NOCoV2 - An open-label, adaptive randomized, controlled multicenter study to evaluate the efficacy and safety of RESP301 plus standard of care (SOC) compared to SOC alone in hospitalized participants with COVID-19 requiring supplemental oxygen

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PAREXEL International

30 Respiratory Limited

RESP301

An open-label, adaptive randomized, controlled multicenter study to evaluate the efficacy and safety of RESP301 plus standard of care (SOC) compared to SOC alone in hospitalized participants with COVID-19 WHO grade 3&4 (NOCoV2)

Statistical Analysis Plan

Version: 2.0

PAREXEL Project Number: CCI [redacted]

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Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with CCI and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: PPD
Review	PPD Project Role: PPD

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	16JUL2020	New document
2.0	05JAN2022	1. Update SAP per new version of Protocol (Final, 16-Sep-2020; Amendment 3 (Version 4.0)) • Change of Title to include 'WHO grade 3 & 4' • Modify Primary Objective/Endpoint for addition of WHO grade 3 or grade 4. • Modify Secondary Objective/Endpoint for addition of WHO grade 3 or grade 4 • Change of wording accordingly to refer to use of supplmental oxygen 'if applicable' because WHO grade 3 do not require supplemental oxygen, so not all study patients will be using supplemental oxygen. • Exclusion criterion 13 updated to specify that mHb >1% is exclusionary • Amendment of Methb threshold from 1% to 2% • Schedule of Activities: Changed description of oxygen measurements pre/post treatment to make clearer and remove repetition • nebulization from 4 minutes to 8 2. Add/modify few abbreviation

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ADaM	Analysis Data Model
ADI	Actual Dose Intensity
AE	Adverse event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
BP	Blood pressure
CHW	Cui/Hung/Wang
CI	Confidence interval
CMH	Cochran Mantel Hensel
COVID-19	Coronavirus disease 2019
CP	Conditional Power
DBP	Diastolic blood pressure
DoD	Date of Discharge
DRE	Disease Related Events
ECG	Electrocardiogram
FiO2	Fraction of Inspired Oxygen
IDI	Intended Dose Intensity
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mHb	Methemoglobin
MMRP	Mixed Model Repeated Measures
NCI	National Cancer Institute
NEWS	National Early Warning Score
PP	Per Protocol Population
PT	Preferred Term

Abbreviation / Acronym	Definition / Expansion
RBC	Red Blood Cells
RDI	Relative Dose Intensity
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard Deviation
SOC	System Organ Class
SP	Safety Population
SpO_2	Oxygen Saturation
TID	Three Times a Day
WBC	White Blood Cells
WHO	World Health Organization

1 INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by a novel coronavirus (SARS-CoV-2). COVID-19 was first described in Wuhan, China, in December 2019 and is now a global pandemic (Matos et al, 2020). Most of those affected have milder illness (80%), 15% will be severely ill (require oxygen) and 5% will require intensive care unit care (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). Of those who are critically ill, most require early intubation and mechanical ventilation.

A critical early component of innate host defense in the airway is the ability of respiratory epithelial cells to produce high levels of NO (Kao et al, 2001). NO functions as a signaling molecule in initiation of the inflammatory response to viruses, and also has direct antiviral effects (Folkerts et al, 1998).

RESP301 is a NO-generating liquid designed to release NO in situ in the upper airways and deep in the alveolar spaces. RESP301 is delivered via a handheld nebulizer and has specific advantages over inhaled NO gas in treating patients with COVID-19 during the current pandemic.

This is an open-label, randomized, multicenter, parallel group, concurrent, controlled study using a sequential adaptive design. Participants will be consented and randomized 2:1 to the Investigational arm or the Control arm. Participants randomized to the Investigational arm will receive inhaled RESP301 (6 mL) administered using a nebulizer 3 times a day (TID) for up to 10 days in addition to the standard of care (SOC) while participants in the Control arm will receive SOC alone.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 4.0 (September 16, 2020)
- electronic Case Report Form (eCRF), Version 3.0 (June 24, 2020)
- RESP301 DMC Charter

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate efficacy of RESP301 in preventing progression of hospitalized COVID-19 participants at level 3 or 4 in the modified World Health Organization (WHO) ordinal scale into higher levels.

2.2 Secondary Objectives

- To assess the effect of RESP301 as measured by room air SpO_2
- To assess the effect of RESP301 as measured by the National Early Warning Score (NEWS) 2 symptom score

- To assess the treatment response on clinical status

Additional Secondary Objectives

- To assess the overall safety profile of RESP301 in COVID-19 participants
- To assess the ability of participants to tolerate nebulization

2.3 Exploratory Objective

- CCI [redacted]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an open-label, randomized, multicenter, parallel group, concurrent, controlled study using a sequential adaptive design to evaluate the efficacy and safety of RESP301 added to standard of care (SOC) in hospitalized patients with COVID-19 (WHO ordinal scale grade 3 & 4).

Central stratified randomization of 300 subjects to assign participants into one of the study treatment arms will occur as follows, RESP301+SOC or SOC (control), with a randomization ratio of 2:1 using an interactive voice response system (IVRS)/interactive web response system (IWRS). Participants will be stratified by country and presence of risk factors for severe outcomes of COVID-19, based on comorbidities and age as follows:

1. Age >65 years
2. Ongoing or currently treated diabetes mellitus
3. Ongoing or currently treated hypertension
4. Ongoing or currently treated cardiovascular disease
5. Ongoing or currently treated chronic lung disease
6. Cancer history of less than 3 years, basal cell skin carcinoma excluded
7. Ongoing or currently treated chronic kidney disease

Participants will be stratified as no risk factor (none of the above criteria), one risk factor (one single of the above) or high-risk factor (2 or more of the above).

There are 3 phases in the overall study design: Screening Period, Intervention Period, Follow-up Period. Figure 1 displays the study schematic.

Screening Period– Patients will be screened up to 2 days prior to treatment administration. Upon signing informed consent, the patient enters the screening phase and is assessed for the inclusion/exclusion criteria. If all eligibility criteria are met, the patient moves into the intervention period.

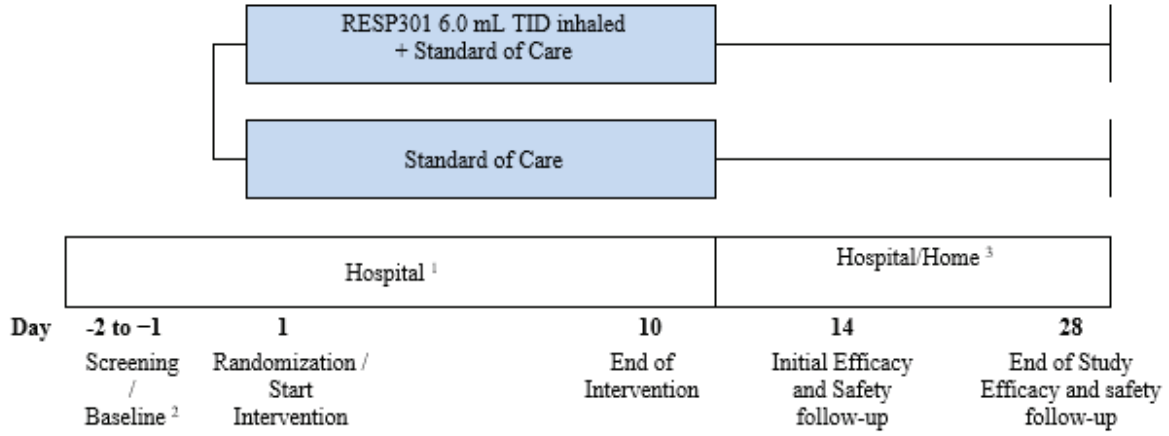
Intervention Period – The intervention period starts on Treatment Initiation (Day 1). Patients will receive treatment three times a day up to Day 10. Patients may end treatment earlier than Day 10 if their symptoms subside following the criteria outline in the protocol section 4.1.

Follow-up Period

- For efficacy - patients will be followed up on Day 14 and Day 28. If patient is no longer hospitalized, follow-up will occur by phone-call.
- For safety - patients will be follow-up 28 days after the first treatment dose is administered. If patient is no longer hospitalized, follow-up will occur by phone-call.

Two interim analyses are planned to assess futility. The first IDMC interim analysis will take place after the first 60 participants have completed Day 10 of the study to evaluate whether the study will be stopped for futility based on change from baseline in room air SpO_2. The second interim analysis will take place after 150 participants have completed Day 14 post-randomization based on event rate for the primary endpoint. The purpose of the second interim analysis will be futility as well as a potential sample size re-estimation in case the actual results differ from the original assumptions.

Figure 1: Study Design



TID=3 times daily

1 Participants may be discharged from hospital before Day 10.

2 Screening period may include Day 1, as participants may be screened and randomized on the same day provided all eligibility criteria are met.

3 The post-treatment efficacy and safety follow-ups may be conducted by telephone for participants who are discharged from the hospital at the time.

3.2 Determination of Sample Size

[redacted]

3.3 Endpoints

3.3.1 Efficacy Variables

Primary:

- Proportion of participants who progress to level >4 of modified WHO ordinal scale due to COVID-19 by Day 14

Key Secondary:

- Change in room air SpO_2 from baseline over time
- Change in NEWS 2 symptom score from baseline over time
- Change from baseline on the modified WHO ordinal scale at each visit up to Day 28
- Time to improvement to at least one level lower of the modified WHO ordinal scale
- Time to progression to at least one level higher of the modified WHO ordinal scale

Additional Secondary:

- Time to hospital discharge
- Incidence of mortality by Day 28

3.3.2 Safety Variables

- Clinical safety laboratory measurements
- Physical examinations
- Vital signs
- Concomitant medications
- Cumulative incidence of AEs and Severe AEs

- Incidence of participants unable to tolerate nebulization due to:
  - Reduction in SpO2 to < 90%, unless well clinically tolerated according to Investigator's opinion
  - Other clinical signs of intolerance according to Investigator's opinion
- Incidence of clinical bronchial hyper-responsiveness related to nebulization

3.4 Exploratory Variables

- CCI [redacted]

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Presentation Considerations

Baseline is the last available pre-treatment assessment. All assessments should have time collected. If time is not collected and date of assessment is the same as the *first dose date,* then assessment will be assumed to be collected prior to treatment unless schedule of assessments and protocol indicate planned collection is always after dosing.

