Clinical trial results:
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 World Health Organization (WHO) grade 3 & 4 (NOCoV2)

Summary

EudraCT number	2020-002120-37
Trial protocol	GB
Global end of trial date	21 May 2021

Results information

Result version number	v1 (current)
This version publication date	26 May 2022
First version publication date	26 May 2022

Trial information

Trial identification

Sponsor protocol code	RESP301-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Thirty Respiratory Limited
Sponsor organisation address	1 Red Place, London, United Kingdom, W1K 6PL
Public contact	Clinical department, Thirty Respiratory Limited, +44 (0)1235 431 201, contact@30.technology
Scientific contact	Clinical department, Thirty Respiratory Limited, +44 (0)1235 431 201, contact@30.technology

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (e.g. advertisements) were submitted to an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study was initiated.
This study was conducted in accordance with the protocol and with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines; Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines; Applicable laws and regulations. Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
The Investigator or his/her representative explained the nature of the study to the participant or his/her legally authorized representative and answered all questions regarding the study.
Participants were informed that their participation was voluntary. Participants or their legally authorized representative were required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	29 July 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 19
Worldwide total number of subjects	19
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	3
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 2 centers in the United Kingdom (UK) that enrolled 19 participants from29-Jul-2020 (first subject first visit) to 21-May-2021 (last subject's last visit).

Pre-assignment

Screening details:

The screening period was 2 days. All the study assessments were performed as per the schedule of assessment.
Participants were randomized in the ratio 2:1 to the investigational arm or the control arm either inhaled RESP301 in addition to the standard of care (SoC) or SoC alone.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This is open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	RESP301+SoC

Arm description:

Participants received inhaled RESP301 administered using a nebulizer three times a day (TID) for up to 10 days in addition to the standard of care (SoC).

Arm type	Experimental
Investigational medicinal product name	RESP301
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Participants received inhaled RESP301 administered using a nebulizer (6 mL; Delivered dose (62 mg) sodium nitrite (NaNO2)) TID (every 8 hours) with at least 6 hours between 2 consecutive doses for up to 10 days.

Investigational medicinal product name	Standard of Care (SoC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Participants received institutional SOC alone for the treatment of COVID-19.

Arm title	Standard of Care (SoC)

Arm description:

Participants received institutional SOC alone for the treatment of COVID-19.

Arm type	Active comparator

Investigational medicinal product name	Standard of care (SoC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Participants received institutional SoC for the treatment of COVID 19.

Number of subjects in period 1	RESP301+SoC	Standard of Care (SoC)
Started	14	5
Completed	10	4
Not completed	4	1
Consent withdrawn by subject	1	-
Lost to follow-up	3	1

Baseline characteristics

Reporting groups	
Reporting group title	RESP301+SoC
Reporting group description:	
Participants received inhaled RESP301 administered using a nebulizer three times a day (TID) for up to 10 days in addition to the standard of care (SoC).	
Reporting group title	Standard of Care (SoC)
Reporting group description:	
Participants received institutional SOC alone for the treatment of COVID-19.	

Reporting group values	RESP301+SoC	Standard of Care (SoC)	Total
Number of subjects	14	5	19
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	59.6	58.8	
standard deviation	± 10.94	± 8.53	-
Gender categorical Units: Subjects			
Female	7	2	9
Male	7	3	10

End points

End points reporting groups

Reporting group title	RESP301+SoC
Reporting group description:	
Participants received inhaled RESP301 administered using a nebulizer three times a day (TID) for up to 10 days in addition to the standard of care (SoC).	
Reporting group title	Standard of Care (SoC)
Reporting group description:	
Participants received institutional SOC alone for the treatment of COVID-19.	

Primary: Proportion of Participants Who Progress by at Least One Level Higher on the Modified WHO Ordinal Scale

End point title	Proportion of Participants Who Progress by at Least One Level Higher on the Modified WHO Ordinal Scale[1]
End point description:	
A modified WHO ordinal scale was used for consistency with the recent study in adults hospitalized with severe COVID-19, to record the participant's status at the time of assessment. The modified WHO ordinal scale included the following levels : 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 extracorporeal membrane oxygenation (ECMO); 7= Death. Higher scores mean worse outcomes. The proportion of participants who progress by at least one level higher on the modified WHO ordinal scale was assessed. The intent-to-treat (ITT) population included all randomized participants.	
End point type	Primary
End point timeframe:	
Baseline, Day 2 and Day 3	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis is available for the primary endpoint.	

