last measurement obtained prior to first dose of study treatment. For the 6MWT distance, the longest distance of the two tests conducted on Day -1/Day1 will be used as the baseline for purposes of analysis.

Demographic information and patient disposition outcomes will be tabulated (including the number and percent of patients who are enrolled, who receive treatment, who prematurely discontinue and reasons for discontinuation, and who complete the study). Summary statistics for days of exposure and duration of exposure will be provided.

Medical history will be coded and tabulated accordingly. Prior and concomitant medications will be coded using the current WHO drug dictionary. Prior and concomitant medications will be listed by participant and summarized by treatment using ATC and preferred term.

15.6. Efficacy

While all analyses will be performed at each protocol-scheduled time point (i.e., Days 14, 28, 56, and 91), conclusions regarding the primary and key secondary endpoints will be based on analysis of Day 91 data. It is possible the effect of LYT-100 may increase over time, and thus the effect (benefit) could be greater at Day 91 than earlier time points. The effect-time profile for each endpoint is also of interest and will be tabulated as below as well as plotted accordingly.

15.6.1. Primary and Key Secondary Efficacy Endpoints

The primary method of analysis for continuous endpoints is consistent with the sample size methodology and will thus utilize mixed models for repeated measures (MMRM), assuming a Gaussian distribution, an unstructured covariance matrix, and the Kenward-Roger approximation for denominator degrees of freedom. Fixed effects will include treatment, visit, the treatment by visit interaction, the baseline value of the endpoint as a covariate, and study center; however, the SAP may specify additional covariates to be added to the model. By-visit pairwise comparisons will be assessed. with primary conclusions based on the Day 91 timepoint. Missing data will be imputed according to the ‘type’ of missingness, ie, data missing at random will be imputed differently than data that are missing NOT at random (eg, missing due to death, hospitalization, discontinuation due to TEAE); the specific imputation strategy for the primary and key secondary endpoints will be described in detail in the SAP.

A sensitivity analysis of the primary and key secondary endpoints will be performed using a nonparametric Wilcoxon rank sum test to test the active vs. placebo comparison at each time point. Analysis of the key secondary efficacy endpoint, dyspnoea-12,will be performed in a similar manner. Primary conclusion regarding efficacy of these endpoints will be based on the ITT population, with sensitivity support based on the FAS and PP populations.

15.6.2. Other Secondary Efficacy Endpoints

Analysis of other secondary and exploratory efficacy endpoints will be performed similarly to the primary efficacy endpoint.

Categorical endpoints will be assessed at each time point using a Cochran-Mantel-Haenszel (CMH) test, stratified by center. For ordinal and other categorical endpoints, a CMH row means scores test (CMH-RMS) (which used modified ridit scores) will be used, stratified by center. Specifically, for the WHO Ordinal Scale for Clinical Improvement, response definitions will include patients with at least 1-point improvement and at least 2-point improvement. WHO outcomes will also be assessed on a continuum using similar MMRM as for the primary efficacy endpoint. Bar charts of the distribution of outcomes will be provided for each visit to allow for visual inspection of any treatment differences.

Analysis of the incidence of pulmonary exacerbations (severe and non-severe will be assessed as separate endpoints. The primary assessment will be the time-to-first severe exacerbation via a Kaplan-Meier plot and logrank test statistic. If there are multiple exacerbations per subject, other methods of analysis may be considered.

The SF-36 (v2) will be assessed via analysis of each of the 8 domains as well as the 2 component scores. The outcomes will be used to allow for a more thorough understanding of the treatment benefit and may be explored via correlation analyses with the 6MWT and other endpoints, as the data warrant.

Kaplan-Meier plot and log-rank tests may assess time to all-cause mortality (if sufficient mortality data exist to allow for meaningful comparisons). The number (%) of patients dying (all-cause mortality) through Day 91 will be tabulated. The time to discharge of hospitalization (in days) and other time-to-event parameters, as the data permit. The number and percent of patients requiring re-hospitalizations will be tabulated.

A correlational analysis may also be undertaken to identify patient factors e.g., age, gender, BMI, etc. and potential biomarkers that are associated with overall survival and successful resolution of all signs and symptoms of the disease. Further, response definitions of select endpoints will be explored to better understand the benefit of LYT-100.

Statistical analyses will be performed using SAS, version 9.4. (SAS, Cary, NC).

15.7. Safety and Tolerability

Safety analyses will be performed using the Safety Population. Adverse events, concomitant medications, clinical laboratory findings, physical examinations, ECGs, and vital signs for each participant will be tabulated or summarized descriptively, where appropriate, as described in the following sections.

15.7.1. Adverse Events

Adverse events will be coded using MedDRA® Version 23.0 (or later); this version has the most up-to-date COVID-19 coding terms. Analysis will focus on treatment-emergent AEs (TEAEs). The number of patients experiencing TEAEs and the number of individual TEAEs will be provided, as well as by SOC and PT. The severity and the relationship to study drug of TEAEs will be summarized. Pre-treatment AEs will be tabulated separately from TEAEs. SAEs, TEAEs leading to discontinuation, and TEAEs leading to death will be tabulated.

15.7.2. Laboratory Evaluations

Laboratory evaluations (including hematology, biochemistry, coagulation and urinalysis) will be listed and summarized by protocol specified collection time point. This will be done both for actual observed laboratory values and for changes from baseline. Shift tables will also be provided for clinical laboratory results.

The abnormal urinalysis results, if applicable, will be listed only.

15.7.3. Vital Signs

Vital signs including SpO_2 will be listed and summarized by protocol specified collection time point. This will be done both for actual observed vital sign values and for changes from baseline.

15.7.4. ECG Values and Result

ECG values will be listed and summarized by protocol specified collection time point. 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. ECG results for QTcF will also be classified as <450 msec, 450-500 msec or >500 msec.

15.8. Population Pharmacokinetics- Part A Only

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.

15.9. Biomarkers- Part A Only

Exploratory analysis of biomarkers changes over time in C-reactive protein (CRP), lymphocyte count, d-dimer, cardiac troponin, ferritin, lactate dehydrogenase (LDH), IL-6, TGF-β1, TNF-α, IL-1β, PDGF- β, GCSF, and VEGF. Correlation of changes in biomarkers with clinical endpoints (e.g., 6MWT, Dyspnoea-12) will be assessed where relevant in an exploratory fashion. Further details of this exploratory biomarker analysis will be provided in the Statistical Analysis Plan.

15.10. Statistical Method for the Open-Label Extension (Part B)

Part B is characterized by open-label treatment, and thus the analysis will be descriptive in nature. Where inferential methods are used, these will be used to better-inform as to the relative magnitudes of the longer-term effects from treatment with LYT-100, and not for hypothesis testing purposes.

The focus of the Part B analysis will be on the LYT-100 to LYT-100 group (as these patients will have been treated with up to 182 days with active treatment), but the Placebo to LYT-100 group will also be analyzed, with a focus on whether there are any meaningful differences in these exploratory efficacy endpoints from Part A compared to Part B.

OLE Safety Population: 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. Other analysis populations may be defined to help inform as to characteristics of the safety and exploratory efficacy profiles.

The primary objective of Part B is to assess safety and tolerability, and thus tabulations will be presented with this goal in mind. Analysis will include data from Part A, so that the slopes of changes over time from Study Day 1 through Study Day 182 can be described.

15.11. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by IEC / IRB / HREC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any participant into the study.

The Investigator is responsible for informing the IEC / IRB / HREC of any amendment to the protocol in accordance with local requirements. In addition, the IEC / IRB / HREC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IEC / IRB / HREC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IEC / IRB / HREC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug (active). The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IEC / IRB / HREC according to local regulations and guidelines.

15.12. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP applicable regulatory requirements and the Sponsor's policy on Bioethics.

15.13. Informed Consent

The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time without prejudice. The participant should be given the opportunity to ask questions and allowed time to consider the information provided before voluntarily signing the written ICF.