Day-of-Discharge (DoD) is the day when patient is discharged from the hospital.

Durations are calculated as the stop date minus the start date plus one.

For elapsed time (e.g. time since the initial diagnosis), if the reference date is on or after the event date, then the elapsed time is the reference date minus the event date plus one. If the reference date is before the event date, then the elapsed time is the reference date minus the event date.

If more than one laboratory value is available for a given study day, the first valid observation will be used in summaries and all observations will be presented in listings. If it is not possible to determine which is the first measurement due to missing times, then the average of all measurements for that time point will be used as the value for that time point.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw

data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

The mixed model with repeated measurements /analysis of covariance model with treatment, country, participant's clinical status at Baseline and visit as the model term, and Baseline value as the covariate will be used to test for the significance of the treatment difference. Least square means, standard errors, 95% CIs and p-values will be presented.

All the categorical variables including the primary endpoint will be summarized by treatment in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Binary primary endpoint: (progression to critical stage/death up to Day 14) will be analyzed by a Cochran-Mantel-Haenszel (CMH) stratified for the factors used in the stratified randomization. Treatment difference will be tested using a Cochran–Mantel–Haenszel (CMH) test stratified by 1) country and 2) participant's clinical status at Baseline. For the categorical endpoints, relative risk and its 95% CI will be presented.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

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

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

4.3 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

4.4 Study Patients

4.4.1 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion. Summaries will include:

- The number of patients randomized.
- Number and percentage of patients randomized by country
- The number and percentage of patients treated (with any amount of study drug).
- Number of patients in the analysis populations
- Number and percentage of patients who completed treatment
- Number and percentage of patients who were discharged from the hospital prior to Day 10.

- Number and percentage of patients withdrew early from treatment (including reasons for early withdrawal)
- Number and percentage of patients who withdrew early from the study (including reasons for early withdrawal)

By-patient listings of randomization details, visit dates, and withdrawal details (including reason for discontinuation and duration of treatment prior to discontinuation) will also be provided.

4.4.2 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures of a study protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.
Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of major protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis population (see Section 4.5 for descriptions of analysis populations), both including and excluding data potentially affected by major protocol deviations.

A patient will be classified as having a protocol deviation if one incurs an event belonging to any one of the following categories: 1) violation of the inclusion/exclusion criteria (see Protocol Section 5.2 and 5.3); 2) taking prohibited medications or treatments; 3) treatment misallocation; 4) violation of discontinuation criteria; 5) error in procedure and tests; and 6) missed visits (including procedures and tests).

Major protocol deviations and any action to be taken regarding the exclusion of patients are defined in the study protocol deviation specifications. The final determination of major protocol deviations and the exclusion of patients from any of the analysis populations will be made prior to database lock.

A summary of the number and percentage of patients with a major protocol deviation by treatment arm as well as by type of deviation will be provided. Also, a by-patient listing of major protocol deviations will be provided.

4.5 Analysis Sets

For purposes of analysis, the following analysis sets are defined:

- The intent-to-treat (ITT) population will include all randomized participants. The ITT participants will be analyzed according to randomized treatment, irrespective of the actual treatment received. Participants who withdraw from treatment early will be followed for the assessment of the Day 14 primary endpoint. All efficacy analyses will be performed using the ITT Population.

- The per-protocol (PP) population will include all participants in the ITT Population with no major protocol deviations that may significantly impact data integrity or patient safety. The PP Population will be used for supportive analyses of the efficacy measurements.

- The safety (SP) population will include all randomized participants who inhale any amount of study intervention or are randomized to the control arm. The SP will be analyzed according to the actual treatment received. The SP will be analyzed according to the actual treatment received. This set will be used for the safety analyses.

The efficacy summaries and analyses will be based on the ITT population**.** In the event that a patient is allocated the incorrect study treatment as per the study randomization list, patients will be summarized and analyzed 'as randomized' (i.e. by randomized treatment arm). In the event that a patient is stratified incorrectly, 'randomized stratum' will be used rather than 'actual stratum'. The PP Population will be used to demonstrate robustness of results for the primary efficacy endpoint

The safety summaries and analyses will be based on the SP population. In the event that a patient is allocated the incorrect study treatment as per the study randomization list, patients will be summarized and analyzed 'as treated' (i.e. by allocated treatment arm).

A by-patient listing of analysis population details will be provided. This listing will be presented by treatment arm and will include: center, patient identifier, inclusion/exclusion flag for each population, and reason for exclusion from each population.

4.6 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by treatment group and overall using the ITT population. The summaries provided will include the following:

- Demographic variables:
    - Age (continuous and categorical (<65 years; ≥65years))
    - Sex
    - Race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White; Other; Multiple)
    - Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
    - Baseline Height (cm)
    - Baseline Weight (kg)
    - Baseline BMI (kg/m^2)
    - Pregnant (Yes, No)
    - Childbearing Potential (Yes, No)

- Baseline disease characteristics:
    - Randomization strata (country; comorbidity category)
    - SARS-CoV-2 Status (positive, negative, borderline, intermediate)
    - Mechanical ventilation (Yes, No)
    - Ventlation rate (liter per minute)

- Mode of Supplemental O2 Administration (Nasal Cannula, Mask)
- Respiratory rate (breaths per minute)
- Heart rate (Beats per minute)
- SpO_2, FiO_2, CCI [redacted]
- NEWS Symptom Score
- WHO 7-point ordinal Scale
- Days since onset of symptoms
- Diastolic blood pressure (<=90 mmHg, >90 mmHg)
- Systolic blood pressure (<=140 mmHg, >140 mmHg)
- Temperature

Medical history will be reported by system organ class and preferred term as coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher.

Age will be reported as calculated in the study database at day of informed consent. BMI will be calculated from baseline height and weight as weight (kg) / height^2 (m^2).

By-patient listings of demographic data and other baseline characteristics will be provided.

4.7 Prior, Concomitant Medication and Prohibited Medication

Prior and concomitant medications will be summarized by drug class and preferred medication name by treatment group and for both treatment groups combined (Total) using the ITT population. Prior and concomitant medications will be summarized separately, concomitant medications will also be summarized overall and by study period. WHO DDE March 2020 will be used to classify medications.

Medication start and stop dates will be compared to the date of first dose of study drug to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Missing or partial start dates will be imputed as described in Section 4.9.1.3. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study drug will be classified as Prior only. If a medication starts before the date of first dose of study drug and stops on or after the date of first dose of study drug, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study drug.

Rescue medication of a ready-to-use nebulization of a bronchodilator will be allowed on study. The number and percentages of the patients using such medications will be summarized by treatment groups, and the impact on efficacy and safety will be analyzed by subgroup analyses.

By-patient listings of prior, concomitant and rescue medications will be provided. Listings will also be provided for any concomitant procedures reported.

4.8 Treatment Compliance

Compliance with study treatment will be assessed via relative dose intensity (RDI). Relative dose intensity is defined as 100% times the actual dose intensity (ADI) divided by the intended dose intensity (IDI). Actual dose intensity for a patient is defined as the total dose received over all treatment days divided by the sum of the lengths of all treatment days. The intended dose intensity is the total dose assigned over all treatment days divided by the sum of the intended lengths of all treatment days. The assigned dose for **RESP301+SOC** is 6.0 mL per treatment administration taken three times a day for 10 days.

For example. the intended dose intensity (IDI) for RESP301 for a patient who completed 10 days of treatment three times a day would be:

6.0 mL* 3 * 10 days/10 days = 18.0 mL

Summaries of ADI, IDI, and RDI will be presented for patients on the RESP301+SOC arm. The average number of dosing days will be presented as well.

A by-patient listing of study treatment compliance data will also be provided, containing the date of randomization, the date of last dose of study treatment, and the calculated RDI. A by-patient listing of exposure data will be provided.

4.9 Efficacy Evaluation

4.9.1 Analysis and Data Conventions

This study is designed to test for superiority. The null hypothesis for the treatment comparison will be that there is no difference in the rate of progression to at least one level higher of the modified WHO ordinal scale in RESP301 + SOC compared to SOC alone. The alternative hypothesis is that RESP301 +SOC reduces the rate of progression to at least one level higher in the modified WHO ordinal scale in COVID-19 at Day 14. Symbolically, this is expressed as follows:

H_0: $pWHO{+}1{+}_{RESP301+SOC} \geq pWHO{+}1{+}_{SOC}$
H_a: $pWHO{+}1{+}_{RESP301+SOC} < pWHO{+}1{+}_{SOC}$

4.9.1.1 Multi-center Studies

All centers will be pooled together in the efficacy analyses. If the results reveal impact of the centers, then ad hoc analyses will be performed. In that case, the centers may be grouped by geographic regions and evaluation of the consistency of treatment effects across geographic regions may be performed.

4.9.1.2 Adjustments for Covariates

The primary efficacy analysis will be adjusted for the following baseline covariates:

1. Country
2. No risk factor (none of the criteria listed in Section 3.1), one risk factor (one single of the criteria in Section3.1) or high-risk factor (2 or more of the criteria).

4.9.1.3 Handling of Dropouts or Missing Data

Any patients that are discharged from the hospital prior to Day 14 due to improvement of clinical status and their status on Day 14 cannot be obtained, then the Last Observation Carried Forward (LOCF) approach will be used to impute missing data. Only post-treatment observations will be carried forward. No baseline observations will be carried forward. To assess the robustness of the study conclusions to the choice of imputation method, a complete-case analysis (all patients with missing data for the primary endpoint are excluded from analysis) will be performed as a sensitivity analysis.

