Statistical Analysis Plan

Protocol Title:	A SINGLE-CENTER, PILOT, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ENSIFENTRINE IN THE RECOVERY OF HOSPITALIZED PATIENTS WITH COVID-19
Protocol Number:	RPL554-COV-201
Investigational Product:	Ensifentrine pMDI
Study Phase:	II
Sponsor Name:	Verona Pharma Inc
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The signatures below indication review and approval of this Statistical Analysis Plan (SAP).

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CI	Confidence Interval
CoV / COV	Coronavirus
CRF / eCRF	Case Report Form / Electronic Case Report Form
CSR	Clinical Study Report
ECMO	Extracorporeal Membrane Oxygenation
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
N	Number of patients/subjects
PCR	Polymerase Chain Reaction
PI	Principal Investigator
pMDI	Pressurized metered dose inhaler
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SD	Standard Deviation
SOC	Standard of Care
US	United States
WHO	World Health Organization

4 PREFACE

The SAP for "*A SINGLE-CENTER, PILOT, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ENSIFENTRINE IN THE RECOVERY OF HOSPITALIZED PATIENTS WITH COVID-19*" describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses.

Any deviation from this SAP will be described and justified in protocol amendments and/or in the clinical study report (CSR), as appropriate.

The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

5 INTRODUCTION

Ensifentrine is a dual inhibitor of Phosphodiesterase 3 (PDE3) and PDE4 which has demonstrated both bronchodilator and anti-inflammatory effects in clinical studies (Singh, 2018; Singh, 2020; Franciosi, 2013). Ensifentrine has been studied in patients with COPD as a nebulized suspension, dry powder inhaler (DPI) and pressurized metered dose inhaler (pMDI). Overall, ensifentrine was well tolerated in 17 clinical studies conducted to date, with adverse event incidence and severity generally similar to those in the placebo-treated group. Verona Pharma is entering Phase III clinical development with nebulized suspension ensifentrine as a maintenance therapy for patients with COPD.

In terms of clinical outcomes, Verona Pharma (the sponsor) hypothesizes that ensifentrine treatment of patients with COVID-19 will effectively result in bronchodilation in patients, reducing symptoms of dyspnea and improve the patient's oxygen levels thus reducing the need for supplemental oxygen. Activity of ensifentrine related to reduction of viral-induced inflammation and CFTR stimulation may facilitate viral clearance more rapidly and help prevent further clinical deterioration resulting from reduced oxygenation and secondary infections related to mucus hypersecretion. As such, the goal of ensifentrine treatment in patients with COVID-19 is to improve clinical status (measured with the 7-point ordinal scale), facilitate recovery and prevent the progression of the disease leading to mechanical ventilation by allowing the patient to breathe better during the infection, to reduce the inflammation in the lung and facilitate patient recovery from COVID-19 infection.

Ensifentrine provides bronchodilation via its inhibition of PDE3 and PDE4. Anti-inflammatory effects following inhaled administration including the potential to decreased viral-induced inflammation, and bronchial cell CFTR stimulation, this pharmacologic therapy, delivered via pMDI, may serve as an innovative treatment for patients with COVID-19.

5.1 Purpose of the Analyses

This SAP encompasses the final analysis of primary and secondary outcome measures. These analyses will be included in the CSR.

This is a pilot study which will expand our knowledge and understanding about how ensifentrine can be used to facilitate recovery or prevent deterioration in hospitalized, COVID-19 patients.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

The purpose of this study is to evaluate the effect of ensifentrine on the proportion of patients hospitalized with COVID-19 infection with recovery over 29 days.

This is a single center, randomized, double-blind, parallel group, placebo-controlled study to determine the efficacy and safety of ensifentrine 2 mg BID administered via pMDI added on to SoC treatment for COVID-19 infection compared to patients receiving SoC plus placebo.

Patients 18 to 80 years of age must be hospitalized with a confirmed diagnosis of SARS-CoV-2 infection confirmed by PCR test and displays at least one of the following: Respiratory rate greater than 24, new cough, new atypical chest pain, new dyspnea, oxygen saturation <97% at rest, chest x-ray with new changes consistent with COVID-19 related airspace disease.

Patients meeting criteria for inclusion and none of the criteria for exclusion at randomization will be randomized to receive study medication within 4 days of hospital admission until hospital discharge or up to 29 days of treatment, whichever comes first. Patients will be randomized 2:1 to receive one of the following study treatments:

- Treatment Arm 1 (n=30): Blinded ensifentrine (2 mg) pMDI BID + Standard of Care treatment for COVID-19 infection
- Treatment Arm 2 (n=15): Blinded placebo pMDI BID + Standard of Care treatment for COVID-19 infection

Randomized patients will receive blinded ensifentrine or placebo twice daily, approximately 12 hours apart in the morning and evening, through 29 days or until discharge from hospital, whichever is first. Patients will self-administer 4 actuations (puffs) pMDI observed by study staff at each dosing event.

During the treatment period, patients will undergo all assessments and procedures as outlined in the schedule of activities until hospital discharge. Patients completing treatment will complete a study contact (telephone or visit as required) within 4 to 10 days of discharge or early withdrawal. All enrolled patients will complete a telephone contact 26 to 32 days (Day 29) and 55-65 days (Day 60) following receipt of 1st dose of study medication for assessment of clinical status via the 7-point ordinal scale, need for re-hospitalization and vital status.

6.2 Objectives

The primary objective is to evaluate the effect of ensifentrine on the proportion of patients with recovery from COVID-19 over 29 days.

Secondary objectives include the evaluation of:

- The effect of ensifentrine on COVID-19 related time to recovery, clinical status and risk of deterioration,
- The effect of ensifentrine on hospitalization, non-invasive and invasive ventilation and oxygen use.

The safety objective is to evaluate the safety and tolerability of ensifentrine in patients with COVID-19.

6.3 Selection of Study Population

Male and non-pregnant female adults ≥18 to 80 years of age or older with COVID-19 and who meet all eligibility criteria will be enrolled at one site.

6.3.1 Inclusion Criteria

- Capable of giving informed consent indicating that they understand the purpose of the study and study procedures and agree to comply with the requirements and restrictions listed in the informed consent form and in this protocol.
- Patient must be at least 18 years of age and less than or equal to 80 years of age at the time of informed consent.
- Males are eligible to participate or females of non-childbearing potential or WOCBP who have a negative pregnancy test at screening are eligible to participate. WOCBP and female partners of male participants agree to either abstinence or use at least one primary form of highly effective contraception not including hormonal contraception from the time of screening through Day 60 following the first dose of study medication (Protocol Appendix 5).
- Clinical status consistent with 3, 4 or 5 on the 7-point ordinal scale AND the patient requires to be hospitalized for at least 72 hours following randomization:
    - 3. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care;
    - 4. Hospitalized, requiring any supplemental oxygen; or
    - 5. Hospitalized, requiring non-invasive ventilation or use of high flow oxygen devices.
- Admission to hospital AND have a confirmed diagnosis of severe acute respiratory syndrome coronavirus (SARS-COV-2) infection confirmed by polymerase chain reaction (PCR) test (or as per hospital testing protocols) AND displays at least one of the following:
    - Respiratory rate > 24 breaths per minute,
    - new cough,
    - new atypical chest pain,
    - new dyspnea,
    - oxygen saturation < 97% at rest,
    - or chest x-ray with new changes consistent with COVID- related airspace disease.
- Capable of complying with all study restrictions and procedures including ability to use the pMDI correctly.

6.3.2 Exclusion Criteria

- Participation in any other clinical trial of an experimental treatment for COVID-19, unless related to an expanded access program as part of Standard of Care.
- Evidence of multiorgan failure.
- Requiring mechanical ventilation at screening.

- Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 X upper limit of normal (ULN) at screening.
- Creatinine clearance < 30 mL/min at screening.
- Pregnancy or lactation at screening.
- Allergy or other contraindication or one of ensifentrine.
- In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments.
- Use of prohibited medications.
- Any other reason that the Investigator considers makes the patient unsuitable to participate.

6.4 Treatments Administered

Once eligibility is confirmed, patients will be randomized in a 2:1 ratio to one of two treatment arms listed in Table 1. Under the direction of study staff, randomized patients will self-administer 4 actuations (puffs) pMDI at each dosing event. Dosing will be performed twice daily approximately 12 hours apart in the morning and evening at approximately the same time each day.

Table 1. Clinical study RPL554-COV-201 treatment arms.

Treatment Arm	n	Treatment
Treatment Arm 1	30	Blinded ensifentrine (2 mg) pMDI BID + SoC*
Treatment Arm 2	15	Blinded placebo pMDI BID + SoC*
Abbreviations: SoC= standard of care, pMDI= pressurized metered dose inhaler, BID= twice daily *SoC treatment for COVID-19 infection based on established practices within UAB		

6.5 Identity of Investigational Product(s)

The International Union of Pure and Applied Chemistry (IUPAC) name for ensifentrine drug substance is 9,10-dimethoxy-2-(2,4,6-trimethylphenylimino)-3-(N-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one. The ensifentrine pMDI is manufactured in accordance with Good Manufacturing Practice (GMP) guidelines.