End point values	RESP301+SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	5		
Units: Count of Participants				
Baseline : WHO 7-point ordinal scale: 1	0	0		
Baseline : WHO 7-point ordinal scale: 2	0	0		
Baseline : WHO 7-point ordinal scale: 3	0	0		
Baseline : WHO 7-point ordinal scale: 4	1	0		
Baseline : WHO 7-point ordinal scale: 5	0	0		
Baseline : WHO 7-point ordinal scale: 6	0	0		
Baseline : WHO 7-point ordinal scale: 7	0	0		
Baseline : WHO 7-point ordinal scale: >3	1	0		
Day 2 : WHO 7-point ordinal scale: 1	0	0		
Day 2 : WHO 7-point ordinal scale: 2	0	0		
Day 2 : WHO 7-point ordinal scale: 3	0	0		
Day 2 : WHO 7-point ordinal scale: 4	1	0		
Day 2 : WHO 7-point ordinal scale: 5	0	0		

Day 2 : WHO 7-point ordinal scale: 6	0	0		
Day 2 : WHO 7-point ordinal scale: 7	0	0		
Day 2 : WHO 7-point ordinal scale: >3	1	0		
Day 3 : WHO 7-point ordinal scale: 1	0	0		
Day 3 : WHO 7-point ordinal scale: 2	0	0		
Day 3 : WHO 7-point ordinal scale: 3	0	0		
Day 3 : WHO 7-point ordinal scale: 4	0	0		
Day 3 : WHO 7-point ordinal scale: 5	1	0		
Day 3 : WHO 7-point ordinal scale: 6	0	0		
Day 3 : WHO 7-point ordinal scale: 7	0	0		
Day 3 : WHO 7-point ordinal scale: >3	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change Time in Room Air Oxygen Saturation (SpO2) From Baseline Over Time

End point title	Change Time in Room Air Oxygen Saturation (SpO2) From Baseline Over Time

End point description:

Pulse oximetry measurements were performed to evaluate SpO2. The effect of RESP301 as measured by room air SpO2 was assessed.
The intent-to-treat (ITT) population included all randomized participants.
Justification: 9999.9999 is an arbitrary number that refers to 0 participant being present in the arm for specific timepoints; data was not available.
99.99 is an arbitrary number that refers to Post-dose nebulization that did not occur in the SOC arm on Day 1. Soc arm data is not applicable.

End point type	Secondary

End point timeframe:

Day 1 (Baseline), Day 2, 3, 4, 5, 6, and 7

End point values	RESP301+SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	5		
Units: Percentage change of Spo2				
arithmetic mean (standard deviation)				
Day 1 - Change from baseline (n=11,5)	0.1 (± 2.84)	99.99 (± 99.99)		
Day 2- Change from baseline (n=9,2)	-1.7 (± 4.09)	1.5 (± 2.12)		
Day 3- Change from baseline (n=8,3)	0.9 (± 2.80)	3.3 (± 2.08)		
Day 4- Change from baseline (n=5,3)	1.4 (± 2.61)	3.0 (± 2.00)		
Day 5- Change from baseline (n=4,3)	0.3 (± 1.26)	4.0 (± 1.0)		
Day 6- Change from baseline (n=2,2)	-1.0 (± 1.41)	4.5 (± 3.54)		
Day 7- Change from baseline (n=2,0)	3.0 (± 2.83)	9.999 (± 9.999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in National Early Warning Score (NEWS) 2 Symptom Score From Baseline Over Time

End point title	Change in National Early Warning Score (NEWS) 2 Symptom Score From Baseline Over Time

End point description:

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. 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.
Each score is 0–3 and individual scores are added together for an overall score. An additional two points are added if the patient is receiving oxygen therapy. The total possible score ranges from 0 to 20. The higher the score the greater the clinical risk. Higher scores indicate the need for escalation, medical review and possible clinical intervention, and more intensive monitoring.
Justification: 9999.9999 is an arbitrary number that refers to 0 participant being present in the arm for specific timepoints; data was not available.