The Per-protocol population analyses will be performed using the same imputation method as for the ITT population analyses.

If the proportion and/or pattern of missing data is found to be different to that assumed, additional sensitivity analyses may be required.

In general, imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in the time to event analyses.

Imputed dates will not be displayed in listings unless otherwise stated.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

- D='Day': indicates that the day portion of the date is imputed
- M='Month': indicates that the month and day portions of the date are imputed
- Y='Year': indicates that the entire date (year, month, and day) is imputed

Imputing partial AE and prior/concomitant medication start dates:

a) If the year is unknown, the date will not be imputed and will be assigned a missing value.

b) If the month is unknown, then:

1. If the year matches the first dose date, then impute to the month and day of the first dose date.
2. Otherwise, assign 'January'.

c) If the day is unknown, then:

1. If the month and year match the first dose date, then impute to the day of the first dose date.
2. Otherwise, assign '01'.

Imputing partial AE and prior/concomitant medication stop dates:

a) If the year is unknown, the date will not be imputed and will be assigned a missing value.
b) If the month is unknown, then assign 'December'.
c) If the day is unknown, then impute to the last day of the month.

Imputing partial death dates:

a) If the month and/or year are unknown, the death date will not be imputed.
b) If the day is missing, then assign '01'.
c) If imputing the first day of the month results in a negative overall survival time, the patient will be censored for overall survival at the randomization date.

A patient data listing will be provided showing all patients with missing values for the primary endpoint. For these patients, the listing will provide all observed data relating to the primary endpoint (i.e. all measurements recorded prior to the missing value, any measurements recorded after the missing value, important baseline characteristics, the recorded reason for study discontinuation, and the date of study discontinuation). The listing will also provide the imputed date(s) used in the primary analysis.

4.9.1.4 Multiple Comparisons/Multiplicity

To account for the multiple testing due to the second interim analysis an adjustment for the type-I-error probability will be applied using the Haybittle-Peto approach with one sided alpha=0.0005 at the second interim analysis and leave one-sided nominal alpha of 0.0249 for the final analysis.

4.9.1.5 Interim Analyses

Two interim analyses will be performed.

1. The first analysis will be conducted when about 60 participants (40 participants in the RESP301+SOC arm and 20 participants in the SOC arm) have completed the Day 10 assessment. The purpose of this analysis is to evaluate efficacy of RESP301 with the application of a futility criterion based on the results on SpO_2 change from baseline on Day 10. The following futility criterion will be used for this first interim analysis:

If the difference in the percentage of participants with at least a 2% improvement in SpO2 between both treatment arms is less than 5%, benefit of RESP301 treatment is not expected. For a final decision to stop the study for futility the results on other endpoints associated with safety and efficacy will be considered as well.

As no other modification of the study at the time of the first interim analysis is considered, no adjustment of the alpha level is required.

2. The second interim analysis will be conducted after 150 participants (100 participants in the RESP301+SOC arm and 50 participants in the SOC arm) have completed the Day 14 assessment. The purpose of this analysis is the assessment of futility or a sample size re-estimation (increase only) in case the actual results differ from the original assumptions for the power calculations of the study, related to the percentage of participants meeting the primary endpoint in the control arm and/or the relative treatment benefit achieved in the RESP301+SOC arm compared to the SOC arm.

To account for the multiple testing due to the second interim analysis an adjustment for the type I error alpha will be applied using the Haybittle-Peto approach which would spend one sided alpha=0.0005 at the second interim analysis and leave one-sided nominal alpha of 0.0249 for the final analysis. The futility criterion for the second interim analysis will be based on the conditional power (CP) for the final results based on the assumption that the remainder of the study will follow the same trend as observed in the interim analysis. If CP at the time of the second interim analysis is less than 20% consideration will be given to stop the study for futility. At the same time sample size re-estimation will be performed to achieve 80% power at the end of the study.

4.9.1.6 Examination of Subgroups

The treatment effect for the primary and key secondary efficacy endpoints will be examined for the following subgroups:

1. Country
2. Age >65 years
3. Ongoing or currently treated diabetes mellitus
4. Ongoing or currently treated hypertension
5. Ongoing or currently treated cardiovascular disease
6. Ongoing or currently treated chronic lung disease
7. Cancer history of less than 3 years, basal cell skin carcinoma excluded

8. Ongoing or currently treated chronic kidney disease

Summaries of the primary and key secondary efficacy variables by treatment group and subgroups will be produced. No formal statistical analysis will be performed within subgroup.

With reviewing the results, the homogeneity of the treatment effect across subgroups may be investigated using graphical and analytical methods.

4.9.2 Primary Efficacy Variable

Progression to level at least one level higher than baseline of modified WHO ordinal COVID-19 scale by Day 14"

The WHO 7-point ordinal scale is as follows:

1. Not hospitalized, no limitations on activities;
2. Not hospitalized, limitation on activities;
3. Hospitalized, not requiring supplemental oxygen;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, on non-invasive ventilation or high-flow oxygen devices;
6. Hospitalized, on invasive mechanical ventilation or ECMO;
7. Death.

The percentage and corresponding 95% CI of patients who progress to at least one level higher from baseline on the WHO 7-point ordinal scale on Day 14 will be summarized by treatment arm and overall. The odds ratio of RESP301 + SOC versus SOC alone and 95% CI intervals and p-values will be estimated using the CMH stratified by country and number of risk factors (as randomized).

WHO 7-point ordinal scale will be assessed daily while patient is hospitalized. Daily scores and changes from baseline will be summarized. Plots of mean score (with standard error bars) by treatment group over time may be produced.
A by-patient listing of the primary efficacy data will be provided

4.9.3 Secondary Efficacy Variables

Other secondary and exploratory endpoints will be analyzed according to the type of endpoint as described below. If data are sparse for any of the exploratory endpoints, summaries may be limited to descriptive statistics of available data or listings only as appropriate. By-patient listings of all secondary and exploratory efficacy endpoint data will be provided.

NEWS 2 scores

The NEWS is based on a simple aggregate scoring system (see Fig 2 for NEWS 2 scoring system) in which a score is allocated to physiological measurements, already recorded in routine practice, when patients present to, or are being monitored in hospital (**Error! Reference source not found.**). Six simple physiological parameters form the basis of the scoring system:

1. Respiration rate
2. Oxygen saturation
3. Systolic blood pressure
4. Pulse rate
5. Level of consciousness or new confusion*
6. Temperature

**The patient has new-onset confusion, disorientation and/or agitation, where previously their mental state was normal – this may be subtle. The patient may respond to questions coherently, but there is some confusion, disorientation and/or agitation. This would score 3 or 4 on the Glasgow Coma Scale (rather than the normal 5 for verbal response), and scores 3 on the NEWS system.*

Standard descriptive statistics (mean, standard deviation, median, minimum, maximum) and change from baseline will be used to summarize each of these scores by treatment group and visit. NEWS scores will be assessed daily while patient is hospitalized. Plots of mean score (with standard error bars) by treatment group over time may be produced.

Figure 2: The National Early Warning Score 2 (NEWS 2) scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Mortality at Day 28

Incidence of mortality by Day 28 is the number of patients who have died by Day 28 and the percentage of patients reaching this endpoint will be summarized by treatment group. A CMH test will be used to test for a treatment effect of RESP301 + SOC versus SOC Alone after adjusting for baseline clinical status. Odds ratios of the treatment effect (RESP301 + SOC versus SOC Alone) with corresponding 95% confidence intervals (CI) will be estimated using a logistic regression model with baseline clinical status as a covariate. A treatment by baseline clinical status interaction may be added to the model along with other covariates of interest.

Overall survival will also be analyzed using time to event methods. Time to death is defined as the time from treatment start to death in days (*date of death – first dose date + 1*). Patients without a recorded death will be censored at their completion or at their early discontinuation date if they withdrew early or at their date of last assessment if they are alive and ongoing in study at time of analysis (*completion date/early discontinuation date/last assessment date – first dose date +1*). Reasons for censoring will be summarized.

The total number of patients with an event, the total number censored and Kaplan-Meier survival estimates with associated 95% CI (25^{th} percentile, median, and 75% percentile, proportion surviving at Days 7, 10, 14, and 28) will be presented by treatment group. A survival plot will be produced with the probability of an event (0 to 100%) along the Y-axis and time in days along the X-axis.

The number of patients at risk will be presented along the X-axis. The hazard ratio of RESP301 + SOC versus SOC Alone with corresponding 95% CI and p-values will be estimated from a Cox Proportional model adjusting for treatment, and patients randomized strata.

Time to hospital discharge survival

Time to hospital discharge is the time in the hospital after first study treatment in days *(date of discharge - first dose date + 1).* Patients who die before leaving the hospital will be considered failures (did not achieve hospital discharge), *date of death – first dose date +1)* and censored. In the case that a patient is still hospitalized at time of analysis or withdraws from the study before leaving the hospital, they will be censored at their date of last assessment in the data cut or early discontinuation date, respectively.

The time to hospital discharge survival will be analyzed using Kaplan-Meier methods. If data allows, survival estimates will be stratified by baseline clinical status. The Cox models adjusting for baseline randomization strata may be performed.

Time to Improvement

Time to improvement is the time in which the patient sees a decrease after first study treatment in the WHO 7-point ordinal scale from baseline to a value at least one level lower in days *(date of decrease in WHO scale - first dose date + 1).* In the case that a patient has not decreased in the WHO scale at time of analysis or withdraws from the study before leaving the hospital, they will

be censored at their date of last assessment in the data cut or early discontinuation date, respectively.

Time to improvement will be analyzed using the Kaplan-Meier methods as described in the above time to event analyses.

Time to Progression

Time to improvement is the time in which the patient sees an increase after first study treatment in the WHO 7-point ordinal scale from baseline to a value at least one level higher in days *(date of increase in WHO scale - first dose date + 1).* In the case that a patient has not increased in the WHO scale at time of analysis or withdraws from the study before leaving the hospital, they will be censored at their date of last assessment in the data cut or early discontinuation date, respectively.