The active formulations of ensifentrine and placebo in pMDI will be double-blind. The placebo is the same as the ensifentrine active formulation, except that the active ingredient is omitted (Table 2). Each actuation of pMDI containing ensifentrine will deliver 0.5 mg, such that 4 puffs will equal a 2 mg dose.

Table 2. Clinical study RPL554-COV-201 study medication composition.

Constituent	Ensifentrine Concentration (% w/w)	Placebo Concentration (% w/w)
Ensifentrine (micronized)	0.648	0
HFA-134a	99.352	99.352
Abbreviations: HFA=hydrofluoroalkane; w/w = weight per weight		

6.6 Method of Assigning Patients to Treatment Groups (Randomization)

Randomization will take place prior to the first study medication administration in the order patients are enrolled and in accordance with a computer-generated randomization list supplied by an independent statistician. Available randomization numbers must be used sequentially for the next enrolled patient. Patients will be dosed with either blinded ensifentrine or placebo according to the randomization scheme.

6.6.1 Selection of Dose in the Study

Ensifentrine has been well-tolerated in clinical studies to date. The dose for this study (2 mg) was selected based on analysis of pharmacokinetic (PK) and pharmacodynamic (PD) data (lung function improvement) from single dose study with pMDI, combined with what is known about PK/PD from multiple studies with a nebulized suspension of ensifentrine in healthy volunteers and patients with COPD, and a clinical study using ensifentrine in dry powder inhaler format.

The dose was selected based on analysis of fine particle dose comparing the pMDI with a DPI and nebulized suspension of ensifentrine, along with pharmacokinetic (PK) and pharmacodynamic (PD) data (lung function improvement) from single dose study with pMDI RPL554-MD-201, combined with what is known about PK/PD from multiple studies with a nebulized suspension of ensifentrine in patients with COPD, and a clinical study using ensifentrine in dry powder inhaler format (RPL554-DP-201). These data support that a 2 mg twice daily dose of ensifentrine pMDI should provide equivalent fine particle dose, PK and lung function improvement as that observed from a twice daily 3 mg nebulized dose, which has shown to be efficacious and well-tolerated over 4 weeks in patients with COPD.

6.6.2 Selection and Timing of Dose for Each Patient

Each patient is randomly assigned 2:1 to a treatment group as described in Section 4.2.3. Study medication dosing starts on Day 1 after randomization and continues twice daily, approximately every 12 hours, until discharge or Day 29, whichever is first.

6.6.3 Blinding

The UAB IDS Pharmacy's unblinded pharmacist will label the study medication and perform accountability measures.

The blind will be broken only if specific emergency treatment would require knowing the treatment status of the patient or if the protocol review committee recommends unblinding data for safety review reasons. If the blind needs to be broken for an individual patient, the Investigator will contact the Sponsor as soon as feasible. The Investigator may unblind the study medication immediately if he/she feels it is necessary prior to contacting the Sponsor. However, the Investigator should promptly document and explain to the Sponsor any premature unblinding. Otherwise, all blinding will be maintained until all queries are resolved and the database is locked.

6.7 Prior and Concomitant Therapy

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

- UAB's standard treatment for COVID-19 infection is permitted, with the exception of prohibited medications listed in Table 3.
- UAB's standard treatment for COVID-19 infection will be recorded in the eCRF from screening to discharge.

Table 3. Clinical study RPL554-COV-201 prohibited concomitant medications.

Medication	Time Interval
Theophylline, PDE4 inhibitors (e.g. roflumilast, apremilast, crisaborole)	48 hours prior to Screening Visit and prohibited during the study
Investigational or experimental medication for COVID-19 infection as part of a clinical trial that is not considered Standard of Care	During study participation
Abbreviations: PDE= phosphodiesterase	

6.8 Treatment Compliance

All days the study medication was received and the doses/day will be recorded on the appropriate eCRF. If study medication dose was missed, decreased or halted, the information will be recorded to track compliance.

7 DEFINITIONS

7.1 General

General clinical study definitions are listed in Table 4.

Table 4. Clinical study RPL554-COV-201 general definitions.

Term	Definition for Study
Baseline	The most recent pre-dose assessment prior to first dose of study medication.
Clinical status assessment	(Protocol Section 8.1.1) Daily clinical status will be assessed using the 7-point ordinal scale adapted from the WHO R&D Blueprint expert group which measures illness severity over time (https://www.who.int/blueprint/priority-diseases/key-action/COVID19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf according to the following criteria: 1. not hospitalized, no limitations of activities 2. not hospitalized, limitation of activities, home oxygen requirement, or both 3. hospitalized, not requiring supplemental oxygen but requiring ongoing medical care* 4. hospitalized, requiring any supplemental oxygen* 5. hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices* 6. hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 7. death ** eligible for study entry*
COVID disease severity	(Protocol Section 8.1.2) At baseline/randomization, the categorization of COVID-19 disease severity will be in accordance with the FDA's document: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (May 2020). • Mild disease (meeting all inclusion and no exclusion criteria): Symptoms of mild illness that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea and no clinical signs indicative of moderate, severe, or critical severity. • Moderate disease (meeting all inclusion and no exclusion criteria): could include any symptom of mild illness or shortness of breath with exertion. Clinical signs suggestive of moderate illness, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute and no clinical signs indicative of severe or critical severity. • Severe disease (meeting all inclusion and no exclusion criteria): could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress. Clinical signs indicative of severe systemic illness, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 and no criteria of critical severity. • Critical disease: evidence of critical illness, defined by at least one of the following: 1) respiratory failure defined based on resource utilization requiring at least one of the following: endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies,

Term	Definition for Study
	but preceding therapies not able to be administered in setting of resource limitation); 2) shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors); or 3) multi-organ dysfunction/failure.
Day	Calendar day
Day 1	The day a patient received their first dose of study medication. • If a patient received their 1st dose of study medication the day following randomization, the study day number will be adjusted so that Day 1 = 1st dose of study medication.
Discharge	The patient is discharged and leaves the hospital alive. This does not include if a patient is moved to another unit. • The time to discharge = the elapsed time (in days) from Day 1 to the earliest day at which the patient is Discharged from hospital (= Day where the 7-point ordinal scale score is equal to 1 or 2).
Improvement in clinical status	A decrease from baseline of at least one point in the 7-point ordinal score (eg, 5 to 4).
Worsening clinical status	An increase from baseline of at least one point in the 7-point ordinal scale score (eg, 5 to 6).

7.2 Endpoints

Clinical study endpoints and associated definitions are listed in Table 5. Additional definitions are included in Section 8. Analysis tables are included in Section 9.3, Section 9.4 and Section 9.5.

Table 5. Clinical study RPL554-COV-201 endpoint definitions.

Endpoints		Definitions
Primary *Refer to Section 9,* *Table* 10	The proportion of patients who are in recovery state at Day 29.	Clinical status assessed using the 7-point ordinal scale score. The proportion of patients in each treatment arm that meet the definition of recovery. Recovery = one of the following two categories from the 7-point ordinal scale: 1. not hospitalized, no limitations of activities; 2. not hospitalized, limitation of activities, home oxygen requirement, or both.
Secondary *Refer to Section 9,* *Table* 11	Time to a recovery state (Day 1-Day 29; measured in days)	Clinical status assessed using the 7-point ordinal scale score. Time to recovery = elapsed time (in days) from Day 1 to the first day on which patients satisfy either 1 or 2 category listed in the primary endpoint.
	Proportion of patients who are in a recovery state at Days 7, 14 and 60.	Clinical status assessed using the 7-point ordinal scale score. The proportion of patients in each treatment arm that meet the definition of recovery. Recovery = one of the following two categories from the 7-point ordinal scale:

Endpoints		Definitions
		1. not hospitalized, no limitations of activities; 2. not hospitalized, limitation of activities, home oxygen requirement, or both.
	Proportion of patients with improvement of one category using the 7-point ordinal scale (Day 1 - Days 7, 14 and 29).	Clinical status assessed using the 7-point ordinal scale score. The proportion of patients in each treatment arm that meet the definition of a one category improvement in clinical status. Improvement in clinical status = a decrease from baseline of one point in the 7-point ordinal score (eg, 5 to 4).
	Proportion of patients with improvement of two categories using the 7-point ordinal scale (Day 1 - Days 7, 14 and 29).	Clinical status assessed using the 7-point ordinal scale score. The proportion of patients in each treatment arm that meet the definition of a two category improvement in clinical status. Improvement in clinical status = a decrease from baseline of two points in the 7-point ordinal score (eg, 5 to 3).
	All-cause mortality at Days 29 and 60.	Clinical status assessed using the 7-point ordinal scale score. Death = 7-point ordinal scale score is equal to 7 or using a vital records search returns a death record, the date on the record will be the date of death.
	Proportion of patients alive and not in respiratory failure (invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) at Days 7, 14 and 29.	Clinical status assessed using the 7-point ordinal scale score. The proportion of patients in each treatment arm that meet the definition of alive and not is respiratory failure. Alive and not in respiratory failure (invasive mechanical ventilation or ECMO) = 7-point ordinal scale score is equal to 1, 2, 3, 4 or 5.
	Proportion of patients needing re-hospitalization (post-dose Day 1 – Day 60).	Assessed following discharge: the eCRF question regarding re-hospitalization will be used at Day 29 and Day 60 follow-up contact. The proportion of patients in each treatment arm that meet the definition of re-hospitalization following discharge. Re-hospitalization = following their treatment with study medication and subsequent discharge from hospital, they were re-admitted to a hospital for COVID related issue(s).