The participant's signed and dated informed consent (written, electronic, or oral) must be obtained before conducting any study procedures. The patients will be informed of their rights to privacy but will be made aware that the study data will be submitted to the Sponsor and possibly to drug regulatory authorities for review and evaluation. They will be informed also that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

The acquisition of informed consent should be documented in the participant's medical records, and the ICF will be signed and personally dated by the participant and by the person who conducted the informed consent discussion.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or legal representative. The date that informed consent was signed will be recorded on the CRF.

15.14. Data Protection

Patients will be informed that data will be held on file by the Sponsor and that these data may be viewed by staff including the study monitor and by external auditors on behalf of the Sponsor and appropriate regulatory authorities. Patients will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication. However, patients will be identified in such reports only by study identification number, gender and age. All participant data will be held in strict confidence.

16. REGULATORY REQUIREMENTS

The Contract Research Organization (CRO) will act as the legal Sponsor, when appropriate for the study and will fulfil the obligations that this role entails. The CRO shall, to the extent required by the applicable laws and regulations, interact when appropriate on behalf of the Sponsor in connection with this study. The planned regulatory pathway for this trial is through the appropriate regulatory agency's scheme. Aside from approval by the IEC / IRB / HREC and notification of the appropriate regulatory agency, no other regulatory approval will be required.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

All source data, clinical records and laboratory data relating to the study will be archived for 25 years after the completion of the study. All data will be available for retrospective review or audit.

Source documents are original documents, data, and records from which the participant's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, angiograms, study drug accountability logs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all study-related (essential) documentation. These include but are not limited to IEC / IRB / HREC correspondence, study drug accountability logs, and curricula vitae of all personnel participating in the study. These files must be suitable for inspection at any time by the Sponsor, monitor, and/or applicable regulatory authorities. All essential documentation should be retained by the institution for 15 years.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. If the Investigator wishes to assign the study records to another party or

move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

17.3. Liability/Indemnity/Insurance

The Sponsor will ensure sufficient insurance is available to enable it to indemnify and hold the Investigator(s) and relevant staff as well as any hospital, institution, ethics committee or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the study drug but only to the extent that the claim is not caused by the fault or negligence of the patients or Investigator(s).

18. PUBLICATION POLICY

18.1. Publication of Results

The publication, presentation or other public disclosure of study results (each, a "Publication") will be accurate and honest, undertaken with integrity and transparency and in accordance with the Sponsor's approval.

Publication of results will be subjected to fair peer-review. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation.

All conflicts arising through disputes about authorship will be reviewed by the Sponsor.

Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organizations providing finance or facilities. Participant confidentiality will be maintained by referring to individual patients by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with the Sponsor's approval.

Study data that have not been published, presented or otherwise disclosed in accordance with the clinical trial agreement shall remain confidential information of the Sponsor, the Investigator may not disclose or permit the disclosure of such unpublished data to any third party, nor may they disclose or permit the disclosure of any study data to any third party in greater detail than the same have been disclosed in any permitted publication, presentation or other disclosure.

The clinical trial will be posted to a clinical trial registry as required by legal agreement, local law or regulation.

18.2. Disclosure and Confidentiality

By signing this protocol, the Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from his/her staff and the local IEC / IRB / HREC. Study documents provided by the Sponsor (Protocols, IBs, eCRFs, etc.) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the study.

The Investigator must ensure that the participant's anonymity is also maintained. Patients should only be identified by their initials and a participant study number on the CRFs and other source documents. Other study-related documents (e.g., signed ICFs) should be kept in strict confidence by the Investigator.

19. QUALITY CONTROL AND QUALITY ASSURANCE

19.1. Compliance with Good Clinical Practice

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 14.3 for more details regarding the audit process.

The study will be carried out in accordance with the current version of the Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects), Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2).

19.2. Archiving and Regulatory Inspection

All study-related documents and records are to be retained for a minimum of 15 years after trial completion. Written agreement from the Sponsor must precede destruction of the same.

In accordance with ICH GCP, this study may be selected for audit. Inspection of site facilities (e.g., pharmacy, medication storage areas, laboratories) and review of study-related records may occur by the Sponsor, the Sponsor's representative(s), or regulatory authority to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

20. CLINICAL STUDY REPORTS

A separate clinical study report (CSR) will be prepared for each Part of the study, A and B. They will reference ICH Guidance E3 and include:

- Details of where the study was carried out.
- Dates of the start and completion of each period of the study.
- Details of the study drug and a statement of production will be provided by the Sponsor.
- A statement confirming that the applicable IEC / IRB / HREC gave written approval for the study in accordance with local regulations.
- A demographic listing for all patients.
- A list of all AEs according to study drug.
- Details of any occurrences which may be of significance to the study outcome.

- Details of all operations, calculations and transformations performed on the reported data.
- The appropriate SAP report will be produced by the Sponsor, or their agents, and will be incorporated into each final report.
- A scientific interpretation of the results.
- A description of the study methods used.

Consideration will be given to any comments on a draft report. The report will incorporate the analytical and statistical results and methods produced by the Sponsor or their agents. A final report will be prepared to contain all those sections in the draft and a statement of compliance covering all the areas of the study conducted at the investigational site and the report, with GCP. The report will be issued under the Sponsor's responsibility.

Where required by the applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review complete study results. The Sponsor will also provide the Investigator with the full summary of study results.

21. SPONSOR AND INVESTIGATOR OBLIGATIONS

21.1. Protocol Amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IEC / IRB / HREC for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial patients. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

21.2. Protocol Deviations

Should any protocol deviation occur, it must be reported to the study monitor as soon as is reasonably practical. The deviation and the reason for its occurrence must be documented, reported to the relevant IEC / IRB / HREC (if required) and included in the CSR.

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APPENDIX 1. ENDPOINT SCALES

Table 10: WHO Ordinal Scale for Clinical Improvement (sample)

Ordinal Scale for Clinical Improvement		
Patient State	**Descriptor**	**Score**
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by ask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Mechanical Ventilation plus additional organ support (i.e. extracorporeal life support (ECLS), continuous renal replacement therapy (CRRT), vasopressors)	7
Dead	Death	8
World Health Organization 2020, February 19, 2020, Geneva Switzerland		

Table 11: 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

Table 12: Chest CT Scan Number of Involved Segments (sample)

Per lung	
Interstitial Change	Pleural effusion □ Right □ Left □ Bilateral □ Lymphadenopathy
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 □ NE
Consolidation	□ Central □ Peripheral □ Diffuse □ Absent □ NE
Reticular pattern	□ Central □ Peripheral □ Diffuse □ Absent □ NE
Mixed pattern	□ Central □ Peripheral □ Diffuse □ Absent □ NE
Honeycomb pattern	□ Central □ Peripheral □ Diffuse □ Absent □ NE
Interstitial Change	□ Septal thickening □ Crazy paving pattern □ Pleural thickening

Table 13: Modified Borg Dyspnoea Scale (sample)

The Modified Borg Dyspnoea Scale is collected on study days per schedule of events (Table 4) and at the beginning of the study visits and after resting for a minimum of 5 minutes.

"This is a scale that asks you to rate the difficulty of your breathing. It starts at number 0 where your breathing is causing you no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal. How much difficulty is your breathing causing you right now?"