Time to progression will be analyzed using the Kaplan-Meier methods as described in the above time to event analyses.

Change from baseline in respiratory outcomes

Respiratory outcomes include the secondary endpoint of SpO_2 and the exploratory endpoint CCI

Standard descriptive statistics (mean, standard deviation, median, minimum, maximum) will be used to summarize each outcome and it's change from baseline by treatment group at Day 10. Only scheduled visits as described in the schedule of assessments (Section 1.3 of protocol) will be included for each endpoint.

Patients who showed an increase 2% or higher in SpO2 from baseline at Day 7 will be flagged and summarized. Patients who have a reduction in SpO2 to < 90% will be flagged and summarized.

In addition, the least square means and least square mean difference (RESP301 + SOC – SOC Alone) along with their respective 95% CIs and p-values will be presented. Least square means and mean difference will be estimated using a Mixed Model with Repeated Measurements (MMRP) /Analysis of Covariance (ANCOVA) with the treatment, patient's country and risk group as randomized and visit as the model terms, and baseline value as the covariate and change from baseline as the dependent variable. Patients will be included as a random effect and an unstructured covariance structure will be specified in the initial model. If the model fails to converge alternative covariance structures will be applied in the following order: heterogenous compound symmetry, compound symmetry.

4.10 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.5.

4.10.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher.

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.

Treatment-related AEs are those with reasonable causality to study drug marked as "related" or "possibly related" on the eCRF. AEs with an outcome of death are those with a grade of 5 or an outcome of "fatal." AEs leading to treatment withdrawal are those with a study drug action taken of "drug withdrawn," while AEs leading to study drug dose reduction or interruption are those with a study drug action taken of "dose reduced" or "drug interruption", respectively.

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to mild, moderate, or severe. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE.

An overall summary table of treatment-emergent AEs (TEAEs) will be provided with the number and percentage of patients (incidence) reporting at least one event, along with the total number of events for the following categories:

- Any AE
- AE of Grade 3 or higher
- Treatment-related AE
- Treatment-related AE of Grade 3 or higher
- Serious AE
- Treatment-related serious AE
- AE leading to death
- Treatment-related AE leading to death
- AE leading to treatment withdrawal
- Treatment-related AE leading to treatment withdrawal
- AE leading to dose reduction
- Treatment-related AE leading to dose reduction
- AE leading to dose interruption
- Treatment-related AE leading to dose interruption

Summary tables will also be presented for the incidence and total number of events by SOC and PT by treatment arm for these categories.

Counts will be by patient, not by event, and patients are only counted once within each SOC or PT. For tables categorized by maximum severity grade, patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.

A by-patient listing of all AEs will be provided. This listing will be presented by treatment arm and will include: center, patient identifier, age, gender, race, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, severity, seriousness, action taken, outcome, and relatedness. The following AE listings will also be provided using a similar layout:

- Patients who died during the study
- Patients with treatment-emergent SAEs
- Patients with treatment withdrawal due to AEs
- Patients with dose reduction due to AEs
- Patients with dose interruption due to AEs

For missing or partially missing dates, imputation will be done according to Section 4.9.1.3.

Disease Related Outcomes Not Qualifying AE/SAEs

The following disease-related events (DREs) are common in participants with COVID-19 and can be serious/life-threatening:

- Fever
- Cough*
- Dyspnea*
- Asthenia
- Loss of sense of taste and smell

** A cough or dyspnea episode related to study intervention administration does not meet the definition of a DRE and should be reported as an AE.*

Because these events are typically associated with the disease under study, they will not be reported as AEs.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

4.10.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Additional, significant AE summaries that will be provided are:

- Number and percentage of patients with serious AEs
- Number and percentage of patients with treatment-related serious AEs
- Number and percentage of patients with fatal AEs

All summaries will follow the same criteria as mentioned in Section 14.10.1.

4.10.3 Clinical Laboratory Evaluation

Local laboratories will be used for laboratory safety evaluations in this study. For a list of the parameters to be evaluated, see Table 1. Laboratory normal ranges will be provided by the local laboratory. For parameters where an NCI CTCAE v.5.0 scale exists, laboratory results will be graded according to the NCI CTCAE v.5.0 severity grade. For parameters for where an NCI CTCAE v.5.0 scale does not exist, an indicator of whether the value is below, within, or above the normal range will represent severity instead.

All laboratory values will be reported in SI units.

Summaries for each laboratory parameter will be presented by treatment group and visit. For by-visit summaries, the first non-missing assessment (including repeat assessments) recorded at each visit will be used. Optional laboratory parameters will not be summarized by dose group, only listed.

For laboratory values reported as a character value, such as <40, will be transformed into numerical values for summary reasons by following the specified guidelines. If a laboratory value is reported using the less than symbol, '<', 0.10 will be subtracted from the original numeric value. If a laboratory value is reported using the greater than symbol, '>', 0.10 will be added to the original numeric value.

A by-patient listing of all laboratory data, with abnormal values flagged, will be provided by treatment group. This listing will include patient identifier, age, gender, race, and visit, as well as laboratory reference ranges for each parameter.

Table 1 List of Laboratory Parameters

Clinical Chemistry	**Hematology**
Blood urea nitrogen Potassium Sodium Aspartate Aminotransferase Total and Direct Bilirubin Creatinine Glucose non-fasting Chloride Bicarbonate/CO2 Serum Glutamic-Oxaloacetic Transaminase Alanine Aminotransferase Serum Glutamic-Pyruvic Transaminase Alkaline phosphatase Lactate dehydrogenase	White blood cell (WBC) count Red blood cell (RBC) count Hemoglobin Hematocrit Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Red cell distribution width Platelet Mean platelet volume Methemoglobin
	Coagulation
	Prothrombin Time International Normalized Ratio Activated Partial Thromboplastin Time

To assess Hy's Law, the number and percentage of patients with potentially clinically significant post-baseline elevations in hepatic parameters shown in Table 2 below will be summarized by treatment.

A listing of the patients with potentially clinically significant post-baseline hepatic elevations will be provided. The listing will contain all a subject's values for parameters meeting the criteria.

Table 2. Potentially Clinically Significant Elevations in Hepatic Parameters

ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured

* ALT = Alanine aminotransferase;

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.

4.10.4 Vital Signs, Physical Findings and Other Observations Related to Safety

Summaries for each vital sign parameter will be presented by treatment arm and visit. Observed and change from baseline values in vital sign results will be analyzed using descriptive statistics. Change from baseline will only apply to post-baseline assessments.

Shifts in ECG results, from baseline to each post-baseline visit (where available) will be summarized by treatment arm. The maximum shift (across all visits) in ECG results from baseline will also be summarized by treatment arm.

By-patient listings of vital sign data, ECG results, and physical examination results will be provided by treatment arm.

4.10.5 Independent Data Monitoring Committee [IDMC]

An IDMC will be responsible for closely reviewing the safety and efficacy data from the interim analyses and for providing their recommendations on continuation of the study. The IDMC will

meet to review after 10 and 20 participants have completed as well as at the time of the two interim analyses (i.e., after 60 and 150 participants have completed; see Section 4.9.1.5).

The IDMC Charter will provide additional details about the IDMC activities. Table 3 outlines the IDMC meetings.

Table 3: Scheduled IDMC Meetings

Meeting	Timing	Review Type
1st Data Review Meeting	After 10 patients	Safety
2nd Data Review Meeting	After 20 patients	Safety
1st Interim Analysis Meeting	After 60 patients have completed Day 10	Safety/ Futility/ Change in SpO2
2nd Interim Analysis Meeting	After 150 patients have completed Day 14	Safety/ Futility/ Superiority/ Sample Size Reassessment

4.11 Determination of Sample Size

CCI [redacted]

CCI [redacted]

4.12 Changes in the Conduct of the Study or Planned Analysis

See Statistical Analysis Plan Addendum.

5 REFERENCES

[1] Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. *Biometrics*. 1999;55(3):853-857. doi:10.1111/j.0006-341x.1999.00853.x

[2] SAS® Version 9.2 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

6 APPENDIX A

Table with examples for the adaptive sample size procedure described in Section 4.11 using Cui/Hung/Wang (CHW) approach using a weighted test for the final analysis

2nd IA results with n=150 patients (50 for SOC, 100 for RESP301+SOC		**CP under observed trend for planned 300**	**Total sample size required for CP 80% under observed trend**	**CP under observed trend if total sample size capped by 600**
15 (30%)	5 (5%)	$p < 0.0005$ → early stop for superior efficacy		
15 (30%)	10 (10%)	99%	Not applicable	Not applicable
15 (30%)	15 (15%)	90%	Not applicable	Not applicable
15 (30%)	18 (18%)	66%	393	Not applicable

15 (30%)	19 (19%)	55%	483	Not applicable
15 (30%)	21 (21%)	34%	[798]	[67%]
15 (30%)	26 (26%)	3.99%	Early stop for futility	
12 (24%)	10 (10%)	92%	Not applicable	Not applicable
12 (24%)	12 (12%)	77%	321	Not applicable
12 (24%)	14 (14%)	54%	498	Not applicable
12 (24%)	15 (15%)	42%	[646]	[77%]
12 (24%)	18 (18%)	14%	[1800]	[31%]
12 (24%)	20 (20%)	2.6%	Early stop for futility	
10 (20%)	8 (8%)	85%	Not applicable	Not applicable
10 (20%)	10 (10%)	64%	412	Not applicable
10 (20%)	11 (11%)	50.4%	534	Not applicable
10 (20%)	13 (13%)	26%	[1014]	[55%]
10 (20%)	15 (15%)	10%	[2460]	[23%]
10 (20%)	18 (18%)	1.4%	Early stop for futility	

Signature Page for CCI [redacted]