Endpoints		Definitions
	Total time of hospitalization between Day 1 - Day 29 (measured in days).	Clinical status assessed using the 7-point ordinal scale score. Hospitalized = # days where the 7-point ordinal scale score is equal to 3, 4, 5 or 6. • *Or 7-point ordinal scale score is equal to 7 if patient dies while hospitalized between Day 1-29.*
	Change from baseline in 7-point ordinal scale (Days 7, 14 and 29).	Clinical status assessed using the 7-point ordinal scale score. The mean change from baseline of the 7-point ordinal scale in each treatment arm as assessed by the statistical analysis.
	Total time on supplemental oxygen (Day 1 - Day 29; measured in days).	Clinical status assessed using the 7-point ordinal scale score. Hospitalized patient supplemental oxygen = # days where the 7-point ordinal scale score is equal to 4, 5, or 6. • *Or 7-point ordinal scale score is equal to 7 if patient dies while hospitalized between Day 1-29.* Not hospitalized patient supplemental oxygen = # days where the 7-point ordinal scale score is equal to 2 (if required to have home oxygen).
	Total time of non-invasive ventilation or high flow oxygen use (post-dose Day 1 - Day 29; measured in days).	Clinical status assessed using the 7-point ordinal scale score. Non-invasive ventilation or high flow oxygen use = # days where the 7-point ordinal scale score is equal to 5 or 6. • *Or 7-point ordinal scale score is equal to 7 if patient dies while hospitalized between Day 1-29.*
	Proportion of patients alive and with oxygen use at Days 7, 14 and 29	Clinical status assessed using the 7-point ordinal scale score. The proportion of patients in each treatment arm that meet the definition of requiring oxygen use. Hospitalized patient supplemental oxygen = the 7-point ordinal scale score is equal to 4, 5, or 6. • *Or 7-point ordinal scale score is equal to 7 if patient dies while hospitalized between Day 1-29.* Not hospitalized patient supplemental oxygen = the 7-point ordinal scale score is equal to 2 (if required to have home oxygen).
	Proportion of patients alive at Days 7, 14 and 29 with non-	Clinical status assessed using the 7-point ordinal scale score.

Endpoints		Definitions
	invasive ventilation or high flow oxygen use	The proportion of patients in each treatment arm that meet the definition of requiring non-invasive ventilation/high-flow oxygen use. Non-invasive ventilation or high flow oxygen use = the 7-point ordinal scale score is equal to 5 or 6. • *Or 7-point ordinal scale score is equal to 7 if patient dies while hospitalized between Day 1-29.*
	Proportion of patients alive and receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at Days 7, 14 and 29).	Clinical status assessed using the 7-point ordinal scale score. The proportion of patients in each treatment arm that meet the definition of requiring invasive mechanical ventilation. The 7-point ordinal scale score is equal to 6. • *Or 7-point ordinal scale score is equal to 7 if patient dies while hospitalized between Day 1-29.*
Safety *Refer to Section 9, Table 12*	Incidence of Adverse Events (AEs).	Number of AEs and number of patients with AEs for all TEAEs and for subcategories of AEs (SAEs, severe AEs, fatal AEs etc). Incidence = proportion of patients in each treatment arm that experience an adverse event.
	Adverse Events (AEs) between Day 1 – 29 or discharge and Day 60.	Time to combined AE (death, SAE, Severe AE or ET/W from study medication) = elapsed time (in days) from Day 1 to the earliest date of any of the events through hospitalization, Day 29 and Day 60.
	Vital signs during hospitalization between Day 1 – Day 29 or discharge.	• Respiration rate (breaths per minute • Heart rate (beats per minute) • Oxygen saturation (SpO2) • Supplemental oxygen use (yes/no) • Body temperature (Celcius) • Blood pressure (mmHg) • Level of consciousness graded on the AVPU scale (Alert, Verbal = voice response present, Pain = pain response present, Unresponsive). Other parameters may include (but are not required per protocol): Dehydration status, Fraction of inhaled oxygen (FiO2), Sternal capillary refill time
	Laboratory values during hospitalization between Day 1 – Day 29 or discharge.	

8 GENERAL STATISTICAL CONSIDERATIONS

8.1 Sample Size

This is a pilot study and it is not powered based on any specific endpoint. Sample size has been set to minimize the number of patients exposed, but still large enough to give reliable estimates on the efficacy and safety of ensifentrine in the target population.

8.2 General Principles

This is a double-blind, placebo controlled randomized pilot study which may inform on treatment effect for future studies.

All analyses are considered exploratory and hypothesis-generating. All tests will be two-sided at 5% significance level. Hypothesis tested for the primary endpoint will be if addition of ensifentrine to SoC for up to 29 days could increase the proportion of patients with recovery versus standard of care plus placebo. The status according to the 7-point ordinal scale of all patients regardless of treatment withdrawal will be followed up during the scheduled treatment period (Day 29) and at a follow-up Day 60, or as far as possible.

Secondary endpoints are tested independently and there will be no adjustment for multiple tests.

8.3 Analysis Populations

Summaries and analysis of safety data will be presented for the Safety Analysis Population.

Summaries and analysis of efficacy data will be presented for the intent-to-treat (ITT) population.

- Intent to treat (ITT): Will consist of all randomized patients. Efficacy will be evaluated as randomized.
- Per protocol population (PP): Will consist of all patients in ITT without any major protocol deviations (determined prior to database lock) deemed to have an effect on efficacy analyses.
- Safety set (SS): Will consist of all randomized and treated patients (at least one dose). Safety will be evaluated by actual treatment.

8.4 Subgroups

In an exploratory manner, we will perform subgroup analyses for outcomes (i.e. the primary and key secondary analyses) where possible (minimum size required) to evaluate the treatment effect across the potential subgroups listed below:

- COVID disease severity: Mild, Moderate, Severe or Critical disease (severe and critical may be combined).
- Randomization day (prior to 1st dose of study medication) clinical status assessed using the 7-point ordinal scale: 3, 4 or 5.
- Gender: Female, Male.
- Race: White; Black/African American; Asian; Other.

- Baseline presence of comorbidities: None, One, Two or more.
- Age group: <40, 40-64, 65 and older (may use two age groups instead of three).
- Smoking history: Never, Current, Past.

8.5 Missing Data

All attempts will be made to collect all data per protocol.

- The patients withdrawn from treatment will be followed up regarding their status according to the 7-point ordinal scale at Day 29 as far as possible (exceptions for patients with withdrawn consent or lost to follow-up) and this data will be the primary source for handling missing data in the study.

Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier.

- If data points are identified as outliers, sensitivity analyses may be performed to examine the impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

For survival analyses, patients with death as outcome will be censored at Day 29 (Day 60), unless the required event was reached prior to death. Patients who are lost to follow-up or terminate the study prior to Day 29 (Day 60) for other reason than death and prior to observing/experiencing the event will be censored at the time of their last observed assessment.

The only time to event analyses is the time to recovery.

For secondary endpoint analyses, the following imputation rules will be used for patients who are lost to follow-up, terminate early from the study, or do not have further outcome data available after discharge for any reason than death:

- Patients with no data collected at the actual time point of interest for other reason than death, the last assessment of their status prior to this time point will be used as a representative for that time point. Especially, if the patient's clinical status scale is 1 or 2 at the last observed assessment, then the patient will be considered to be recovered through Day 29.
- For endpoints assessing total time (oxygen or non-invasive ventilator care), the status for patients with no data collected for other reason than death, will be assumed unchanged from last assessment of the score up to last day in the definition of the endpoint (Day 29). Thus, no extra days will be added for patients without oxygen or patients without non-invasive ventilator care at last assessment.
- Patients that die in the study will be handled as worst case in all the analyses, that is they are considered to be on oxygen need, non-invasive and invasive mechanical ventilator need for all time points following the death.
- In analyses of oxygen need, patients in ventilator care (non-invasive or invasive mechanical) will be considered in oxygen need for the corresponding time period and patients with death as outcome will be considered in oxygen need for the remainder of the time period of evaluation.
- In analyses of non-invasive ventilator need, patients that require invasive mechanical ventilation will be considered also as having a non-invasive ventilator need. Patients with death as an outcome will be considered as having non-invasive ventilator need from

time of death for the remainder of the time period of evaluation.

- In analyses of invasive mechanical ventilator need, patients with death as an outcome will be considered in invasive mechanical ventilator need for the remainder of the time period of evaluation
- The change from baseline in the 7-point ordinal scale will use the baseline score and the score at the endpoint using imputation for missing data as stated above, that is the last assessment of their status prior to this time point will be used.
- If the patient is discharged and no further hospitalization data are available, then the patient will be assumed to not have been readmitted. Thus, no additional imputed days on hospitalization will be added to the number of days recorded on available assessments for these patients.