0	**Nothing at all**
0.5	**Very, very slight (just noticeable)**
1	**Very slight**
2	**Slight**
3	**Moderate**
4	**Somewhat severe**
5	**Severe**
6	
7	**Very severe**
8	
9	**Very, very severe (almost maximal)**
10	**Maximal**

Table 14: The Borg Scale Used in 6-minute Walk test (sample)

0	**Nothing at all**
0.5	**Extremely weak (just noticeable)**
1	**Very weak**
2	**Weak (light)**
3	**Moderate**
4	
5	**Strong (heavy)**
6	
7	**Very strong**
8	
9	
10	**Extremely strong (maximal)**

Thinking back to the last time you took the 6MWT:

Please grade your level of ***shortness of breath*** using this scale. _____

Please grade your level of ***leg fatigue*** using this scale. _____

Shortness of breath and fatigue during 6MWT

Shortness of breath and *fatigue* are also measured with the 6MWT assessment using the same scale. At the beginning of the 6-minute walk test, the scale is shown to the patient who is asked:

1) "Please grade your level of shortness of breath using this scale." _____

2) Following the response to #1, the patient is then asked, "Please grade your level of leg fatigue using this scale." _____

3) At the end of the exercise, patient is reminded of the breathing number chosen before walking and then asked to grade their "breathing level" again. _____

4) The patient is then reminded of their grade before exercise and is asked to grade their level of leg fatigue. _____

Table 15: Charlson Comorbidity Index (sample)

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

Adapted from: Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis.1987; 40: 373-83.

Calculation: Add all items of the Comorbidity score: The total score is the Charlson Comorbidity Index.

COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease

Table 16: St. George's Respiratory Questionnaire-I (sample)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problem, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Name: …… Date: …….

ID Number: ……..

Age: …….. Sex: Male/Female

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

St. George's Respiratory Questionnaire-I (continued)

Part 1

Questions about how much chest trouble you currently have. Please tick in one box for each question.

	Almost every day	Only with chest infections	Not at all
1. I cough:	☐	☐	☐
2. I bring up phlegm (sputum):	☐	☐	☐
3. I have shortness of breath:	☐	☐	☐
4. I have attacks of wheezing:	☐	☐	☐

5. In a typical week how many attacks of chest trouble do you have? Please tick (✓) one:

More than 1 attack ☐

No attacks ☐

6. In a typical week how often do you have good days? Please tick (✓) one:

None ☐

A few days ☐

Every day is a good day ☐

Part 2

Section 1:

If you have ever had paid employment:

Please tick (✓) one:

My lung condition interferes or made me stop work ☐

My lung problem does not affect my job ☐

St. George's Respiratory Questionnaire-I (continued)

Section 2: Questions about what activities usually make you feel breathless. Please tick in each box that applies to you <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days:*

		True	False
1.	Getting washed or dressed	☐	☐
2.	Walking around the home	☐	☐
3.	Walking outside on the level	☐	☐
4.	Walking up a flight of stairs	☐	☐
5.	Playing sports or games	☐	☐

Section 3: Some more questions about your cough and breathlessness. Please tick in each box that applies to you <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days:*

		True	False
1.	My cough hurts	☐	☐
2.	My cough makes me tired	☐	☐
3.	I am breathless when I talk	☐	☐
4.	I am breathless when I bend over	☐	☐
5.	My cough or breathing disturbs my sleep	☐	☐
6.	I get exhausted easily	☐	☐

Section 4: Questions about other effects that your chest trouble may have on you. Please tick in each box that applies to you <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days:*

		True	False
1.	My cough or breathing is embarrassing in public	☐	☐
2.	My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
3.	I get afraid or panic when I cannot get my breath	☐	☐
4.	I feel that I am not in control of my chest problem	☐	☐
5.	Exercise is not safe for me	☐	☐
6.	Everything seems too much of an effort	☐	☐

St. George's Respiratory Questionnaire-I (continued)

Section 5: These are questions about how your activities might be affected by your breathing. Please tick in each box which you think applies to you because of your breathing

	True	False
1. Jobs such as housework take a long time, or I have to stop for rests	☐	☐
2. If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
3. If I hurry or walk fast, I have to stop or slow down	☐	☐
4. My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
5. My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 6: We would like to know how your chest usually affects your daily life. Please tick in each box that applies to you because of your chest trouble

	True	False
1. I cannot play sports or games	☐	☐
2. I cannot go out of the house to do the shopping	☐	☐
3. I cannot do housework	☐	☐
4. I cannot move far from my bed or chair	☐	☐

Now, would you tick in the box (one only) which you think best describes how your chest affects you:-

It does not stop me doing anything I would like to do	☐
It stops me doing one or two things I would like to do	☐
It stops me doing most of the things I would like to do	☐
It stops me doing everything I would like to do	☐

Table 17: Dyspnoea-12 (sample)

"This questionnaire is designed to help us learn more about how your breathing is troubling you.

Please read each item and then tick in the box that best matches your breathing **these days**. If you do not experience an item tick the 'none' box. Please respond to all items.

Name: _____ID: _____Date: ____/____/____

Item	None	Mild	Moderate	Severe
1. My breath does not go in all the way				
2. My breathing requires more work				
3. I feel short of breath				
4. I have difficulty catching my breath				
5. I cannot get enough air				
6. My breathing is uncomfortable				
7. My breathing is exhausting				
8. My breathing makes me feel depressed				
9. My breathing makes me feel miserable				
10. My breathing is distressing				
12. My breathing makes me feel agitated				
13. My breathing is irritating				

Table 18: SF-36 v2 (sample)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer each question by choosing just one answer. If you are unsure how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

□1 Excellent □2 Very good □3 Good □4 Fair □5 Poor

2. Compared to one year ago, how would you rate your health in general now?

□ 1 Much better now than one year ago

□ 2 Somewhat better now than one year ago

□ 3 About the same

□ 4 Somewhat worse now than one year ago

□ 5 Much worse now than one year ago

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	YES, limited a lot	YES, limited a little	NO, not limited at all
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	□1	□2	□3
4. Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	□1	□2	□3
5. Lifting or carrying groceries	□1	□2	□3
6. Climbing several flights of stairs	□1	□2	□3
7. Climbing one flight of stairs	□1	□2	□3
8. Bending, kneeling or stooping	□1	□2	□3
9. Walking more than a mile	□1	□2	□3
10. Walking several hundred yards.	□1	□2	□3
11. Walking one hundred yards	□1	□2	□3
12. Bathing or dressing yourself	□1	□2	□3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	YES	NO
13. Cut down the amount of time you spent on work or other activities	□1	□2
14. Accomplished less than you would like.	□1	□2
15. Were limited in the kind of work or other activities.	□1	□2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	□1	□2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	Yes,	No
17. Cut down the amount of time you spent on work or other activities	□1	□2
18. Accomplished less than you would like.	□1	□2
19. Did work or other activities less carefully than usual.	□1	□2

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

□ 1 Not at all

□ 2 Slightly

□ 3 Moderately

□ 4 Quite a bit

□ 5 Extremely

21. How much bodily pain have you had during the past 4 weeks?

□ 1 None

□ 2 Very mild

□ 3 Moderate

□ 4 Severe

□ 5 Very severe

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

□1 Not at all

□2 A little bit

□3 Moderately

□4 Quite a bit

□5 Extremely

These questions are about how you feel and how thing have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks….

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of life?	□1	□2	□3	□4	□5	□6
24. Have you been very nervous?	□1	□2	□3	□4	□5	□6
25. Have you felt so down in the dumps that nothing could cheer you up?	□1	□2	□3	□4	□5	□6
26. Have you felt calm & peaceful?	□1	□2	□3	□4	□5	□6

27. Did you have a lot of energy?	□1	□2	□3	□4	□5	□6
28. Have you felt down-hearted and depressed?	□1	□2	□3	□4	□5	□6
29. Did you feel worn out?	□1	□2	□3	□4	□5	□6
30. Have you been happy?	□1	□2	□3	□4	□5	□6
31. Did you feel tired?	□1	□2	□3	□4	□5	□6

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

□ 1 All of the time

□ 2 Most of the time

□ 3 Some of the time

□ 4 A little bit of the time

□ 5 None of the time

How TRUE or FALSE is each of the following statements for you.					
	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	□1	□2	□3	□4	□5
34. I am as healthy as anybody I know	□1	□2	□3	□4	□5
35. I expect my health to get worse	□1	□2	□3	□4	□5
36. My health is excellent	□1	□2	□3	□4	□5

APPENDIX 2. BLOOD VOLUMES

Estimates for the total volumes of blood drawn over the course of the study are presented below in Table 19 and will be confirmed by the central or local laboratory prior to commencement of the study. Further details will be provided in the Laboratory Manual and/or patient ICF.

Table 19. Estimated Blood Volumes- Part A

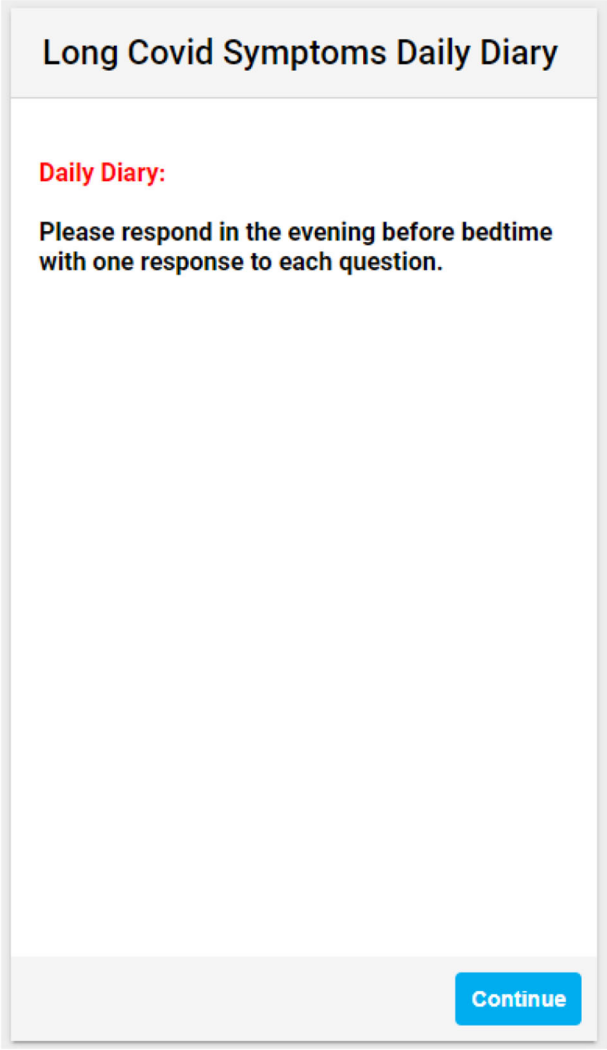
Test	Per Test Volume	Total Number of Samples	Total Volume
Hematology Panel with Reticulocytes	3 mL	6	18 mL
Chemistry	5 mL	6	30 mL
FSH X1	from above chemistry	-	-
Coagulation Panel (PT/INR, PTT)	4.5 mL	6	27 mL
Safety Biomarkers:			
• D-dimer	2.7 mL	6	16.2 mL
• C-reactive Protein • Ferritin	5 mL	6	30 mL
• Cardiac Troponin	3.5 mL	6	21 mL
• Lymphocyte Count	3 mL	6	18 mL
Inflammatory and Fibrotic Biomarkers: • IL-6 • TGF-β1 • TNF-α • PDGF • IL-1b • GCSF • VEGF	10 mL	6	60 mL
PK	4 mL	5	20 mL
Estimated Overall Blood Volume Collected Per Participant			241 mL

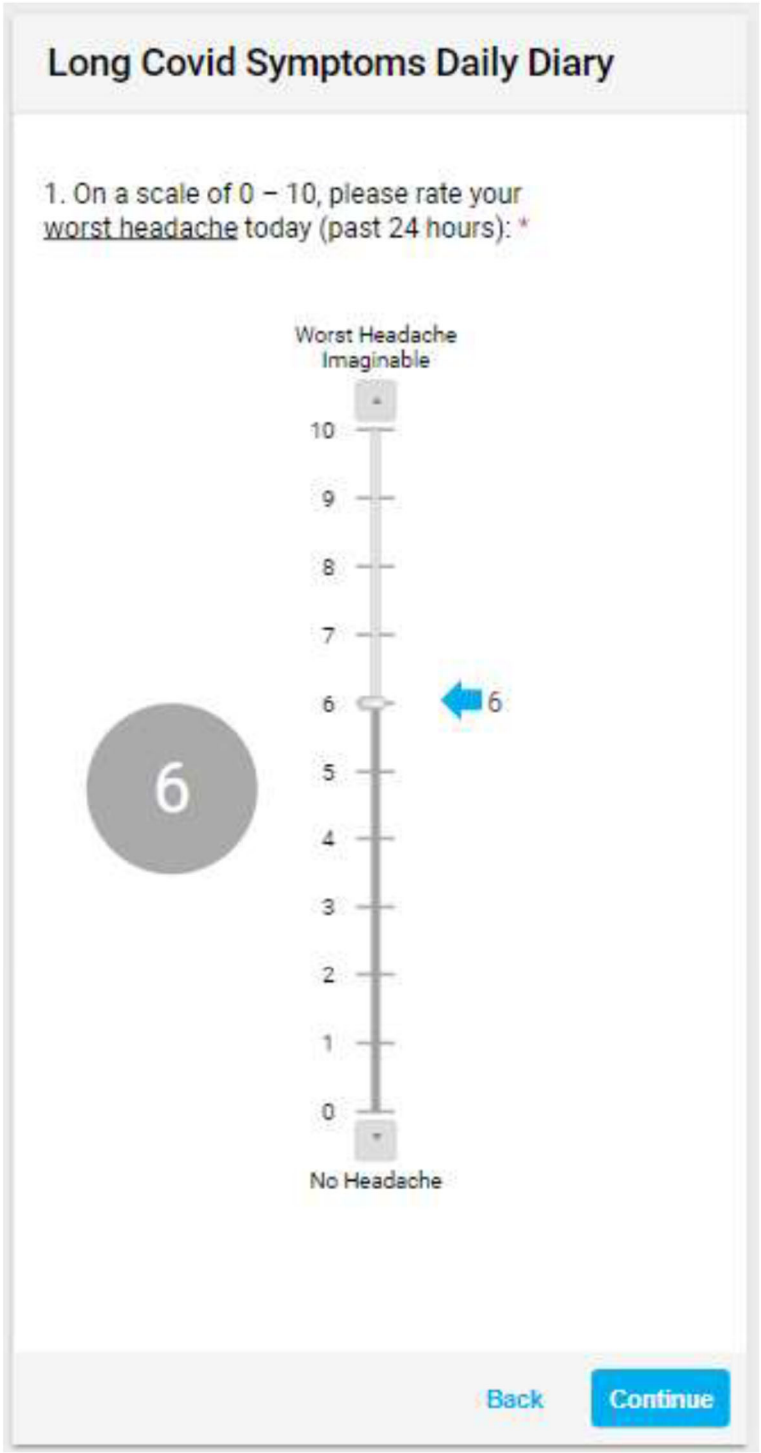
Table 20. Estimated Blood Volumes- Part B

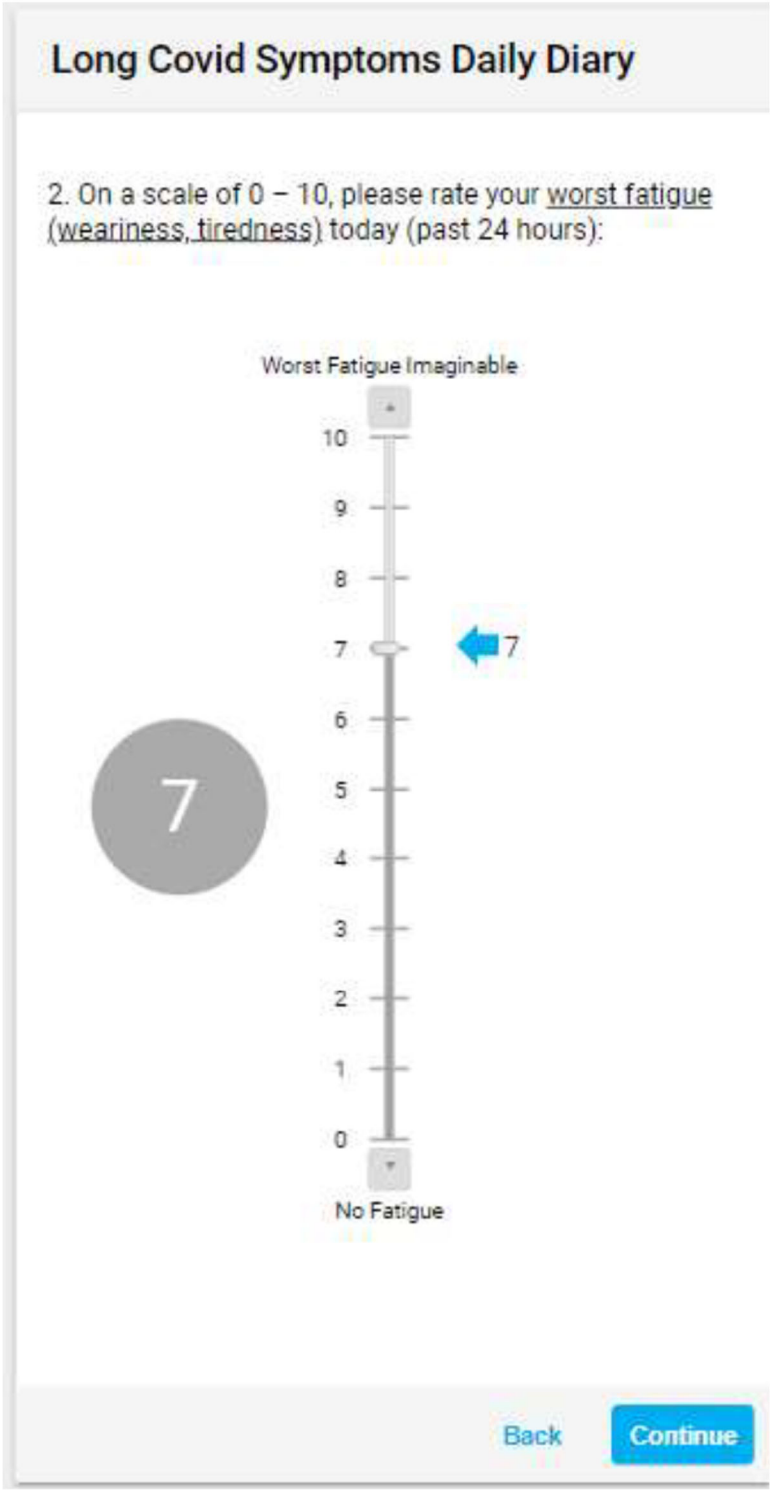
Test	Per Test Volume	Total Number of Samples	Total Volume
Hematology Panel with Reticulocytes	3 mL	6	18 mL
Chemistry	5 mL	6	30 mL
FSH X1	from above chemistry	-	-
Coagulation Panel (PT/INR, PTT)	4.5 mL	6	27 mL
Estimated Overall Blood Volume Collected Per Participant			75 mL

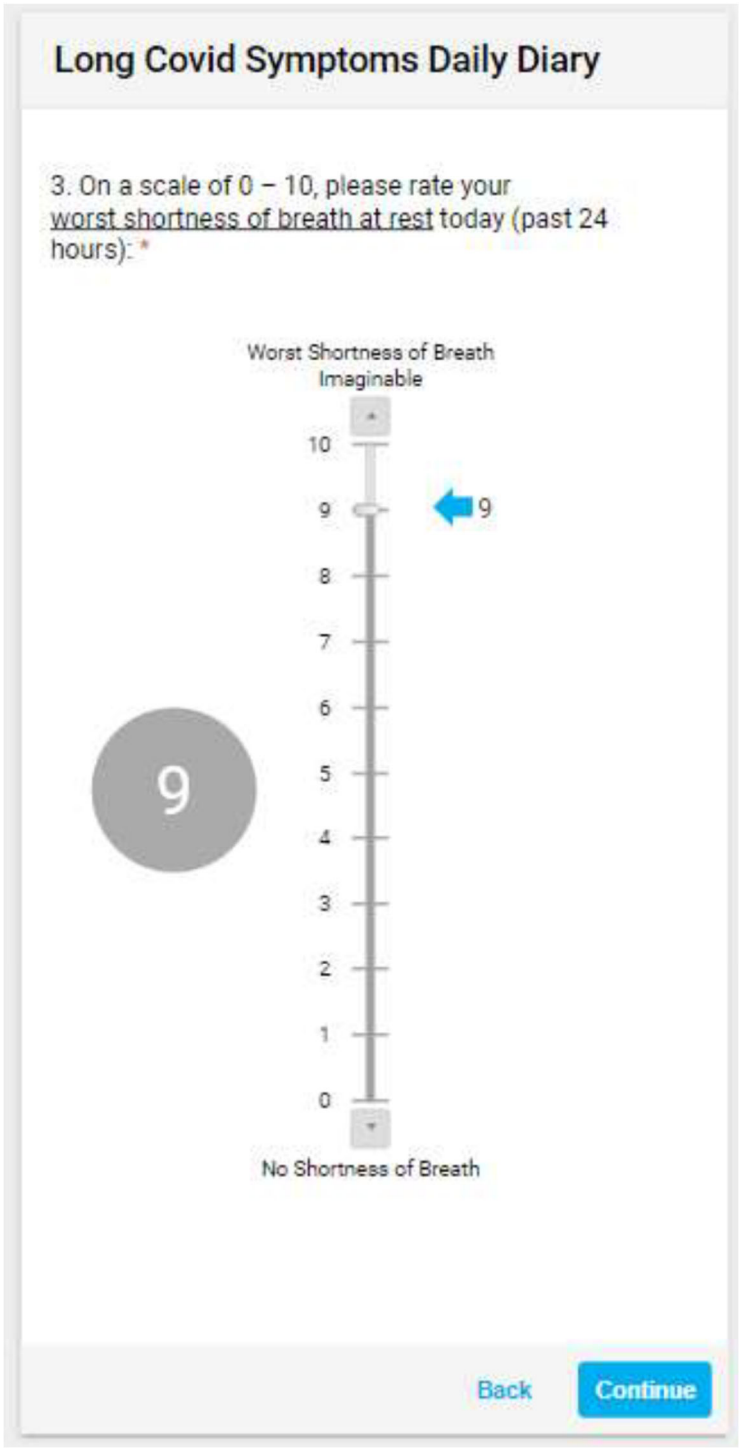
Table 21: COVID Symptom Assessments

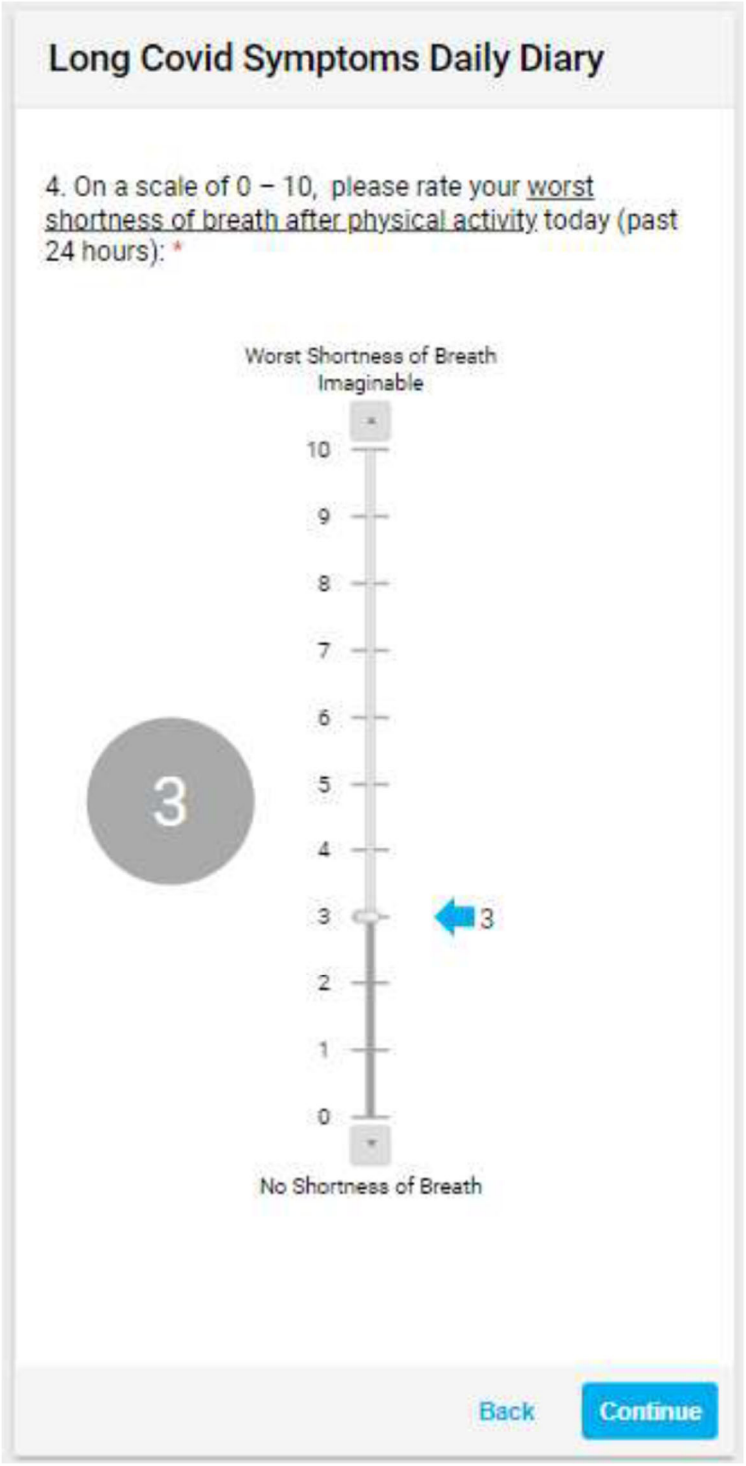
Table 21.1: Daily Covid Symptom Diary

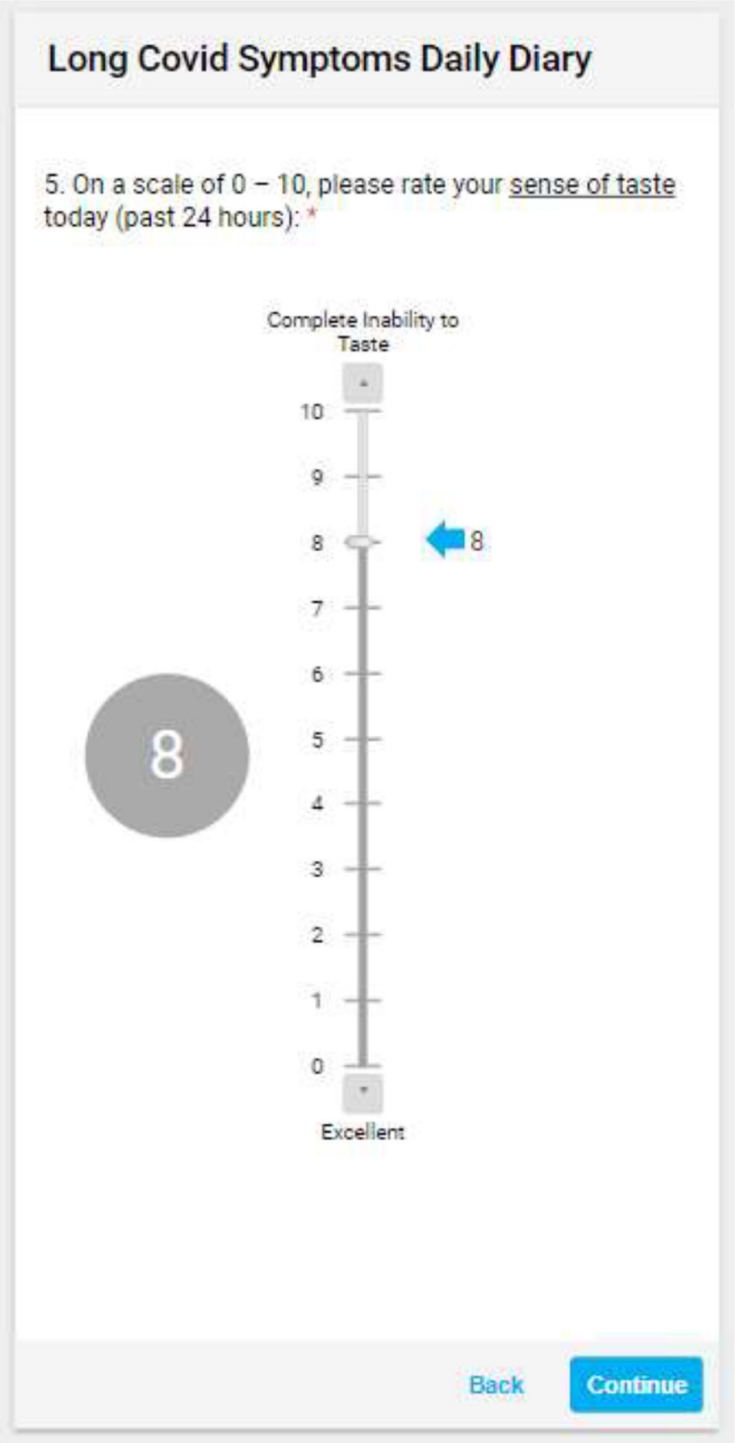


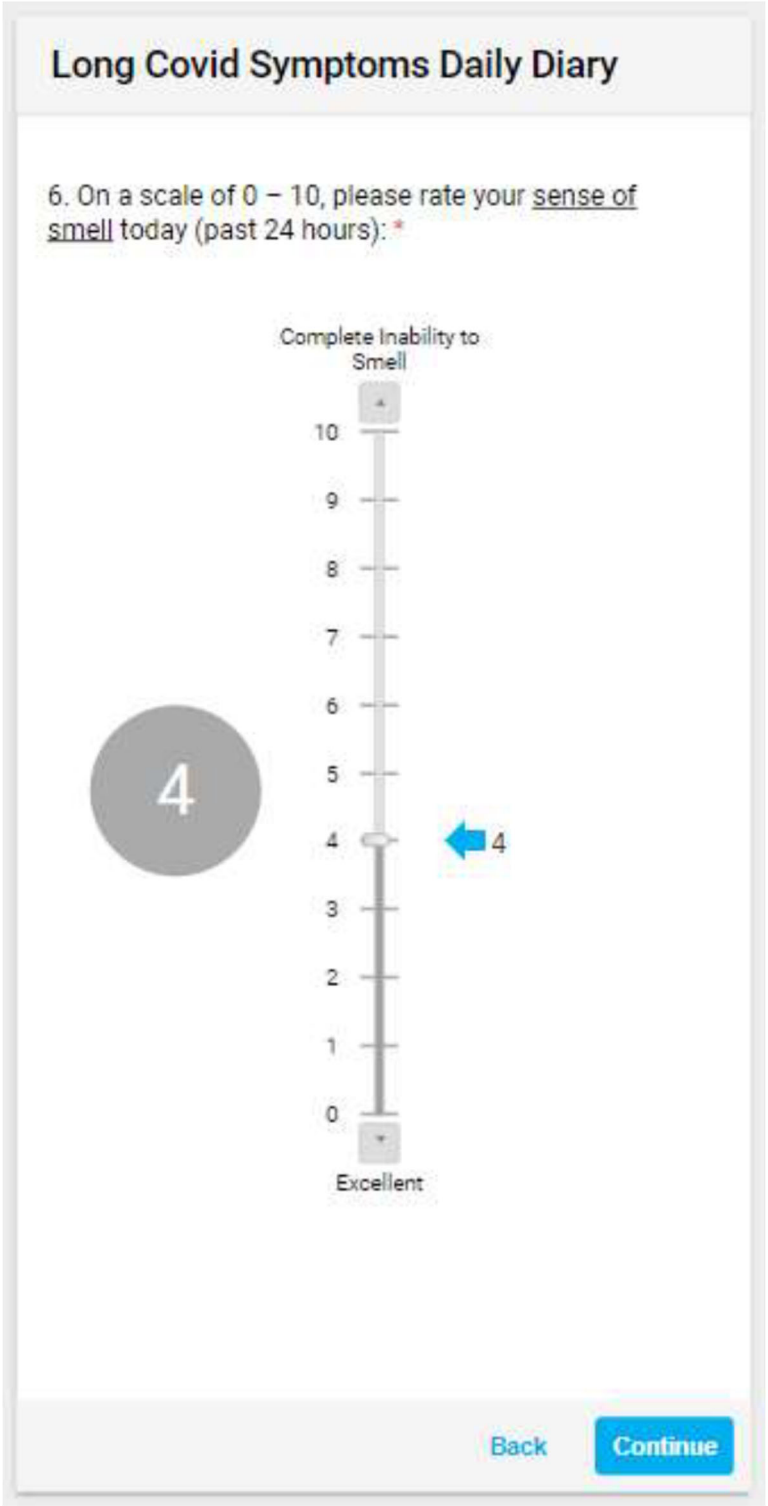

Long Covid Symptoms Daily Diary
1. On a scale of 0 – 10, please rate your worst headache today (past 24 hours): *
Worst Headache Imaginable
10
9
8
7
6
5
4
3
2
1
0
No Headache
6
6
Back
Continue


Long Covid Symptoms Daily Diary
2. On a scale of 0 – 10, please rate your worst fatigue (weariness, tiredness) today (past 24 hours):
Worst Fatigue Imaginable
10
9
8
7
7
6
5
4
3
2
1
0
No Fatigue
7
Back
Continue


Long Covid Symptoms Daily Diary
3. On a scale of 0 – 10, please rate your worst shortness of breath at rest today (past 24 hours): *
Worst Shortness of Breath Imaginable