Reason for signing: Approved	PPD [redacted] 21-Jan-2022 12:01:56 GMT+0000

Reason for signing: Approved	PPD [redacted] 21-Jan-2022 12:09:12 GMT+0000

Reason for signing: Approved	PPD [redacted] -2022 13:49:21 GMT+0000

Reason for signing: Approved	PPD [redacted] Jan-2022 15:12:08 GMT+0000

Reason for signing: Approved	PPD [redacted] 21-Jan-2022 15:37:06 GMT+0000

Signature Page for CCI [redacted]

PAREXEL International

30 Respiratory Limited

RESP301

An open-label, adaptive randomized, controlled multicenter study to evaluate the efficacy and safety of RESP301 plus standard of care (SOC) compared to SOC alone in hospitalized participants with COVID-19 requiring supplemental oxygen (NOCoV2)

Statistical Analysis Plan

Version: 1.0

PAREXEL Project Number: CCI [redacted]

SPONSOR SIGNATURE PAGE

Approved by: _____ _____

PPD Date

PPD

Thirty Respiratory Ltd

PAREXEL SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: PPD

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	16JUL2020	New document

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ADaM	Analysis Data Model
ADI	Actual Dose Intensity
AE	Adverse event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
BP	Blood pressure
CHW	Cui/Hung/Wang
CI	Confidence interval
CMH	Cochran Mantel Hensel
COVID	Coronavirus
CP	Conditional Power
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DoD	Date of Discharge
DRE	Disease Related Events
ECG	Electrocardiogram
FiO2	Fraction of Inspired Oxygen
IDI	Intended Dose Intensity
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRP	Mixed Model Repeated Measures
NCI	National Cancer Institute
NEWS	National Early Warning Score
PP	Per Protocol Population
PT	Preferred Term
RBC	Red Blood Cells
RDI	Relative Dose Intensity

Abbreviation / Acronym	Definition / Expansion
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard Deviation
SOC	System Organ Class
SP	Safety Population
TID	Three Times a Day
WBC	White Blood Cells
WHO	World Health Organization

1 INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by a novel coronavirus (SARS-CoV-2). COVID-19 was first described in Wuhan, China, in December 2019 and is now a global pandemic (**Error! Reference source not found.**). Most of those affected have milder illness (80%), 15% will be severely ill (require oxygen) and 5% will require intensive care unit care (**Error! Reference source not found.**). Of those who are critically ill, most require early intubation and mechanical ventilation.

A critical early component of innate host defense in the airway is the ability of respiratory epithelial cells to produce high levels of NO (**Error! Reference source not found.**). NO functions as a signaling molecule in initiation of the inflammatory response to viruses, and also has direct antiviral effects (**Error! Reference source not found.**).

RESP301 is a NO-generating liquid designed to release NO in situ in the upper airways and deep in the alveolar spaces. RESP301 is delivered via a handheld nebulizer and has specific advantages over inhaled NO gas in treating patients with COVID-19 during the current pandemic.

This is an open-label, randomized, multicenter, parallel group, concurrent, controlled study using a sequential adaptive design. Participants will be consented and randomized 2:1 to the Investigational arm or the Control arm. Participants randomized to the Investigational arm will receive inhaled RESP301 (6 mL) administered using a nebulizer 3 times a day (TID) for up to 10 days in addition to the standard of care (SOC) while participants in the Control arm will receive SOC alone.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 3.0 (June 10, 2020)
- electronic Case Report Form (eCRF), Version 3.0 (June 24, 2020)
- RESP301 DMC Charter

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate efficacy of RESP301 in preventing progression of hospitalized COVID-19 participants at level 4 in the modified World Health Organization (WHO) ordinal scale into levels >4

2.2 Secondary Objectives

- To assess the effect of RESP301 as measured by room air SpO_2
- To assess the effect of RESP301 as measured by the National Early Warning Score (NEWS) 2 symptom score

- To assess the treatment response on clinical status

Additional Secondary Objectives

- To assess the overall safety profile of RESP301 in COVID-19 participants
- To assess the ability of participants to tolerate nebulization

2.3 Exploratory Objective

- CCI [redacted]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an open-label, randomized, multicenter, parallel group, concurrent, controlled study using a sequential adaptive design to evaluate the efficacy and safety of RESP301 added to standard of care (SOC) in hospitalized patients with COVID-19 requiring supplemental oxygen.

Central stratified randomization of 300 subjects to assign participants into one of the study treatment arms will occur as follows, RESP301+SOC or SOC (control), with a randomization ratio of 2:1. Participants will be stratified by country and presence of risk factors for severe outcomes of COVID-19, based on comorbidities and age as follows:

1. Age >65 years
2. Ongoing or currently treated diabetes mellitus
3. Ongoing or currently treated hypertension
4. Ongoing or currently treated cardiovascular disease
5. Ongoing or currently treated chronic lung disease
6. Cancer history of less than 3 years, basal cell skin carcinoma excluded
7. Ongoing or currently treated chronic kidney disease

Participants will be stratified as no risk factor (none of the above criteria), one risk factor (one single of the above) or high-risk factor (2 or more of the above).

There are 3 phases in the overall study design: Screening Period, Intervention Period, Follow-up Period. Figure 1 displays the study schematic.

Screening Period– Patients will be screened up to 2 days prior to treatment administration. Upon signing informed consent, the patient enters the screening phase and is assessed for the inclusion/exclusion criteria. If all eligibility criteria are met, the patient moves into the intervention period.

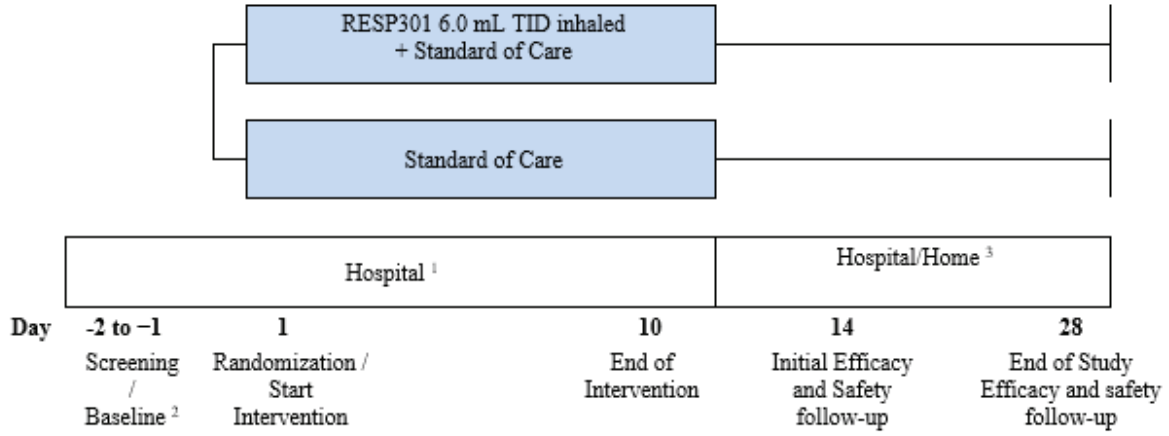
Intervention Period – The intervention period starts on Treatment Initiation (Day 1). Patients will receive treatment three times a day up to Day 10. Patients may end treatment earlier than Day 10 if their symptoms subside following the criteria outline in the protocol section 4.1.

Follow-up Period

- For efficacy - patients will be followed up on Day 14 and Day 28. If patient is no longer hospitalized, follow-up will occur by phone-call.
- For safety - patients will be follow-up 28 days after the first treatment dose is administered. If patient is no longer hospitalized, follow-up will occur by phone-call.

Two interim analyses are planned to assess futility. The first IDMC interim analysis will take place after the first 60 participants have completed Day 10 of the study to evaluate whether the study will be stopped for futility based on change from baseline in room air SpO_2. The second interim analysis will take place after 150 participants have completed Day 14 post-randomization based on event rate for the primary endpoint. The purpose of the second interim analysis will be futility as well as a potential sample size re-estimation in case the actual results differ from the original assumptions.

Figure 1: Study Design



TID=3 times daily

1 Participants may be discharged from hospital before Day 10.

2 Screening period may include Day 1, as participants may be screened and randomized on the same day provided all eligibility criteria are met.

3 The post-treatment efficacy and safety follow-ups may be conducted by telephone for participants who are discharged from the hospital at the time.

3.2 Determination of Sample Size

CCI [redacted]

3.3 Endpoints

3.3.1 Efficacy Variables

Primary:

- Proportion of participants who progress to level >4 of modified WHO ordinal scale due to COVID-19 by Day 14

Key Secondary:

- Change in room air SpO_2 from baseline over time
- Change in NEWS 2 symptom score from baseline over time
- Change from baseline on the modified WHO ordinal scale at each visit up to Day 28
- Time to improvement to a lower level (<4) of modified WHO ordinal scale
- Time to progression to a higher level (>4) of modified WHO ordinal scale

Additional Secondary:

- Time to hospital discharge
- Incidence of mortality by Day 28

3.3.2 Safety Variables

- Clinical safety laboratory measurements
- Physical examinations
- Vital signs
- Concomitant medications
- Cumulative incidence of AEs and Severe AEs
- Incidence of participants unable to tolerate nebulization due to:
    - Reduction in SpO2 to < 90%, unless well clinically tolerated according to Investigator's opinion
    - Other clinical signs of intolerance according to Investigator's opinion
- Incidence of clinical bronchial hyper-responsiveness related to nebulization

3.4 Exploratory Variables

- CCI [redacted]

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Presentation Considerations

Baseline is the last available pre-treatment assessment. All assessments should have time collected. If time is not collected and date of assessment is the same as the *first dose date,* then assessment will be assumed to be collected prior to treatment unless schedule of assessments and protocol indicate planned collection is always after dosing.

Day-of-Discharge (DoD) is the day when patient is discharged from the hospital.

Durations are calculated as the stop date minus the start date plus one.