8.6 Interim Analyses

No interim analyses will be performed.

8.7 Safety Analysis

Time to first combined event.

Any patients that are lost to follow-up or terminated early prior to experiencing any of the events will be censored at the day of their last observed assessment.

Patients who complete follow-up but do not experience any of the events will be censored at the day of their Day 29 visit.

9 ANALYSIS

9.1 Descriptive Information

Table 6 lists the summaries for patient disposition, analysis populations and protocol deviations.

Table 6. Clinical study RPL554-COV-201 analysis tables - Disposition.

Table #	Table Name	Table Contents
14.1.1	Patient Disposition.	The disposition of patients by treatment group and include study milestones • total number screened, randomized, completed 7, 14, 29 days of treatment, completed Day 29 and Day 60 follow-ups and withdrawn patients in total and by withdrawal reason.
14.1.2	Screen Failures.	A summary of the reasons that patients were screened but not enrolled.
14.1.3	Major Protocol Deviations.	Major protocol deviations summarized by the reason for the deviation, the deviation category, treatment group, COVID disease severity and (separately) site for all patients.
14.1.4	Analysis Sets	The composition of analysis populations, including reasons for patient exclusion by treatment group.

Tables summarizing patient demographics are displayed in Table 7. Demographics include age/DOB, sex, height, weight, BMI (calculated), ethnicity, and race; smoking history, date of randomization and date of inhaler training.

Table 7. Clinical study RPL554-COV-201 analysis tables - Demographics.

Table #	Table Name	Table Contents
14.1.5	Baseline Demographic Characteristics.	Overall, by treatment group, by COVID disease severity and by baseline clinical status assessment using the 7-point ordinal scale for ITT, PP and SS (if different).

Summaries of baseline clinical characteristics are displayed in Table 8. Baseline clinical characteristics include brief physical exam findings, vital signs, clinical status assessment using the 7-point ordinal scale score, COVID-19 symptom onset, admission date, COVID disease severity, existing co-morbidities, surgical history, prior medications, concomitant medications, and COVID-19 standard medications and treatments.

Table 8. Clinical study RPL554-COV-201 analysis tables - Baseline Clinical Characteristics.

Table #	Table Name	Table Contents
14.1.6	Baseline clinical characteristics (Eg. 7-point ordinal scale score, vital sign values, COVID disease severity, co-morbid conditions - obesity, hypertension, diabetes 1, asthma, and COPD).	Overall, by treatment group and COVID disease severity for ITT, PP and SS (if different).
14.1.7	Proportion patients with 7-point ordinal scale score or 3, 4 and 5, ITT.	Overall and by treatment group.
14.1.8	Proportion patients with COVID disease severity of mild, moderate, severe and critical, ITT.	Overall and by treatment group.
14.1.9	Disease onset (days with COVID symptoms, hospital admission date, COVID disease severity and oxygen need at randomization), ITT.	Overall and by treatment group.
14.1.10	Number and proportion taking concomitant dexamethasone or remdesivir, ITT.	Overall, by treatment group and COVID disease severity.
14.1.11	COVID-19 treatment and other respiratory medications introduced after randomization, ITT.	Overall, by treatment group and COVID disease severity.

9.2 Study Medication Compliance

Summaries of study non-medication compliance are listed in Table 9.

Table 9. Clinical study RPL554-COV-201 analysis tables - Study Medication Compliance.

Table #	Table Name	Table Contents
14.2.1	Study Medication Compliance (number of patients who had study medication halted/slowed and the number of patients with missed doses)	The number of patients with discontinued or missed doses (except due to discharge) by treatment group for ITT and PP.
14.2.2	Patient study medication discontinuation by study day.	By treatment group for ITT and PP.

9.3 Primary Endpoint Analysis

The proportion of patients with recovery at Day 29 will be compared between treatment groups using a logistic regression model adjusting for treatment and COVID disease severity. The difference between treatment arms will be expressed as a difference in proportions as measured by the Cochran Mantel-Haenzel (stratum)-weighted estimator based on the fitted logistic regression model. The delta method will be used to calculate the standard error for the difference and the associated confidence interval [Ge, 2011]. In addition, the raw proportions per treatment group will be given. If 0 events in any of the groups only raw proportions will be given.

- Sub-group analysis will only be performed for sub-groups with a minimum size.

Summaries of the results of the primary analysis are displayed in Table 10.

Table 10. Clinical study RPL554-COV-201 analysis tables - Primary Analysis.

Table #	Table Name	Table Contents
14.2.3	Proportion of Patients with Recovery at 29 Days, ITT	Overall and by Treatment Group • By Age Group • By Gender • By COVID Disease Severity • By Smoking History • By # co-morbidities
14.2.4	Proportion of Patients with Recovery at 29 Days, PP	Overall and by Treatment Group

9.4 Secondary Endpoint Analysis

Patients that die in the study will be handled as worst case in all analyses.

To have an evaluation using all patients we will count an event as the type of need or worse (eg, patients with oxygen need; non-invasive ventilator need; ventilator need; or with death at time of evaluation will be counted as having data supporting oxygen need), and included in both denominator and numerator (refer to Section 8.5).

9.4.1 Time to a recovery state (Day 1 - Day 29; measured in days)

The time to recovery from Day 1 to Day 29 will be compared between treatment groups using a log-rank test; patients not in recovery at end-of study/withdrawal will be censored at last observed time point in the treatment period or at last time status was assessed if collected post treatment-withdrawal. Patients with death as outcome will be censored at the scheduled end-of-study Day 29. Data will be illustrated using Kaplan-Meier plots and the median time to recovery estimated if appropriate. Stratification in the model with respect to COVID disease severity will be done if the randomization outcome has sufficient numbers in each group with respect to these characteristics.

9.4.2 Proportion of patients endpoint analyses

Secondary endpoints assessing proportion of patients fulfilling an event will be compared between treatments using a logistic regression model adjusting for treatment and COVID disease severity state. The difference between treatment arms will be expressed as a difference in proportions as measured by the Cochran Mantel-Haenzel (stratum)-weighted estimator based on the fitted logistic regression model. The delta method will be used to calculate the standard error for the difference and the associated confidence interval. For endpoints with a low number of events, the baseline disease state will be dropped from the model. In addition, the raw proportions per treatment group will be given. If 0 events in any of the groups only raw proportions will be given.

- Proportion of patients who are in a recovery state (Days 7, 14 and 60).
- Proportion of patients with improvement of one category using the 7-point ordinal scale (Days 7, 14 and 29).
- Proportion of patients with improvement of two categories using the 7-point ordinal scale (Days 7, 14 and 29).
- Proportion of patients in use of oxygen (Days 7, 14 and 29).
- Proportion of patients alive and not in respiratory failure (invasive mechanical ventilation or ECMO (Days 7, 14 and 29).

- Proportion of patients receiving non-invasive ventilation (Days 7, 14 and 29).
- All-cause mortality.

9.4.2.1 Sub-sets based on post-randomization outcome

Descriptive summaries of the proportion of patients as well as the duration of the worsening following initiation of study medication will be provided for these endpoints:

- Proportion of patients needing re-hospitalization (post-dose Day 1 – Day 60).
    - Applies to the sub-set of patients that were randomized, treated with study medication and discharged from the hospital alive then re-admitted to the hospital for COVID-19 related treatment.
- Proportion of patients and duration of new oxygen use (post-dose Day 1 - Day 29; measured in days).
    - Applies to the sub-set of patients that were randomized and treated with study medication but then had a new need for supplemental oxygen (score worsened to 4, 5 or 6).
    - Or those which improved during hospitalization (to 3) and then their clinical status worsened again (to 4, 5 or 6).
- Proportion of patients and duration of new non-invasive ventilation or high flow oxygen use (post-dose Day 1 - Day 29; measured in days).
    - Applies to the sub-set of alive patients that were randomized and treated with study medication but then had a new need for non-invasive ventilation or high-flow oxygen use (score worsened to 5 or 6).
    - Or those which improved during hospitalization (to 3 or 4) and then their clinical status worsened again (to 5 or 6)

The total number of days with recorded use will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals.

9.4.3 Change from baseline in 7-point ordinal scale (Days 7, 14 and 29).

Change from baseline in 7-point ordinal scale will be compared between treatments using ANCOVA models with treatment and COVID disease severity state as factors and baseline as a covariate. Estimated treatment difference with 95% confidence intervals and associated 2-sided p-value will be given. Sub-group analysis will only be performed for sub-groups with a minimum size.

9.4.4 Total time on supplemental oxygen (Day 1 - Day 29; measured in days).

The total number of days with recorded use will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. Results will be summarized by descriptive statistics including medians and quartiles by treatment arm and compared between treatment groups using Wilcoxon rank sum test. Patients that do not reach the specified score on any day will be counted as 0 days.

9.4.5 Total time on non-invasive ventilator use (Day 1 - Day 29; measured in days).

The total number of days with recorded use will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. Results will be summarized by descriptive statistics including medians and quartiles by treatment arm and compared between treatment groups using Wilcoxon rank sum test. Patients that do not reach the specified score

on any day will be counted as 0 days.