End point type	Secondary

End point timeframe:

Day 1 (Baseline), Day 2, 3, 4, 5, 6, and 7

End point values	RESP301+SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	5		
Units: Score on a NEWS scale				
arithmetic mean (standard deviation)				
Change from Baseline: Day 2 (n=12, 5)	-0.8 (± 1.99)	1.4 (± 0.89)		
Change from Baseline: Day 3 (n=9,5)	-1.3 (± 1.87)	-0.2 (± 1.3)		
Change from Baseline: Day 4 (n=5,4)	1.0 (± 2.55)	0.5 (± 0.58)		
Change from Baseline: Day 5 (4,4)	-2.0 (± 3.37)	-0.5 (± 3.11)		
Change from Baseline: Day 6 (n=2,3)	-1.5 (± 2.12)	-2.0 (± 0.00)		
Change from Baseline: Day 7 (n=2,0)	-1.0 (± 2.83)	9999.9999 (± 9999.9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline for Number of Participants on the Modified WHO Ordinal Scale at Each Visit

End point title	Change From Baseline for Number of Participants on the Modified WHO Ordinal Scale at Each Visit

End point description:

A modified WHO ordinal scale was used for consistency with the recent study in adults hospitalized with severe COVID-19, to record the participant's status at the time of assessment. The modified WHO ordinal scale included the following levels : 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 extra corporeal membrane oxygenation (ECMO); 7= Death. Higher scores mean worse outcome. Change from baseline for Number of participants on the modified WHO ordinal scale was assesed.
The intent-to-treat (ITT) population included all randomized participants.

End point type	Secondary

End point timeframe:

Day 1 (Baseline), Day 2, 3, 4, 5, 6, and 7

End point values	RESP301+SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	5		
Units: Count of Participants				
Day 2: Modified WHO 7-point ordinal scale -3	0	0		
Day 2: Modified WHO 7-point ordinal scale -2	0	0		
Day 2:Modified WHO 7-point ordinal scale -1	4	0		
Day 2: Modified WHO 7-point ordinal scale 0	8	5		
Day 2: Modified WHO 7-point ordinal scale 1	0	0		
Day 2: Modified WHO 7-point ordinal scale 2	0	0		
Day 2: Modified WHO 7-point ordinal scale 3	0	0		
Day 2: Modified WHO 7-point ordinal scale 4	0	0		
Day 3: Modified WHO 7-point ordinal scale -3	0	0		
Day 3: Modified WHO 7-point ordinal scale -2	3	1		
Day 3: Modified WHO 7-point ordinal scale -1	1	0		
Day 3: Modified WHO 7-point ordinal scale 0	4	4		
Day 3: Modified WHO 7-point ordinal scale 1	1	0		
Day 3: Modified WHO 7-point ordinal scale 2	0	0		
Day 3: Modified WHO 7-point ordinal scale 3	0	0		
Day 3: Modified WHO 7-point ordinal scale 4	0	0		
Day 4: Modified WHO 7-point ordinal scale -3	0	0		
Day 4: Modified WHO 7-point ordinal scale -2	1	0		