For elapsed time (e.g. time since the initial diagnosis), if the reference date is on or after the event date, then the elapsed time is the reference date minus the event date plus one. If the reference date is before the event date, then the elapsed time is the reference date minus the event date.

If more than one laboratory value is available for a given study day, the first valid observation will be used in summaries and all observations will be presented in listings. If it is not possible to determine which is the first measurement due to missing times, then the average of all measurements for that time point will be used as the value for that time point.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

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

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

4.3 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

4.4 Study Patients

4.4.1 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion. Summaries will include:

- The number of patients randomized.
- Number and percentage of patients randomized by country
- The number and percentage of patients treated (with any amount of study drug).
- Number of patients in the analysis populations
- Number and percentage of patients who completed treatment
- Number and percentage of patients who were discharged from the hospital prior to Day 10.
- Number and percentage of patients withdrew early from treatment (including reasons for early withdrawal)
- Number and percentage of patients who withdrew early from the study (including reasons for early withdrawal)

By-patient listings of randomization details, visit dates, and withdrawal details (including reason for discontinuation and duration of treatment prior to discontinuation) will also be provided.

4.4.2 Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of major protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis population (see Section 4.5 for descriptions of analysis populations), both including and excluding data potentially affected by major protocol deviations.

A patient will be classified as having a protocol deviation if one incurs an event belonging to any one of the following categories: 1) violation of the inclusion/exclusion criteria; 2) taking prohibited medications or treatments; 3) treatment misallocation; 4) violation of discontinuation criteria; 5) error in procedure and tests; and 6) missed visits (including procedures and tests).

Major protocol deviations and any action to be taken regarding the exclusion of patients are defined in the study protocol deviation specifications. The final determination of major protocol deviations and the exclusion of patients from any of the analysis populations will be made prior to database lock.

A summary of the number and percentage of patients with a major protocol deviation by treatment arm as well as by type of deviation will be provided. Also, a by-patient listing of major protocol deviations will be provided.

4.5 Analysis Sets

- The intent-to-treat (ITT) population will include all randomized participants. The ITT participants will be analyzed according to randomized treatment, irrespective of the actual treatment received. Participants who withdraw from treatment early will be followed for the assessment of the Day 14 primary endpoint. All efficacy analyses will be performed using the ITT Population.

- The per-protocol (PP) population will include all participants in the ITT Population with no major protocol deviations that may significantly impact data integrity or patient safety. The PP Population will be used for supportive analyses of the efficacy measurements.

- The safety (SP) population will include all randomized participants who inhale any amount of study intervention or are randomized to the control arm. The SP will be analyzed according to the actual treatment received. The SP will be analyzed according to the actual treatment received. This set will be used for the safety analyses.

The efficacy summaries and analyses will be based on the ITT population**.** In the event that a patient is allocated the incorrect study treatment as per the study randomization list, patients will be summarized and analyzed ‘as randomized’ (i.e. by randomized treatment arm). In the event that a patient is stratified incorrectly, ‘randomized stratum’ will be used rather than ‘actual stratum’. The PP Population will be used to demonstrate robustness of results for the primary efficacy endpoint

The safety summaries and analyses will be based on the SP population. In the event that a patient is allocated the incorrect study treatment as per the study randomization list, patients will be summarized and analyzed ‘as treated’ (i.e. by allocated treatment arm).

A by-patient listing of analysis population details will be provided. This listing will be presented by treatment arm and will include: center, patient identifier, inclusion/exclusion flag for each population, and reason for exclusion from each population.

4.6 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by treatment group and overall using the ITT population. The summaries provided will include the following:

- Demographic variables:
  - Age (continuous and categorical (<65 years; ≥65years))
  - Sex
  - Race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White; Other; Multiple)
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
  - Baseline Height
  - Baseline Weight
  - Baseline Body Mass Index (BMI)
  - Pregnant (Yes, No)

- Baseline disease characteristics:
  - Randomization strata (country; comorbidity category)
  - SARS-CoV-2 Status (positive, negative, borderline, intermediate)
  - SpO_2, FiO_2, CCI [redacted]
  - Baseline WHO Ordinal Scale
  - Baseline NEWS Total Score
  - Days since onset of symptoms
  - Baseline diastolic blood pressure (<=90 mmHg, >90 mmHg)
  - Baseline systolic blood pressure (<=140 mmHg, >140 mmHg)
  - Baseline Temperature

Medical history will be reported by system organ class and preferred term as coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher.

Age will be reported as calculated in the study database at day of informed consent. BMI will be calculated from baseline height and weight as weight (kg) / height^2 (m^2).

By-patient listings of demographic data and other baseline characteristics will be provided.

4.7 Prior, Concomitant Medication and Prohibited Medication

Prior and concomitant medications will be summarized by drug class and preferred medication name by treatment group and for both treatment groups combined (Total) using the ITT population. Prior and concomitant medications will be summarized separately, concomitant medications will also be summarized overall and by study period. WHO DDE March 2020 will be used to classify medications.

Medication start and stop dates will be compared to the date of first dose of study drug to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only.

Missing or partial start dates will be imputed as described in Section 4.9.1.3. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study drug will be classified as Prior only. If a medication starts before the date of first dose of study drug and stops on or after the date of first dose of study drug, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study drug.

Rescue medication of a ready-to-use nebulization of a bronchodilator will be allowed on study. The number and percentages of the patients using such medications will be summarized by treatment groups, and the impact on efficacy and safety will be analyzed by subgroup analyses.

By-patient listings of prior, concomitant and rescue medications will be provided. Listings will also be provided for any concomitant procedures reported.

4.8 Treatment Compliance

Compliance with study treatment will be assessed via relative dose intensity (RDI). Relative dose intensity is defined as 100% times the actual dose intensity (ADI) divided by the intended dose intensity (IDI). Actual dose intensity for a patient is defined as the total dose received over all treatment days divided by the sum of the lengths of all treatment days. The intended dose intensity is the total dose assigned over all treatment days divided by the sum of the intended lengths of all treatment days. The assigned dose for **RESP301+SOC** is 6.0 mL per treatment administration taken three times a day for 10 days.

For example. the intended dose intensity (IDI) for RESP301 for a patient who completed 10 days of treatment three times a day would be:

6.0 mL* 3 * 10 days/10 days = 18.0 mL

Summaries of ADI, IDI, and RDI will be presented for patients on the RESP301+SOC arm. The average number of dosing days will be presented as well.

A by-patient listing of study treatment compliance data will also be provided, containing the date of randomization, the date of last dose of study treatment, and the calculated RDI. A by-patient listing of exposure data will be provided.

4.9 Efficacy Evaluation

4.9.1 Analysis and Data Conventions

This study is designed to test for superiority. The null hypothesis for the treatment comparison will be that there is no difference in the rate of progression to level 5 and above of the WHO 7-point ordinal scale in RESP301 + SOC compared to SOC alone. The alternative hypothesis is that RESP301 +SOC reduces the rate of progression to level 5 and above in the modified WHO ordinal scale in COVID-19 at Day 14. Symbolically, this is expressed as follows:

H_0: $pWHO5+_{RESP301+SOC} \geq pWHO5+_{SOC}$
H_a: $pWHO5+_{RESP301+SOC} < pWHO5+_{SOC}$

4.9.1.1 Multi-center Studies

All centers will be pooled together in the efficacy analyses. If the results reveal impact of the centers, then ad hoc analyses will be performed. In that case, the centers may be grouped by geographic regions and evaluation of the consistency of treatment effects across geographic regions may be performed.

4.9.1.2 Adjustments for Covariates

The primary efficacy analysis will be adjusted for the following baseline covariates:

1. Country
2. No risk factor (none of the criteria listed in Section 3.1), one risk factor (one single of the criteria in Section3.1) or high-risk factor (2 or more of the criteria).

4.9.1.3 Handling of Dropouts or Missing Data

Any patients that are discharged from the hospital prior to Day 14 due to improvement of clinical status and their status on Day 14 cannot be obtained, then the Last Observation Carried Forward (LOCF) approach will be used to impute missing data. Only post-treatment observations will be carried forward. No baseline observations will be carried forward. To assess the robustness of the study conclusions to the choice of imputation method, a complete-case analysis (all patients with missing data for the primary endpoint are excluded from analysis) will be performed as a sensitivity analysis.

The Per-protocol population analyses will be performed using the same imputation method as for the ITT population analyses.

If the proportion and/or pattern of missing data is found to be different to that assumed, additional sensitivity analyses may be required.

In general, imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in the time to event analyses.

Imputed dates will not be displayed in listings unless otherwise stated.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

- D='Day': indicates that the day portion of the date is imputed
- M='Month': indicates that the month and day portions of the date are imputed
- Y='Year': indicates that the entire date (year, month, and day) is imputed

Imputing partial AE and prior/concomitant medication start dates:

a) If the year is unknown, the date will not be imputed and will be assigned a missing value.

b) If the month is unknown, then:
    1. If the year matches the first dose date, then impute to the month and day of the first dose date.
    2. Otherwise, assign ‘January’.

c) If the day is unknown, then:
    1. If the month and year match the first dose date, then impute to the day of the first dose date.
    2. Otherwise, assign ‘01’.

Imputing partial AE and prior/concomitant medication stop dates:

a) If the year is unknown, the date will not be imputed and will be assigned a missing value.
b) If the month is unknown, then assign ‘December’.
c) If the day is unknown, then impute to the last day of the month.

Imputing partial death dates:

a) If the month and/or year are unknown, the death date will not be imputed.
b) If the day is missing, then assign ‘01’.
c) If imputing the first day of the month results in a negative overall survival time, the patient will be censored for overall survival at the randomization date.

A patient data listing will be provided showing all patients with missing values for the primary endpoint. For these patients, the listing will provide all observed data relating to the primary endpoint (i.e. all measurements recorded prior to the missing value, any measurements recorded after the missing value, important baseline characteristics, the recorded reason for study discontinuation, and the date of study discontinuation). The listing will also provide the imputed date(s) used in the primary analysis.

4.9.1.4 Multiple Comparisons/Multiplicity

To account for the multiple testing due to the second interim analysis an adjustment for the type-I-error probability will be applied using the Haybittle-Peto approach with one sided alpha=0.0005 at the second interim analysis and leave one-sided nominal alpha of 0.0249 for the final analysis.

4.9.1.5 Interim Analyses

Two interim analyses will be performed.

1. The first analysis will be conducted when about 60 participants (40 participants in the RESP301+SOC arm and 20 participants in the SOC arm) have completed the Day 10 assessment. The purpose of this analysis is to evaluate efficacy of RESP301 with the application of a futility criterion based on the results on SpO_2 change from baseline on Day 10. The following futility criterion will be used for this first interim analysis:

If the difference in the percentage of participants with at least a 2% improvement in SpO2 between both treatment arms is less than 5%, benefit of RESP301 treatment is not expected. For a final decision to stop the study for futility the results on other endpoints associated with safety and efficacy will be considered as well.

As no other modification of the study at the time of the first interim analysis is considered, no adjustment of the alpha level is required.

2. The second interim analysis will be conducted after 150 participants (100 participants in the RESP301+SOC arm and 50 participants in the SOC arm) have completed the Day 14 assessment. The purpose of this analysis is the assessment of futility or a sample size re-estimation (increase only) in case the actual results differ from the original assumptions for the power calculations of the study, related to the percentage of participants meeting the primary endpoint in the control arm and/or the relative treatment benefit achieved in the RESP301+SOC arm compared to the SOC arm.

To account for the multiple testing due to the second interim analysis an adjustment for the type I error alpha will be applied using the Haybittle-Peto approach which would spend one sided alpha=0.0005 at the second interim analysis and leave one-sided nominal alpha of 0.0249 for the final analysis. The futility criterion for the second interim analysis will be based on the conditional power (CP) for the final results based on the assumption that the remainder of the study will follow the same trend as observed in the interim analysis. If CP at the time of the second interim analysis is less than 20% consideration will be given to stop the study for futility. At the same time sample size re-estimation will be performed to achieve 80% power at the end of the study.

4.9.1.6 Examination of Subgroups

The treatment effect for the primary and key secondary efficacy endpoints will be examined for the following subgroups:

1. Country
2. Age >65 years
3. Ongoing or currently treated diabetes mellitus
4. Ongoing or currently treated hypertension
5. Ongoing or currently treated cardiovascular disease
6. Ongoing or currently treated chronic lung disease
7. Cancer history of less than 3 years, basal cell skin carcinoma excluded
8. Ongoing or currently treated chronic kidney disease

Summaries of the primary and key secondary efficacy variables by treatment group and subgroups will be produced. No formal statistical analysis will be performed within subgroup.

With reviewing the results, the homogeneity of the treatment effect across subgroups may be investigated using graphical and analytical methods.

4.9.2 Primary Efficacy Variable

Progression to level >4 of modified WHO ordinal COVID-19 scale by Day 14"

The WHO 7-point ordinal scale is as follows:

1. Not hospitalized, no limitations on activities;
2. Not hospitalized, limitation on activities;
3. Hospitalized, not requiring supplemental oxygen;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, on non-invasive ventilation or high-flow oxygen devices;
6. Hospitalized, on invasive mechanical ventilation or ECMO;
7. Death.

The percentage and corresponding 95% CI of patients who progress to a level >4 on the WHO 7-point ordinal scale on Day 14 will be summarized by treatment arm and overall. The odds ratio of RESP301 + SOC versus SOC alone and 95% CI intervals and p-values will be estimated using the CMH stratified by country and number of risk factors (as randomized).

WHO 7-point ordinal scale will be assessed daily while patient is hospitalized. Daily scores and changes from baseline will be summarized. Plots of mean score (with standard error bars) by treatment group over time may be produced.

4.9.3 Secondary Efficacy Variables

Other secondary and exploratory endpoints will be analyzed according to the type of endpoint as described below. If data are sparse for any of the exploratory endpoints, summaries may be limited to descriptive statistics of available data or listings only as appropriate. By-patient listings of all secondary and exploratory efficacy endpoint data will be provided.

NEWS 2 scores

The NEWS is based on a simple aggregate scoring system in which a score is allocated to physiological measurements, already recorded in routine practice, when patients present to, or are being monitored in hospital (**Error! Reference source not found.**). Six simple physiological parameters form the basis of the scoring system:

1. Respiration rate
2. Oxygen saturation
3. Systolic blood pressure
4. Pulse rate
5. Level of consciousness or new confusion*
6. Temperature

**The patient has new-onset confusion, disorientation and/or agitation, where previously their mental state was normal – this may be subtle. The patient may respond to questions coherently, but there is some confusion, disorientation and/or agitation. This would score 3 or 4 on the Glasgow Coma Scale (rather than the normal 5 for verbal response), and scores 3 on the NEWS system.*

Standard descriptive statistics (mean, standard deviation, median, minimum, maximum) and change from baseline will be used to summarize each of these scores by treatment group and visit. NEWS scores will be assessed daily while patient is hospitalized. Plots of mean score (with standard error bars) by treatment group over time may be produced.

Figure 2: The National Early Warning Score 2 (NEWS 2) scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Mortality at Day 28

Incidence of mortality by Day 28 is the number of patients who have died by Day 28 and the percentage of patients reaching this endpoint will be summarized by treatment group. A CMH test will be used to test for a treatment effect of RESP301 + SOC versus SOC Alone after adjusting for baseline clinical status. Odds ratios of the treatment effect (RESP301 + SOC versus SOC Alone) with corresponding 95% confidence intervals (CI) will be estimated using a logistic regression model with baseline clinical status as a covariate. A treatment by baseline clinical status interaction may be added to the model along with other covariates of interest.

Overall survival will also be analyzed using time to event methods. Time to death is defined as the time from treatment start to death in days (*date of death – first dose date + 1*). Patients without a recorded death will be censored at their completion or at their early discontinuation date if they withdrew early or at their date of last assessment if they are alive and ongoing in study at time of analysis (*completion date/early discontinuation date/last assessment date – first dose date +1*). Reasons for censoring will be summarized.

The total number of patients with an event, the total number censored and Kaplan-Meier survival estimates with associated 95% CI (25th percentile, median, and 75% percentile, proportion surviving at Days 7, 10, 14, and 28) will be presented by treatment group. A survival plot will be produced with the probability of an event (0 to 100%) along the Y-axis and time in days along the X-axis.

The number of patients at risk will be presented along the X-axis. The hazard ratio of RESP301 + SOC versus SOC Alone with corresponding 95% CI and p-values will be estimated from a Cox Proportional model adjusting for treatment, and patients randomized strata.

A by-patient listing of the primary efficacy data will be provided

Time to hospital discharge survival

Time to hospital discharge is the time in the hospital after first study treatment in days *(date of discharge - first dose date + 1).* Patients who die before leaving the hospital will be considered failures (did not achieve hospital discharge), *date of death – first dose date +1)* and censored. In the case that a patient is still hospitalized at time of analysis or withdraws from the study before leaving the hospital, they will be censored at their date of last assessment in the data cut or early discontinuation date, respectively.

The time to hospital discharge survival will be analyzed using Kaplan-Meier methods. If data allows, survival estimates will be stratified by baseline clinical status. The Cox models adjusting for baseline randomization strata may be performed.

Time to Improvement

Time to improvement is the time in which the patient sees a decrease after first study treatment in the WHO 7-point ordinal scale from baseline to a value <4 in days *(date of decrease in WHO scale - first dose date + 1).* In the case that a patient has not decreased in the WHO scale at time of analysis or withdraws from the study before leaving the hospital, they will be censored at their date of last assessment in the data cut or early discontinuation date, respectively.

Time to improvement will be analyzed using the Kaplan-Meier methods as described in the above time to event analyses.

Time to Progression

Time to improvement is the time in which the patient sees an increase after first study treatment in the WHO 7-point ordinal scale from baseline to a value > 4 in days *(date of increase in WHO scale - first dose date + 1).* In the case that a patient has not increased in the WHO scale at time of analysis or withdraws from the study before leaving the hospital, they will be censored at their date of last assessment in the data cut or early discontinuation date, respectively.

Time to progression will be analyzed using the Kaplan-Meier methods as described in the above time to event analyses.

A by-patient listing of the key secondary efficacy data will be provided.

Change from baseline in respiratory outcomes

Respiratory outcomes include the secondary endpoint of SpO_2 and the exploratory endpoint CCI .

Standard descriptive statistics (mean, standard deviation, median, minimum, maximum) will be used to summarize each outcome and it's change from baseline by treatment group at Day 10. Only scheduled visits as described in the schedule of assessments (Section 1.3 of protocol) will be included for each endpoint.

Patients who showed an increase 2% or higher in SpO2 from baseline at Day 7 will be flagged and summarized. Patients who have a reduction in SpO2 to < 90% will be flagged and summarized.

In addition, the least square means and least square mean difference (RESP301 + SOC – SOC Alone) along with their respective 95% CIs and p-values will be presented. Least square means and mean difference will be estimated using a Mixed Model with Repeated Measurements (MMRP) /Analysis of Covariance (ANCOVA) with the treatment, patient's country and risk group as randomized and visit as the model terms, and baseline value as the covariate and change from baseline as the dependent variable. Patients will be included as a random effect and an unstructured covariance structure will be specified in the initial model. If the model fails to converge alternative covariance structures will be applied in the following order: heterogenous compound symmetry, compound symmetry.

A by-patient listing of the primary efficacy data will be provided.

4.10 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.5.

4.10.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher.

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.

Treatment-related AEs are those with reasonable causality to study drug marked as "related" or "possibly related" on the eCRF. AEs with an outcome of death are those with a grade of 5 or an outcome of "fatal." AEs leading to treatment withdrawal are those with a study drug action taken of "drug withdrawn," while AEs leading to study drug dose reduction or interruption are those with a study drug action taken of "dose reduced" or "drug interruption", respectively.