10
9
8
7
6
5
4
3
2
1
0
9
9
No Shortness of Breath
Back
Continue


Long Covid Symptoms Daily Diary
4. On a scale of 0 – 10, please rate your worst shortness of breath after physical activity today (past 24 hours): *
Worst Shortness of Breath Imaginable
10
9
8
7
6
5
4
3
2
1
0
3
3
No Shortness of Breath
Back
Continue


Long Covid Symptoms Daily Diary
5. On a scale of 0 – 10, please rate your sense of taste today (past 24 hours): *
Complete Inability to Taste
10
9
8
7
6
5
4
3
2
1
0
Excellent
8
8
Back
Continue


Long Covid Symptoms Daily Diary
6. On a scale of 0 – 10, please rate your sense of smell today (past 24 hours): *
Complete Inability to Smell
10
9
8
7
6
5
4
3
2
1
0
Excellent
4
4
Back
Continue

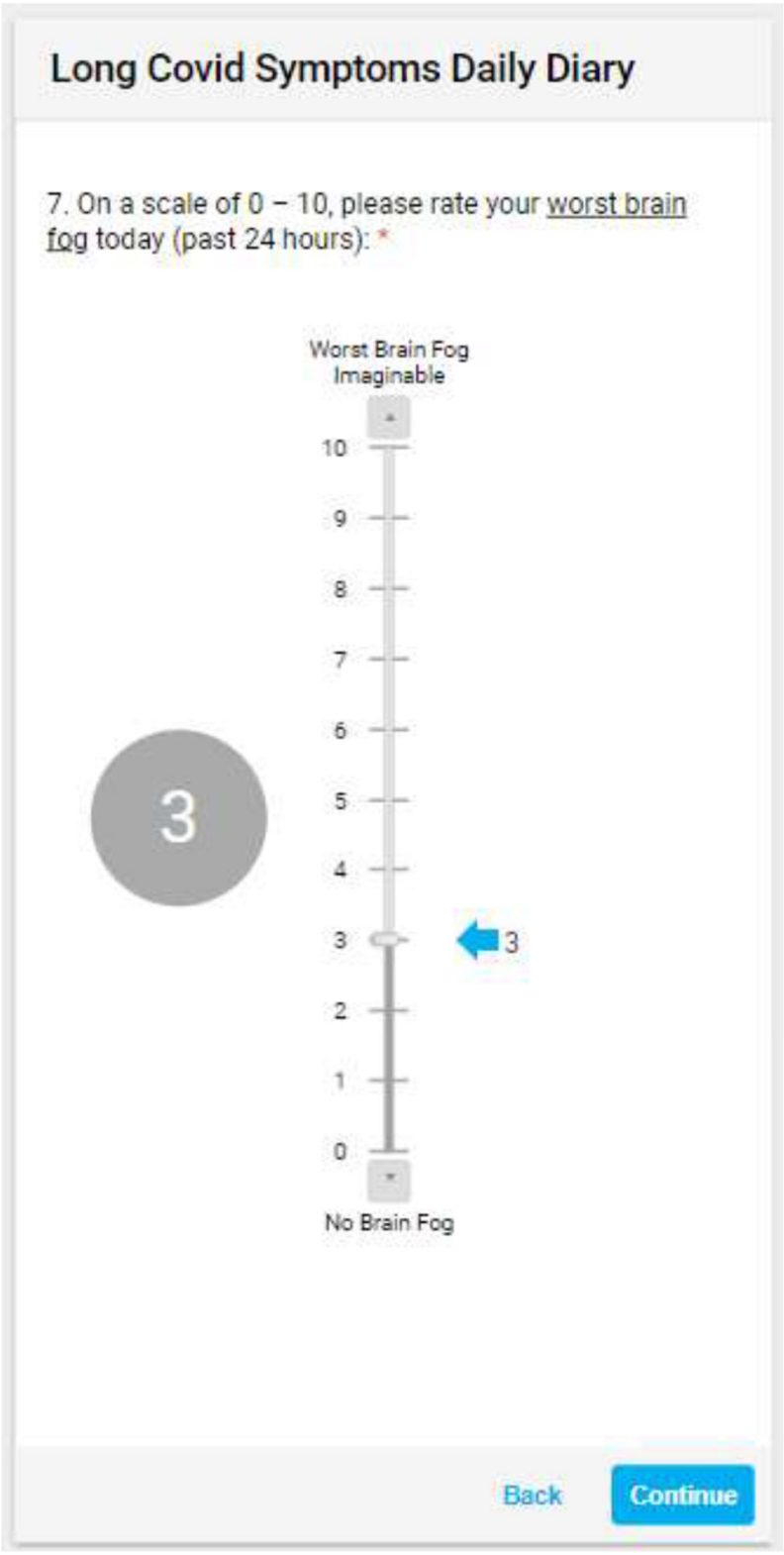


Table 21.2: Patient Global Item of Severity (PGIS)

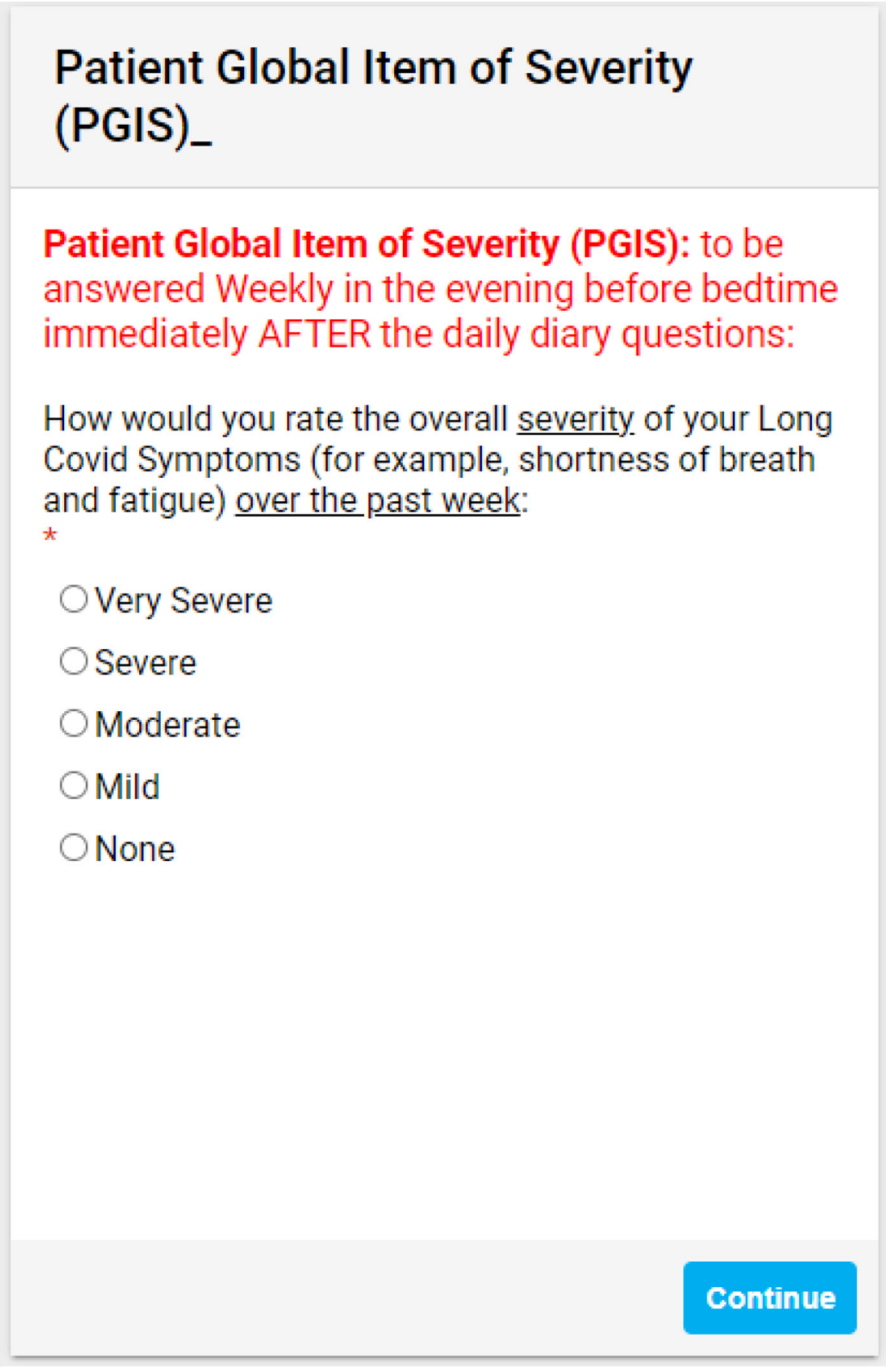
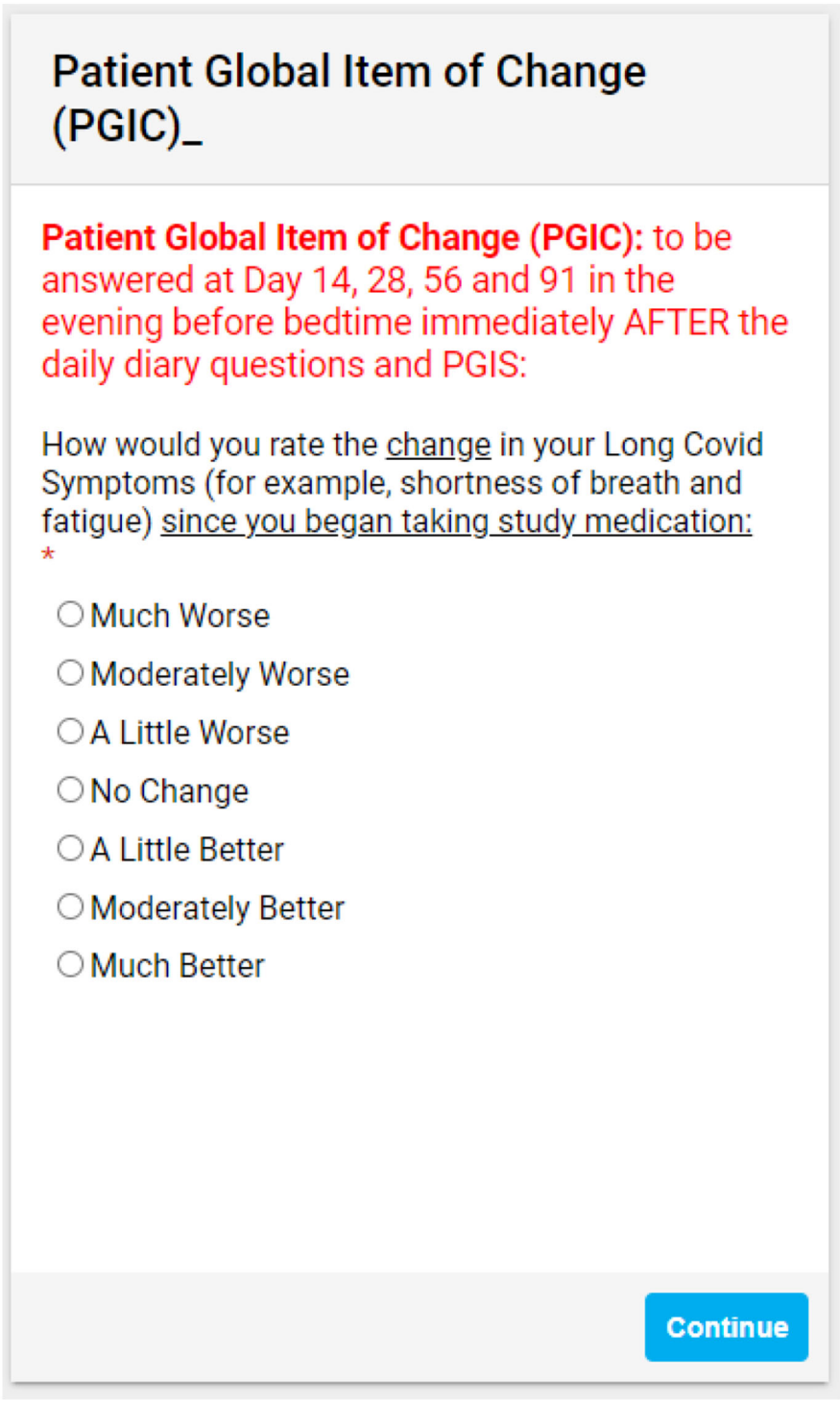


Table 21.3: Patient Global Item of Change (PGIC)



Patient Global Item of Change (PGIC)_

Patient Global Item of Change (PGIC): to be answered at Day 14, 28, 56 and 91 in the evening before bedtime immediately AFTER the daily diary questions and PGIS:

How would you rate the change in your Long Covid Symptoms (for example, shortness of breath and fatigue) since you began taking study medication: *

- ○ Much Worse
- ○ Moderately Worse
- ○ A Little Worse
- ○ No Change
- ○ A Little Better
- ○ Moderately Better
- ○ Much Better

Continue