Day 4: Modified WHO 7-point ordinal scale -1	0	0		
Day 4: Modified WHO 7-point ordinal scale 0	4	4		
Day 4: Modified WHO 7-point ordinal scale 1	0	0		
Day 4: Modified WHO 7-point ordinal scale 2	0	0		
Day 4: Modified WHO 7-point ordinal scale 3	0	0		
Day 4: Modified WHO 7-point ordinal scale 4	0	0		
Day 5: Modified WHO 7-point ordinal scale -3	0	0		
Day 5: Modified WHO 7-point ordinal scale -2	2	1		
Day 5: Modified WHO 7-point ordinal scale -1	0	2		
Day 5: Modified WHO 7-point ordinal scale 0	2	1		
Day 5: Modified WHO 7-point ordinal scale 1	0	0		
Day 5: Modified WHO 7-point ordinal scale 2	0	0		
Day 5: Modified WHO 7-point ordinal scale 3	0	0		
Day 5: Modified WHO 7-point ordinal scale 4	0	0		
Day 6: Modified WHO 7-point ordinal scale -3	0	0		
Day 6: Modified WHO 7-point ordinal scale -2	0	2		
Day 6: Modified WHO 7-point ordinal scale -1	1	0		
Day 6: Modified WHO 7-point ordinal scale 0	1	0		
Day 6: Modified WHO 7-point ordinal scale 1	0	0		
Day 6: Modified WHO 7-point ordinal scale 2	0	0		
Day 6: Modified WHO 7-point ordinal scale 3	0	0		
Day 6: Modified WHO 7-point ordinal scale 4	0	0		
Day 7: Modified WHO 7-point ordinal scale -3	0	0		
Day 7: Modified WHO 7-point ordinal scale -2	1	0		
Day 7: Modified WHO 7-point ordinal scale -1	0	0		
Day 7: Modified WHO 7-point ordinal scale 0	0	0		
Day 7: Modified WHO 7-point ordinal scale 1	0	0		
Day 7: Modified WHO 7-point ordinal scale 2	0	0		
Day 7: Modified WHO 7-point ordinal scale 3	0	0		
Day 7: Modified WHO 7-point ordinal scale 4	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement of at Least One Level Lower on the Modified WHO Ordinal Scale

End point title	Time to Improvement of at Least One Level Lower on the Modified WHO Ordinal Scale

End point description:

Time to improvement is the time in which the participant 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 would be censored at their date of last assessment in the data cut or early discontinuation date, respectively.
The intent-to-treat (ITT) population included all randomized participants.

End point type	Secondary

End point timeframe:

From Baseline to Day 28

End point values	RESP301+SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	5		
Units: day				
median (full range (min-max))	4.00 (2.00 to 10.50)	5.00 (3.00 to 5.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression of at Least One Level Higher on the Modified WHO Ordinal Scale

End point title	Time to Progression of at Least One Level Higher on the Modified WHO Ordinal Scale

End point description:

Time to progression 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 would be censored at their date of last assessment in the data cut or early discontinuation date, respectively.
The intent-to-treat (ITT) population included all randomized participants.
Justification: 999.99 is an arbitrary number that refers to only 1 participant was evaluable, hence Median and Full range is not calculable.

End point type	Secondary

End point timeframe:

From Baseline to Day 28

End point values	RESP301+SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0[2]		
Units: day				
median (full range (min-max))	999.99 (999.99 to 999.99)	(to)		

Notes:

[2] - Data is not available.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events

End point description:

AEs (non-serious) as variables of safety and tolerability of RESP301 were assessed.
The safety analysis set included the safety population (SP) would include all randomized participants who inhale any amount of study intervention or were randomized to the control arm. The SP would be analyzed according to the actual treatment received. This set will be used for the safety analyses.

End point type	Secondary

End point timeframe:

From screening to safety follow up (Day 28)

End point values	RESP301+SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	5		
Units: Participants				
Participants with at least one AE	10	2		
Participants with at least 1 AE of Grade 3/ higher	1	0		
Participants with at least 1 treatment-related AE	3	0		
Participants with at least one severe AE	1	0		
At least 1 AE leading to study drug withdrawal	3	0		
Atleast 1 treatment-related AE leading to withdraw	1	0		
At least one AE leading to dose interruption	1	0		
Atleast 1 treatment-related AE lead to interrupt	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Hospital Discharge

End point title	Time to Hospital Discharge

End point description:

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 would be considered failures (did not achieve hospital discharge) 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 would be censored at their date of last assessment in the data cut or early discontinuation date, respectively.

End point type	Secondary

End point timeframe:

Day 10

End point values	RESP301+SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	5		
Units: day				
median (full range (min-max))	4.00 (3.00 to 6.00)	6.00 (5.00 to 6.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Mortality

End point title	Number of Participants with Mortality

End point description:

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 would be summarized by treatment group.
The safety analysis set included the safety population (SP) would include all randomized participants who inhale any amount of study intervention or were randomized to the control arm. The SP would be analyzed according to the actual treatment received. This set will be used for the safety analyses.