Summary tables will be presented for AEs by treatment arm. An overall presentation of AE information will include the following:

- Number and percentage of patients with at least one AE
- Number and percentage of patients with at least one AE of Grade 3 or higher
- Number and percentage of patients with at least one treatment-related AE
- Number and percentage of patients with at least one treatment-related AE of Grade 3 or higher
- Number and percentage of patients with at least one serious AE
- Number and percentage of patients with at least one treatment-related serious AE
- Number and percentage of patients with at least one AE leading to death
- Number and percentage of patients with at least one treatment-related AE leading to death
- Number and percentage of patients with at least one AE leading to treatment withdrawal
- Number and percentage of patients with at least one treatment-related AE leading to treatment withdrawal
- Number and percentage of patients with at least one AE leading to dose reduction
- Number and percentage of patients with at least one treatment-related AE leading to dose reduction
- Number and percentage of patients with at least one AE leading to dose interruption
- Number and percentage of patients with at least one treatment-related AE leading to dose interruption

AE information will also be presented by NCI CTCAE severity grade and by relationship to study treatment. If a patient had more than one occurrence of an AE, the most severe grade will be used in the summary tables.

The following summaries will be provided:

- Number and percentage of patients for each AE, categorized by SOC and PT
- Number and percentage of patients for each AE of Grade 3 or higher, categorized by SOC and PT
- Number and percentage of patients for each AE, categorized by SOC, PT, and maximum CTCAE grade
- Number and percentage of patients for each AE, categorized by SOC, PT, and relationship to study drug
- Number and percentage of patients for each treatment-related AE, categorized by SOC and PT
- Number and percentage of patients for each treatment-related AE of Grade 3 or higher, categorized by SOC and PT
- Number and percentage of patients for each treatment-related AE, categorized by SOC, PT, and maximum CTCAE grade
- Number and percentage of patients for each treatment-related AE leading to treatment withdrawal, categorized by SOC and PT

Counts will be by patient, not by event, and patients are only counted once within each SOC or PT. For tables categorized by maximum CTCAE grade, patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.

A by-patient listing of all AEs will be provided. This listing will be presented by treatment arm and will include: center, patient identifier, age, gender, race, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, CTCAE grade, seriousness, action taken, outcome, and relatedness. The following AE listings will also be provided using a similar layout:

- Patients who died during the study
- Patients with treatment-emergent SAEs
- Patients with treatment withdrawal due to AEs
- Patients with dose reduction due to AEs
- Patients with dose interruption due to AEs

For missing or partially missing dates, imputation will be done according to Section 4.9.1.3.

Disease Related Outcomes Not Qualifying AE/SAEs

The following disease-related events (DREs) are common in participants with COVID-19 and can be serious/life-threatening:

- Fever
- Cough*
- Dyspnea*
- Asthenia
- Loss of sense of taste and smell

** A cough or dyspnea episode related to study intervention administration does not meet the definition of a DRE and should be reported as an AE.*

Because these events are typically associated with the disease under study, they will not be reported as AEs.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

4.10.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Additional, significant AE summaries that will be provided are:

- Number and percentage of patients with serious AEs
- Number and percentage of patients with treatment-related serious AEs
- Number and percentage of patients with fatal AEs

All summaries will follow the same criteria as mentioned in Section 14.10.1.

4.10.3 Clinical Laboratory Evaluation

Local laboratories will be used for laboratory safety evaluations in this study. For a list of the parameters to be evaluated, see Table 1. Laboratory normal ranges will be provided by the local laboratory. For parameters where an NCI CTCAE v.5.0 scale exists, laboratory results will be graded according to the NCI CTCAE v.5.0 severity grade. For parameters for where an NCI CTCAE v.5.0 scale does not exist, an indicator of whether the value is below, within, or above the normal range will represent severity instead.

All laboratory values will be reported in SI units.

Summaries for each laboratory parameter will be presented by treatment group and visit. For by-visit summaries, the first non-missing assessment (including repeat assessments) recorded at each visit will be used. Optional laboratory parameters will not be summarized by dose group, only listed.

For laboratory values reported as a character value, such as <40, will be transformed into numerical values for summary reasons by following the specified guidelines. If a laboratory value is reported using the less than symbol, '<', 0.10 will be subtracted from the original numeric value. If a laboratory value is reported using the greater than symbol, '>', 0.10 will be added to the original numeric value.

Shifts in grade from baseline to the maximum shift(across all visits) will be summarized by treatment group.

A by-patient listing of all laboratory data, with abnormal values flagged, will be provided by treatment group. This listing will include patient identifier, age, gender, race, and visit, as well as laboratory reference ranges for each parameter.

Table 1 List of Laboratory Parameters

Clinical Chemistry	Hematology
Blood urea nitrogen Potassium Sodium Aspartate Aminotransferase Total and Direct Bilirubin Creatinine Glucose non-fasting Chloride Bicarbonate/CO_2 Serum Glutamic-Oxaloacetic Transaminase Alanine Aminotransferase Serum Glutamic-Pyruvic Transaminase Alkaline phosphatase Lactate dehydrogenase	White blood cell (WBC) count red blood cell (RBC) count hemoglobin hematocrit mean corpuscular volume mean corpuscular hemoglobin mean corpuscular hemoglobin concentration red cell distribution width platelet mean platelet volume Methemoglobin
	Coagulation
	Prothrombin Time International Normalized Ratio Activated Partial Thromboplastin Time

To assess Hy's Law, the number and percentage of patients with potentially clinically significant post-baseline elevations in hepatic parameters shown in Table 2 below will be summarized by treatment.

A listing of the patients with potentially clinically significant post-baseline hepatic elevations will be provided. The listing will contain all a subject's values for parameters meeting the criteria.

Table 2. Potentially Clinically Significant Elevations in Hepatic Parameters

ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured

* ALT = Alanine aminotransferase;

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.

4.10.4 Vital Signs, Physical Findings and Other Observations Related to Safety

Summaries for each vital sign parameter will be presented by treatment arm and visit. Observed and change from baseline values in vital sign results will be analyzed using descriptive statistics. Change from baseline will only apply to post-baseline assessments.

For systolic blood pressure (SBP) and diastolic blood pressure (DBP), observed values will be classified as abnormal. The criteria for determining abnormal values are as follows:

- SBP <90 mmHg or >=160 mmHg
- DBP <60 mmHg or >=90 mmHg

The number and percentage of patients with abnormal change values will be summarized for each vital sign parameter by treatment arm and visit.

Shifts in ECG results, from baseline to each post-baseline visit (where available) will be summarized by treatment arm. The maximum shift (across all visits) in ECG results from baseline will also be summarized by treatment arm.

By-patient listings of vital sign data, ECG results, and physical examination results will be provided by treatment arm.

4.10.5 Independent Data Monitoring Committee [IDMC]

An IDMC will be responsible for closely reviewing the safety and efficacy data from the interim analyses and for providing their recommendations on continuation of the study. The IDMC will meet to review after 10 and 20 participants have completed as well as at the time of the two interim analyses (i.e., after 60 and 150 participants have completed; see Section 4.9.1.5).

The IDMC Charter will provide additional details about the IDMC activities. Table 3 outlines the IDMC meetings.

Table 3: Scheduled IDMC Meetings

Meeting	Timing	Review Type
1st Data Review Meeting	After 10 patients	Safety
2nd Data Review Meeting	After 20 patients	Safety
1st Interim Analysis Meeting	After 60 patients have completed Day 10	Safety/ Futility/ Change in SpO2
2nd Interim Analysis Meeting	After 150 patients have completed Day 14	Safety/ Futility/ Superiority/ Sample Size Reassessment

4.11 Determination of Sample Size

CCI

[redacted]

4.12 Changes in the Conduct of the Study or Planned Analysis

Updates to the planned analyses will be documented in this section.

5 REFERENCES

[1] Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. *Biometrics*. 1999;55(3):853-857. doi:10.1111/j.0006-341x.1999.00853.x

[2] SAS® Version 9.2 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

6 APPENDIX A

Table with examples for the adaptive sample size procedure described in Section 4.11 using Cui/Hung/Wang (CHW) approach using a weighted test for the final analysis

2nd IA results with n=150 patients (50 for SOC, 100 for RESP301+SOC		**CP under observed trend for planned 300**	**Total sample size required for CP 80% under observed trend**	**CP under observed trend if total sample size capped by 600**
15 (30%)	5 (5%)	$p < 0.0005$ → early stop for superior efficacy		
15 (30%)	10 (10%)	99%	Not applicable	Not applicable
15 (30%)	15 (15%)	90%	Not applicable	Not applicable
15 (30%)	18 (18%)	66%	393	Not applicable
15 (30%)	19 (19%)	55%	483	Not applicable
15 (30%)	21 (21%)	34%	[798]	[67%]
15 (30%)	26 (26%)	3.99%	Early stop for futility	
12 (24%)	10 (10%)	92%	Not applicable	Not applicable
12 (24%)	12 (12%)	77%	321	Not applicable
12 (24%)	14 (14%)	54%	498	Not applicable
12 (24%)	15 (15%)	42%	[646]	[77%]
12 (24%)	18 (18%)	14%	[1800]	[31%]
12 (24%)	20 (20%)	2.6%	Early stop for futility	
10 (20%)	8 (8%)	85%	Not applicable	Not applicable

10 (20%)	10 (10%)	64%	412	Not applicable
10 (20%)	11 (11%)	50.4%	534	Not applicable
10 (20%)	13 (13%)	26%	[1014]	[55%]
10 (20%)	15 (15%)	10%	[2460]	[23%]
10 (20%)	18 (18%)	1.4%	Early stop for futility	

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Reason for signing: Approved	PPD Date of signature: 16-Jul-2020 17:47:42 GMT+0000

Reason for signing: Approved	PPD Date of signature: 13-Aug-2020 12:12:54 GMT+0000

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