9.4.6 Duration of hospitalization (Day 1 - Day 29; measured in days)

The total number of days with recorded use will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. Results will be summarized by descriptive statistics including medians and quartiles by treatment arm and compared between treatment groups using Wilcoxon rank sum test.

Summaries of the results of the secondary analyses are displayed in Table 11.

Table 11. Clinical study RPL554-COV-201 analysis tables - Secondary Analyses.

Table #	Table Name	Table Contents
14.2.5	Time to recovery, Day 1 - Day 29	Overall and by Treatment group
14.2.6	Proportion of patients in recovery at Day 60, ITT	Overall and by Treatment group Day 1 – Day 7 Day 1 – Day 14
14.2.7	Proportion of patients with improvement of one category using the 7-point ordinal scale from Day 1, ITT	Overall and by Treatment group Day 1 – Day 7 Day 1 – Day 14 Day 1 – Day 29
14.2.8	Proportion of patients with improvement of two categories using the 7-point ordinal scale from Day 1, ITT	Overall and by Treatment group Day 1 – Day 7 Day 1 – Day 14 Day 1 – Day 29
14.2.9	All-cause mortality, ITT	Overall and by Treatment group At Day 29 At Day 60
14.2.10	Proportion of patients alive and not in respiratory failure (invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at Day 29, ITT	Overall and by Treatment group Day 1 – Day 7 Day 1 – Day 14
14.2.11	Summary of the proportion of patients re-hospitalized following initiation of study medication and subsequent discharge (over 60 days), ITT	Overall and by Treatment group
14.2.12	Duration of hospitalization from Day 1 (Day 1 - Day 29; measured in days), ITT	Overall and by Treatment group
14.2.13	Change from baseline in 7-point ordinal scale at Days 7, 14 and 29, ITT	Overall and by Treatment group Baseline – Day 7 Baseline – Day 14 Baseline – Day 29
14.2.14	Total time on supplemental oxygen (Day 1 - Day 29; measured in days), ITT	Overall and by Treatment group
14.2.15	Total time of non-invasive ventilation or high flow oxygen use (post-dose Day 1 - Day 29; measured in days).	Overall and by Treatment group
14.2.16	Summary of the proportion of patients with oxygen use at Days 7, 14 and 29, ITT	Overall and by Treatment group
14.2.17	Summary of the proportion of patients with non-invasive ventilation or high flow oxygen use at Days 7, 14 and 29), ITT	Overall and by Treatment group
14.2.18	Proportion of patients receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO, 7-point ordinal scale criteria #6) at Days 7, 14 and 29, ITT	Overall and by Treatment group Day 1 – Day 7 Day 1 – Day 14 Day 1 – Day 29

9.5 Safety Analysis

Safety endpoints include SAEs and AEs (Protocol Appendix 4). Adverse events will be analyzed using quantitative and qualitative measures.

Treatment-emergent adverse events will be summarized by treatment group for all AEs, related AEs, serious adverse events, deaths, adverse events leading to discontinuation of study medication or to withdrawal from study, adverse events of different severity and adverse events of different chronicity.

Treatment-emergent adverse events will be coded using MedDRA and summarized by system organ class and preferred term for each treatment group.

The time to the composite AE endpoint (death, SAE, severe AE or ET/W of treatment during first 29 days) will be compared between treatment groups using the log-rank test and difference between treatment arms will be expressed as a difference in proportions as measured by the Cochran Mantel-Haenzel (stratum)-weighted estimator based on the fitted logistic regression model

- If ‘0’ events, proportions will be presented.

Summaries of the results of the safety analysis are displayed in Table 12.

Table 12. Clinical study RPL554-COV-201 analysis tables - Safety Analyses.

Table #	Table Name
14.3.1	Time to first composite AE (Safety Analysis Set)
14.3.2	Number/Proportion Treatment emergent adverse events summary (Safety Analysis Set)
14.3.3	Number/Proportion TEAEs by system organ class and preferred term (Safety Analysis Set)
14.3.4	Number/Proportion TEAEs leading to discontinuation of study treatment by system organ class and preferred term (Safety Analysis Set)
14.3.5	Number/Proportion TEAEs causally related to the study treatment by system organ class and preferred term (Safety Analysis Set)
14.3.6	Number/Proportion TEAEs by maximum severity by system organ class and preferred term (Safety Analysis Set)
14.3.7	Number/Proportion Serious TEAEs by system organ class and preferred term (Safety Analysis Set)
14.3.8	Number/Proportion Serious TEAEs causally related to the study treatment by system organ class and preferred term (Safety Analysis Set)
14.3.9	Number/Proportion Serious TEAEs by maximum severity by system organ class and preferred term (Safety Analysis Set)
14.3.10	Number/Proportion Serious TEAEs leading to discontinuation of study treatment by system organ class and preferred term (Safety Analysis Set)
14.3.11	Number/Proportion TEAEs with an outcome of death by system organ class and preferred term (Safety Analysis Set)

9.5.1 Deaths, Serious Adverse Events and other Significant Adverse Events

Narratives will be provided for deaths and serious adverse events.

9.5.2 Pregnancies

For any patients in the Safety population who become pregnant during the study, every attempt will be made to follow these patients to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery.

9.6 Other or Exploratory Analyses

Proportion of patients in recovery, Day 1 – 7 and Day 1 – 14.

Proportion of patients alive and not in respiratory failure (invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO): Day 1- 7 and Day 1 – 14.

Description of the distribution of the 7-point ordinal scale outcomes using plots (e.g., stacked bar plots representing the proportion of patients in each category, by treatment arm, over time).

Descriptive summary of the number of days between hospital admission, positive PCR test (or as per hospital testing protocol) and randomization.

Proportion of total patients requiring any oxygen at randomization.

- For those that required oxygen, the mean/standard deviation or median/IQR for the oxygen amount (in FiO2).

Oxygen use while hospitalized and undergoing study treatment.

- Measurement of the oxygen requirement: compare the oxygen requirement (mean and median) for each arm using daily supplemental oxygen flow (L/min).

9.7 Figures

The study specific figures are displayed in Table 13.

Table 13. Clinical study RPL554-COV-201 Figures.

Figure #	Figure Name
1	Patient disposition (adapted from the Consort Statement).
2	Kaplan–Meier plot of time to Recovery, ITT.
3	Histogram of ordinal scores at Day 7, 14, 29 by treatment group and baseline ordinal scale, ITT.
4	Proportion of patients in oxygen need by day in study.

10 LISTINGS

Data is presented on a by-patient basis in this section. The study specific listings are displayed in Table 14. The following categories apply to the listings:

- 16.2.1 Patient Dispositions, Patient Eligibility
    - Listing of disposition: It should be clear which patients discontinued the study early, their study treatment, when they discontinued and the reason;
    - Listing of visit dates
    - Listing of eligibility: e.g. confirmation patients met the inclusion/exclusion criteria
- 16.2.2 Protocol Deviations
    - Listing of all patients with protocol deviations, with the deviation specified.
- 16.2.3 Study Populations
    - Listing of patients and whether they are included in each population;
    - Listing of patients excluded from key population(s) e.g. the efficacy population
- 16.2.4 Demographic and Baseline Characteristic Data
    - Listing of demographics;
    - Listing of other baseline data (e.g. COVID disease severity; brief physical examination findings; medical history; hospital admission information)
    - Listing of prior and concomitant medications
- 16.2.5 Compliance with study medication
- 16.2.6 Individual Efficacy Data - Listing of efficacy data
- 16.2.7 Adverse Event Listings - Listing of all adverse event information
- 16.2.8 Laboratory Safety Tests - Listings of all laboratory data.
- 16.2.9 Vital Signs, Physical Findings and Other Observations

Table 14. Clinical study RPL554-COV-201 Listings.

Listing Name	Listing Contents
Completed/Discontinued Patients	A patient listing of analysis population eligibilities.
Protocol Deviations	All patient-specific protocol deviations and non-patient specific protocol deviations.
Patients Excluded from Analysis Sets	A listing of patients overall.
Analysis Population Inclusions/Exclusions	A listing of patients by Treatment Group.
Patients who Early Terminated or Discontinued Treatment	A listing of patients by Treatment Group who discontinued dosing or terminated study follow-up and the reason.
Patient-Specific Protocol Deviations	A listing of patients by Treatment Group.
Non-Patient-Specific Protocol Deviations	A listing of deviations.

Listing Name	Listing Contents
Baseline Demographic Characteristics	Individual listings for all demographic information by Treatment Group.
Baseline Disease Characteristics	Individual listings for all baseline COVID information by Treatment Group.
Baseline Medical History	Individual listing for all co-morbid conditions and surgical history by Treatment Group.
Baseline Brief Physical Exam Findings	Individual listing by Treatment Group.
Study Medication Compliance for each study day	Individual listings for all patients who received at least at least one dose of study medication, including the number of days taken and number of doses received; and for all patients who discontinued dosing, missed doses, or halted or slowed doses
7-point ordinal scale score at baseline and for each study day	Individual listing by Treatment Group.
Vital signs at baseline and for each study day	Individual listing by Treatment Group.
Prior and Concomitant Medications at baseline and for each study day	Individual listings of medications that were started prior to dosing and continuing at the time of dosing by Treatment Group (those listed in the concomitant medication list as: Other (and comments), Medical History or Adverse Event).
Medications for the Treatment of COVID-19 (Standard of Care) at baseline and for each study day	Individual listing by Treatment Group (those listed in the concomitant medication list as: Treatment of COVID-19). Medication classes: 1. Angiotensin converting enzyme inhibitors (ACE inhibitors), 2. Angiotensin II receptor blockers (ARBs), 3. Antibiotics, 4. Antifungal agent, 5. Antiviral agent, 6. Corticosteroid, 7. Immunosuppressant agents (not oral steroids), 8. Intravenous fluids, 9. Non-steroidal anti-inflammatory (NSAIDs), 10. Oral/orogastric fluids, 11. Other targeted COVID-19 medications (comments)
Treatment or Therapy for COVID-19 (Standard of Care) at baseline and for each study day	Individual listings for all standard of care COVID-related treatments/therapies (excluding medications) received while hospitalized and the duration.
Standard of Care Laboratory Test Results at baseline and for each study day	Individual listings for all standard of care laboratory results while hospitalized.
New respiratory illness or other illness during hospitalization	Individual listing by Treatment Group
Listing of Non-Serious Adverse Events	Individual listing by Treatment Group.
Safety Laboratory Results at screening and discharge	Individual listing by Treatment Group.
Listing of Death and Other Serious Adverse Events	Individual listing by Treatment Group.
Pregnancy Reports	Individual listing by Treatment Group.

11 REPORTING CONVENTIONS

P-values will be reported to 3 decimal places; p-values less than 0.0005 will be reported as "<0.001" and p-values greater than 0.9995 will be reported as ">0.999".

The mean, standard deviation, and other statistics will be reported to1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data.

Proportions will be presented as 2 decimal places; values greater than zero but <0.005 will be presented as "<0.01".

Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

12 TECHNICAL DETAILS

Additional summaries/data points may be included in the final version of a table, figure, or listing.

Additional tables, figures, and listings may be generated to supplement the planned output.

13 REFERENCES

1 Singh D, Abbott-Banner K, Bengtsson T, Newman K. The short-term bronchodilator effects of the dual phosphodiesterase 3 and 4 inhibitor RPL554 in COPD. Eur Respir J. 2018 Nov 1; 52 (5). pii: 1801074. doi: 10.1183/13993003.01074-2018.

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3 Franciosi LG, Diamant Z, Banner KH, Zuiker R, Morelli N, Kamerling IM, de Kam ML, Burggraaf J, Cohen AF, Cazzola M, Calzetta L, Singh D, Spina D, Walker MJ, Page CP. Efficacy and safety of RPL554, a dual PDE3 and PDE4 inhibitor, in healthy volunteers and in patients with asthma or chronic obstructive pulmonary disease: findings from four clinical trials. Lancet Respir Med. 2013 Nov; 1 (9): 714-27. doi: 10.1016/S2213-2600(13)70187-5.

4 Ge M, Durham LK, Meyer RD, Xie W, Thomas N. Covariate-adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences. Drug Information Journal, Vol. 45, pp. 481–493, 2011

14 EXAMPLE SHELLS

Table 14.1.1 Patient Disposition

Patient Disposition	Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Completed Day 7			
Completed Day 14			
Completed Day 29			
Completed post-Discharge Follow-up (outpatient)			
Completed D29 post Follow-up (outpatient)			
Completed D60 post Follow-up (outpatient)			
Withdrawal			
Reason of withdrawal			
Adverse Event			
Death			
Lost to follow up			
Pregnancy			
Protocol Violation			
Physician Decision			
Study Termination by Sponsor			
Withdrawal by Patient			
Other			
Change of Consent by Patient - Reconsent (withdrawl from study medication, continued in follow-up)			

Total number screened: 122 (77 failed screen)
Discharge=The patient is discharged and leaves the hospital alive.
Eligible patients were randomized within 4 days of hospital admission.
Randomized patients received study medication until hospital discharge or up to 29 days of treatment, whichever was first.
Completed Day 7=patient randomized and hospitalized taking study medication for ≥7 days.
Completed Day 14= patient randomized and hospitalized taking study medication for ≥14 days.
Completed Day 29= patient randomized and hospitalized taking study medication for 29 days.
Discharge f/u= 4-10 days after hospital discharge.
Day 29 f/u = 26-32 days following receipt of 1st dose of study medication for telephone review of the 7-point ordinal scale, need for re-hospitalization and vital status
Day 60 f/u = 55-65 days following receipt of 1st dose of study medication for telephone review of the 7-point ordinal scale, need for re-hospitalization and vital status

Table 14.1.2: Screen Failures

Reasons Patients were Screened but not Enrolled	N (%)
Investigator decision - patient unsuitable to participate	
Creatinine clearance < 30 mL/min at screening	
Participation in any other clinical trial	
Evidence of multiorgan failure	
Total	

Table 14.1.3: Major Protocol Deviations

Table 14.1.4: Analysis Sets

	Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Number Randomized			
Number iTT			
Number Per Protocol			
Number Safety Set			

Table 14.1.5: Baseline Demographic Characteristics

Baseline Demographic Characteristics		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Age	**Mean, Years (SD)**			
	Median			
	(min, max)			
Gender	**Female**			
	Male			
Height	**Height (cm) (SD)**			
Weight	**Weight (kg) (SD)**			
BMI	**BMI (kg/m^2) (SD)**			
Ethnicity	**Hispanic or Latino**			
	Not Hispanic or Latino			
	Not Reported			
Race	**American Indian or Alaska**			
	Asian			
	Black or African American			
	Native Hawaiian/Other Pacific Islanders			
	Other			
	White			
Smoking History	**Never a smoker**			
	Present tobacco smoker			
	Pretentious tobacco smoker			

* %: uses Column total as the denominator.
[a] All randomized participants reported 2-Moderate of COVID disease severity at baseline

Table 14.1.5a: Baseline Demographic Characteristics by Baseline Clinical Status: Scale = 3[a]

Baseline Demographics (Baseline Clinical Status = 3)		Enrolled (N=1)	Ensifentrine (N=1)	Placebo (N=0)
Age	**Years of Age (SD)**			
Gender	**Female**			
	Male			
Height	**Height (cm) (SD)**			
Weight	**Weight (kg) (SD)**			
BMI	**BMI (kg/m^2) (SD)**			
Ethnicity	**Hispanic or Latino**			
	Not Hispanic or Latino			
	Not Reported			
Race	**American Indian or Alaska**			
	Asian			
	Black or African American			
	Native Hawaiian/Other Pacific Islanders			
	Other			
	White			
Smoking History	**Never a smoker**			
	Present tobacco smoker			
	Previous tobacco smoker			

[a]7-point scale: Scale 3-Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care

Table 14.1.5b: Baseline Demographic Characteristics by Baseline Clinical Status: Scale = 4[b]

Baseline Demographic Characteristics (Baseline Clinical Status = 4)		Enrolled (N=44)	Ensifentrine (N=1)	Placebo (N=0)
Age	**Years of Age (SD)**			
Gender	**Female**			
	Male			
Height	**Height (cm) (SD)**			
Weight	**Weight (kg) (SD)**			
BMI	**BMI (kg/m^2) (SD)**			
Ethnicity	**Hispanic or Latino**			
	Not Hispanic or Latino			
	Not Reported			
Race	**American Indian or Alaska**			
	Asian			
	Black or African American			
	Native Hawaiian/Other Pacific Islanders			
	Other			
	White			
Smoking History	**Never a smoker**			
	Present tobacco smoker			
	Previous tobacco smoker			

[b]7-point scale: Scale 4-Hospitalized, requiring any supplemental oxygen

Table 14.1.6: Baseline Clinical Characteristics

Baseline Clinical Characteristics	Mean (SD) or Count %	Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
		n	n	n
7-Point Ordinal Scale	3-Hospitalized, no supplemental oxygen			
	4-Hospitalized, any supplemental oxygen			
	5-Hospitalized, requiring non-intensive ventilation or use of high flow oxygen devices			
COVID disease severity	Mild			
	moderate			
	Severe			
Symptom display for eligibility				
	Respiratory rate: >24 bpm			
	New cough			
	New atypical chest pain			
	New dyspnea			
	O2 saturation: <97%			
	Chest x-ray: new changes consistent with COVID related airspace disease			
Temperature	ºC (SD)			
Pulse Rate/Heart Rate	beats per minute			
Respiratory Rate	beats per minute			
Blood Pressure (SBP)	mmHg			
Blood Pressure (DBP)	mmHg			
Arterial Blood Pressure	mmHg			
Oxygen Saturation	SPO2			
Supplemental Oxygen	FiO2			
Co-morbid conditions	None			
	One			
	Two or more			

Baseline Clinical Characteristics		Mean (SD) or Count %	Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
			n	n	n
Obesity	**Yes**				
	No				
Hypertension	**Yes**				
	No				
Diabetes Type 1	**Yes**				
	No				
Asthma	**Yes**				
	No				
COPD	**Yes**				
	No				

FDA's document: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (May 2020).
• Mild disease (meeting all inclusion and no exclusion criteria): Symptoms of mild illness that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea and no clinical signs indicative of moderate, severe, or critical severity.
• Moderate disease (meeting all inclusion and no exclusion criteria): could include any symptom of mild illness or shortness of breath with exertion. Clinical signs suggestive of moderate illness, such as respiratory rate ≥20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute and no clinical signs indicative of severe or critical severity.
• Severe disease (meeting all inclusion and no exclusion criteria): could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress. Clinical signs indicative of severe systemic illness, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 and no criteria of critical severity.

Table 14.1.9: Disease onset, ITT

		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
		N	N	n
Days with COVID Symptoms before randomization	**Mean (SD)**			
	Median (Min. – Max.)			
		N	N	n
Oxygen at Randomization	**Yes**			
	No			

Table 14.1.10: Number and Proportion Taking Dexamethasone or Remdesivir, ITT

Overall, and by Treatment Group from initiation of study medication

		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Taking Dexamethasone and Remdesivir	**Yes**			
	No[&]			
Taking Dexamethasone only	**Yes**			
	No			
Taking Remdesivir only	**Yes**			
	No			

[&]No Dexamethasone and No Remdesivir

[a] All randomized participants reported 2-Moderate of COVID disease severity at baseline

Table 14.1.11: COVID-19 Treatment and other Concomitant Respiratory Medications, ITT

Medications Introduced from initiation of study medication

		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Taking COVID-19 Treatment	**Yes**			
	No			
Antibiotics	**Yes**			
	No			
Antiviral Agent	**Yes**			
	No			
Corticosteroid	**Yes**			
	No			
Intravenous Fluids	**Yes**			
	No			
Non-steroidal Anti-inflammatory	**Yes**			
	No			
other	**Yes**			
	No			

Table 14.2.1: Study Medication Compliance from initiation of study medication

		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Missed dose of study medication after administration of 1st	**Yes**			
	No*			

*No means 100% compliance
Listing will have information for doses missed

Table 14.2.2: Patient last day receiving study medication from initiation of study medication, by study day

	Study Day	Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Patient final day receiving study medication	**2**			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			

Study day of when the patient was administered their last dose of study medication (post-1st dose on Day 1).

Table 14.2.3: Proportion of Patients with Recovery* from initiation of study medication at 29 Days, ITT

		Ensifentrine (N=30)	Placebo (N=15)
Proportion Recovered (scored 1 or 2) at Day 29 Overall Analysis results		N	N
Proportion recovered by:			
Age Group	**< 65 years old**	N (XX%)	N
	≥ 65 years	N	N
Gender	**Male**	N	N
	Female	N	N
Disease Severity	**Moderate**	N	N
Smoking History	**Present**	N	N
	Previous	N	N
	Never	N	N
# of Co- morbidities	**None**	N	N
	One	N	N
	Two or more	N	N

n = number of patients with recorded value
* Recovery = one of the following two categories from the 7-point ordinal scale:
1. not hospitalized, no limitations of activities;
2. not hospitalized, limitation of activities, home oxygen requirement, or both.

Table 14.2.4: Proportion of Patients with Recovery* from initiation of study medication at 29 Days, PP

		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Overall				
Patient with Recovery	**Yes**			
	No			

* Recovery = one of the following two categories from the 7-point ordinal scale:
1. not hospitalized, no limitations of activities;
2. not hospitalized, limitation of activities, home oxygen requirement, or both.

Table 14.2.5: Time to recovery*, from initiation of study medication - Day 29 (or discharge, whichever was first)

		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)	p-value (log-rank)
Days to recovery	**n**				
	Mean (SD)				
	Median (Min. – Max.)				

n = number of patients with recorded value
* Recovery = one of the following two categories from the 7-point ordinal scale:
1. not hospitalized, no limitations of activities;
2. not hospitalized, limitation of activities, home oxygen requirement, or both.

Table 14.2.6: Proportion of patients in recovery* from initiation of study medication, ITT

		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Recovery through Day 60	**n**			
	Yes			
	No			
Recovery Day 1 - Day 7	**n**			
	Yes			
	No			
Recovery Day 1 - Day 14	**n**			
	Yes			
	No			

n = number of patients with recorded value
* Recovery = one of the following two categories from the 7-point ordinal scale:
1. not hospitalized, no limitations of activities;
2. not hospitalized, limitation of activities, home oxygen requirement, or both.

Table 14.2.7: Proportion of patients with improvement of one category using the 7-point ordinal scale from initiation of study medication, ITT

		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
One Category Improvement, Day 1 - Day 7	**n**			
	Yes			
	No			
One Category Improvement, Day 1 - Day 14	**n**			
	Yes			
	No			
One Category Improvement, Day 1 - Day 29	**n**			
	Yes			
	No			

Improvement = A decrease from baseline of at least one point in the 7-point ordinal score (or discharge, whichever was first)

Table 14.2.8: Proportion of patients with improvement of two categories using the 7-point ordinal scale from initiation of study medication, ITT

		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Two Categories Improvement, Day 1 - Day 7	**n**			
	Yes			
	No			
Two Categories Improvement, Day 1 - Day 14	**n**			
	Yes			
	No			
Two Categories Improvement, Day 1 - Day 29	**n**			
	Yes			
	No			

Improvement = An increase from baseline of at least one point in the 7-point ordinal scale score (or discharge, whichever was first)

Table 14.2.9: All-cause mortality, ITT

	Ensifentrine (N=30)	Placebo (N=15)
Reason of death at Day 29	0 (0%)	
Reason of death at Day 60	0 (0%)	

Table 14.2.10: Proportion of patients Alive and not in Respiratory Failure* from initiation of study medication, ITT

Proportion of Patients Alive and not in Respiratory Failure (Scales less than 6)		Ensifentrine (N=30)	Placebo (N=15)
Day 1 - Day 7	**n**		
	Yes		
	No		
Day 1 - Day 14	**n**		
	Yes		
	No		
Day 1 - Day 29	**n**		
	Yes		
	No		

(or discharge, whichever was first)
*7-point ordinal scale score = 1, 2, 3, 4 or 5.
n = number of patients with recorded value

Table 14.2.11: Summary of Proportion of patients re-hospitalized following initiation of study medication and subsequent discharge (over 60 days), ITT

Proportion of Patients Re-hospitalized		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Day 1 - Day 60	**n**			
	Yes			
	No			

n = number of patients with recorded value

Table 14.2.12: Duration of hospitalization from initiation of study medication (Day 1 - Day 29 (or discharge, whichever was first); measured in days), ITT

Days of hospitalization from Day 1	Enrolled (N=45	Ensifentrine (N=30)	Placebo (N=15)	p-value*
Median (Q1 - Q3)				

*Wilcoxon rank sum test
Hospitalized = # days where the 7-point ordinal scale score = 3, 4, 5 or 6.
Discharge = The patient is discharged and leaves the hospital alive.

Table 14.2.13: Change from Baseline in 7-point Ordinal Scale at Days 7, 14, and 29, ITT

Change from Baseline in 7-point Ordinal Scale		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Day 7	**n**			
	Mean (SD)			
Day 14	**n**			
	Mean (SD)			
Day 29	**n**			
	Mean (SD)			

Computed from Day 1 scale minus Day 7, Day 14, and Day 29 scale accordingly (or discharge)
(or discharge, whichever was first)

Table 14.2.14: Total time on Supplemental Oxygen (Day 1 - Day 29; measured in days), ITT

Days of Supplemental Oxygen (Scale=4)		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Day 1 - 29	**Median (Q1 - Q3)**			

Hospitalized patient: 7-point ordinal scale score = 4, 5, or 6. Or 7-point ordinal scale score is equal to 7 if patient dies while hospitalized between Day 1-29.
Not hospitalized patient supplemental oxygen = # days where the 7-point ordinal scale score is equal to 2 (if required to have home oxygen).

Table 14.2.15: Total time of non-invasive ventilation or high flow oxygen use (post-dose Day 1 - Day 29 (or discharge, whichever was first); measured in days)

Days of non-invasive ventilation or High Flow Oxygen Use (Scale=5)		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Day 1 - 29	**Median (Q1 - Q3)**			

Non-invasive ventilation or high flow oxygen use = # days where the 7-point ordinal scale score is equal to 5 or 6. Or 7-point ordinal scale score is equal to 7 if patient dies while hospitalized between Day 1-29.

Table 14.2.16: Summary of the Proportion of Patients Alive and with Oxygen Use at Days 7, 14 and 29 (or discharge, whichever was first), ITT

Proportion of Patients with Oxygen Use (Scales in 4, 5, and 6)		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Day 7	**Yes**			
	No			
Day 14	**Yes**			
	No			
Day 29	**Yes**			
	No			

Hospitalized patient supplemental oxygen = the 7-point ordinal scale score is equal to 4, 5, or 6.
Not hospitalized patient supplemental oxygen = the 7-point ordinal scale score is equal to 2 (if required to have home oxygen).

Table 14.2.17: Summary of the Proportion of Patients Alive and with non-invasive Ventilation or High Flow Oxygen Use at Days 7, 14 and 29 (or discharge, whichever was first), ITT

Proportion of Patients with Non-invasive Ventilation or High Flow Oxygen Use (Scale=5)		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Day 7	**Yes**			
	No			
Day 14	**Yes**			
	No			
Day 29	**Yes**			
	No			

Non-invasive ventilation or high flow oxygen use = the 7-point ordinal scale score is equal to 5 or 6.

Table 14.2.18: Proportion of Patients Alive and Receiving Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation (ECMO, 7-point ordinal scale criteria #6) at Days 7, 14 and 29 (or discharge, whichever was first), ITT

Proportion of Patients with ECMO (Scale=6)		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Day 7	**Yes**			
	No			
Day 14	**Yes**			
	No			
Day 29	**Yes**			
	No			

IMV = The 7-point ordinal scale score is equal to 6.

Table 14.3.1: Time to first composite AE

		Enrolled (N=45)	Ensifentrine (N=30)	Placebo (N=15)
Proportion of AE	**Yes**			
	No			
Time to first composite AE[a]	**Days from consent (SD)**			
	Median (min. - Max.)			

[a] Consider those who experienced Adverse events

Table 14.3.2: Number/Proportion Treatment emergent adverse events

TEAE Category	Statistic	Total	Ensifentrine (N=30)	Placebo (N=15)
Any TEAE	N (%)			
Any TEAE leading to study medication discontinuation				
Any TEAE related to study medication				
Any serious TEAE				
Any serious TEAE leading to study medication discontinuation				
Any serious TEAE leading to death				
Any TEAE classified by maximum severity				
Mild				
Moderate				
Severe				
Any serious TEAE classified by maximum severity				
Moderate				
Severe				

Abbreviations: AE, adverse event; N, number of patients in treatment group; n, number of patients in analysis; TEAE, treatment-emergent adverse event; %, percentage of patients calculated relative to the total number of patients in the treatment group.

TEAEs were defined as all AEs that started after the first dose of study treatment or started after the first dose of study treatment or started prior to first dose of study treatment and worsened, based on the Investigator's assessment of severity on or after the first dose of study treatment. TEAEs with a missing severity were classified as severe

Table 14.3.3: Number/Proportion TEAEs by System Organ Class and Preferred Term

System Organ Class Preferred Term	Statistic	Total	Ensifentrine (N=30)	Placebo (N=15)
Patients with at least one TEAE	N (%)			
Metabolism and nutrition disorders	N (%)			
Dehydration, hyperglycemia	N (%)			
Gastrointestinal disorders				
Diarrhoea				
Investigations	N (%)			
Alanine aminotransferase increased, Aspartate aminotransferase increased	N (%)			
Vascular disorders	N (%)			
Hypertension	N (%)			
Shock	N (%)			

n = number of patients

Table 14.3.4: Number/Proportion TEAEs Leading to Discontinuation of Study by System Organ Class and Preferred Term

Table 14.3.5: Number/Proportion TEAEs Causally Related to the Study Treatment by System Organ Class and Preferred Term

Table 14.3.6: Number/Proportion TEAEs by Maximum Severity by System Organ Class and Preferred Term

System Organ Class Preferred Term	Severity	Statistic	Total	Ensifentrine (N=30)	Placebo (N=15)
Patients with at least one TEAE	Severe	N (%)			
	Moderate	N (%)			
	Mild	N (%)			
SOC	Severe				
	Moderate				
	Mild				
Preferred Term	Severe				
	Moderate				
	Mild				

Table 14.3.7: Number/Proportion Serious TEAEs by System Organ Class and Preferred Term

Table 14.3.8: Number/Proportion Serious TEAEs Causally Related to the Study Treatment by System Organ Class and Preferred Term

Table 14.3.9: Number/Proportion Serious TEAEs by Maximum Severity by System Organ Class and Preferred Term

Table 14.3.10: Number/Proportion Serious TEAEs Leading to Discontinuation of Study by System Organ Class and Preferred Term

Table 14.3.11: Number/Proportion Serious TEAEs with an Outcome of Death by System Organ Class and Preferred Term

Exploratory Analyses

ECMO: invasive mechanical ventilation or extracorporeal membrane oxygenation

Description of the distribution of the 7-point ordinal scale outcomes using plots (e.g., stacked bar plots representing the proportion of patients in each category, by treatment arm, over time).

Descriptive summary of the number of days between hospital admission, positive PCR test (or as per hospital testing protocol) and randomization.

Proportion of total patients requiring any oxygen at randomization.

- For those that required oxygen, the mean/standard deviation or median/IQR for the oxygen amount (in FiO2).
- Oxygen use while hospitalized and undergoing study treatment.

Measurement of the oxygen requirement: compare the oxygen requirement (mean and median) for each arm using daily supplemental oxygen flow (L/min).

Figures

Figure 1: Patient Disposition

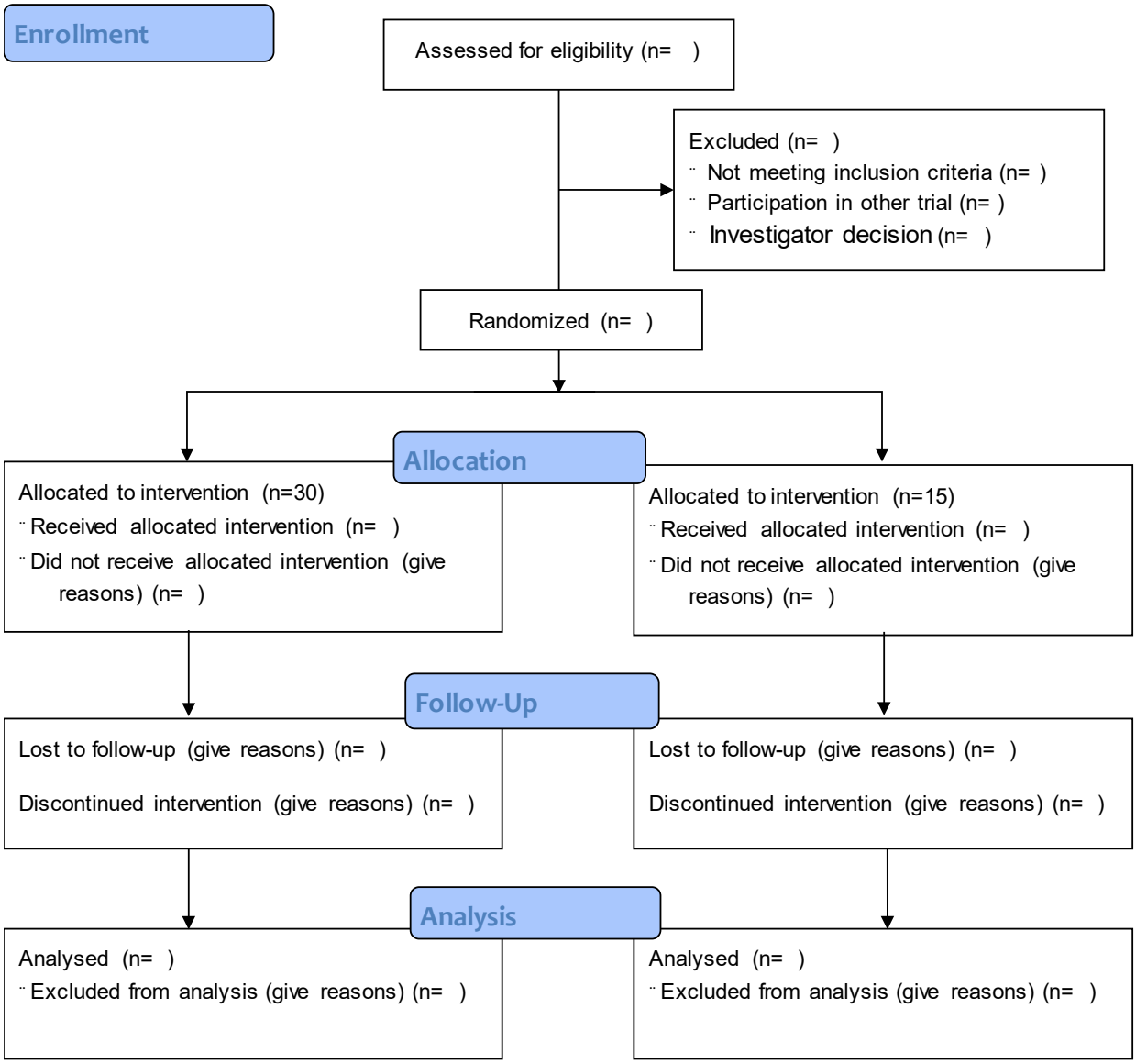

Figure 2: Kaplan–Meier plot of time to Recovery

Figure 3: Histogram of ordinal scores at Day 7, 14, 29 by treatment group and baseline ordinal scale

Figure 4: Proportion of Patients in Oxygen Need by Day in Study