End point type	Secondary

End point timeframe:

Day 28

End point values	RESP301+SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	5		
Units: Count of Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in Oxygen Saturation (SpO2) to <90%

End point title	Reduction in Oxygen Saturation (SpO2) to <90%

End point description:

Room Air SpO2 for a summary of participants with reduction to < 90%, unless well clinically tolerated according to Investigator's opinion was assessed.
The intent-to-treat (ITT) population included all randomized participants.
Justification: 99.999 is an arbitrary number that refers to Post-dose nebulization that did not occur in the SOC arm on specific timepoints. Soc arm data is not applicable.
999.99 is an arbitrary number that refers to only 1 participant was evaluable, hence SD is not calculable.
9999.9999 is an arbitrary number that refers to 0 participant being present in the arm for specific timepoints; Data not available.

End point type	Secondary

End point timeframe:

Day 1 (Baseline), Day 2, Day 3

End point values	RESP301+SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	5		
Units: Percentage of SpO2				
arithmetic mean (standard deviation)				
Day 1 Pre-Nebulization (n=1,0)	95.0 (± 999.99)	9999.9999 (± 9999.9999)		
Day 1 Post-Nebulization (n= 2,5)	93.5 (± 2.12)	99.999 (± 99.999)		
Day 2 Pre-Nebulization (n=1,0)	94.0 (± 999.99)	9999.9999 (± 9999.9999)		
Day 2 Post-Nebulization (n=1,5)	86.0 (± 999.99)	99.999 (± 99.999)		
Day 3 Pre-Nebulization (n=1,0)	96.0 (± 999.99)	9999.9999 (± 9999.9999)		
Day 3 Post-Nebulization (n=1,5)	94.0 (± 999.99)	99.999 (± 99.999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Events of Clinical Bronchial Hyper Responsiveness Related to Nebulization

End point title	Events of Clinical Bronchial Hyper Responsiveness Related to Nebulization

End point description:

Incidence of clinical bronchial hyper responsiveness related to nebulization was assessed. Oxygen saturation decreased and wheezing was assessed as an incidence of clinical bronchial hyper-responsiveness related to nebulization, requiring temporal increase of supplemental oxygen.
The safety analysis set included the safety population (SP) would include all randomized participants who inhale any amount of study intervention or were randomized to the control arm. The SP was analyzed according to the actual treatment received. This set was used for the safety analyses.

End point type	Secondary

End point timeframe:

From screening to safety follow up (Day 28)

End point values	RESP301+SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	5		
Units: Events	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From screening to safety follow up (30 days)	
Adverse event reporting additional description:	
Severe AEs is defined as an event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	RESP301+SoC
Reporting group description:	
Participants received inhaled RESP301 administered using a nebulizer three times a day (TID) for up to 10 days in addition to the standard of care (SoC).	
Reporting group title	Standard of Care (SoC)
Reporting group description:	
Participants received institutional SOC alone for the treatment of COVID-19.	

Serious adverse events	RESP301+SoC	Standard of Care (SoC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 5 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	RESP301+SoC	Standard of Care (SoC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 14 (71.43%)	2 / 5 (40.00%)	
Investigations			
Oxygen Saturation Decreased			
subjects affected / exposed	2 / 14 (14.29%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Liver Function Test Increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

Lymphocyte Count Decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 14 (7.14%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Loss Of Consciousness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 14 (7.14%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Abdominal Pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 14 (7.14%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Oropharyngeal discomfort			
subjects affected / exposed	2 / 14 (14.29%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Dyspnoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Haemoptysis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Respiratory Tract Infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

Sepsis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 5 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2020	The original protocol was updated to include important safety guidelines for RESP301 administration for the first 10 participants (i.e., up to the first IDMC safety review). It was also updated to align with the IB Version 2.0, dated 27 May 2020.
10 June 2020	The protocol was updated to clarify that staggered dosing was required for all participants treated before completion of the first IDMC review, and to clarify exclusionary criteria and monitoring of mHb. Information was added to ensure that Investigators are aware of the potential risk of interaction between NO and other NO donor agents.
16 September 2020	The amendment included changes to (a) expand the inclusion criteria to allow enrolment also of patients in hospital with COVID-19 but not yet requiring supplemental oxygen, (b) to allow a minor temporary temperature excursion in the storage conditions of RESP301 to facilitate transport from the manufacturer to the clinical site or from the clinical site pharmacy to the bedside, and (c) to raise the exclusionary level for mHb to >2%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported