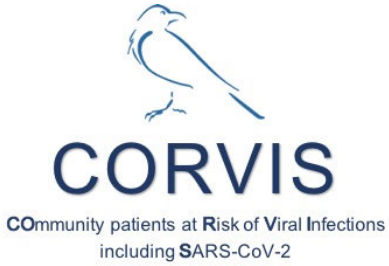
CLINICAL STUDY PROTOCOL



Protocol Title:	Community participants with COPD or bronchiectasis and at risk of Respiratory Viral Infections including SARS-CoV-2: An open-label, multicentre feasibility study of an inhaled nitric oxide generating solution (RESP301)
Short Title:	**CO**mmunity patients at **R**isk of **V**iral **I**nfections including **S**ARS-CoV-2 (CORVIS)
Compound:	RESP301
Indication:	COPD and bronchiectasis
Study Sponsor:	Thirty Respiratory Limited 1 Red Place, London, W1K 6PL, United Kingdom
Chief Investigator:	Professor [redacted], Newcastle Hospitals, UK
Protocol Number:	RESP301-005
Study Phase:	Phase 2
IRAS ID:	290709
EudraCT No:	2020-004951-34
Approval Date of Current Version:	18 November 2021
Dates and Versions of Previous Protocols:	v.2.0 07DEC20; v.3.0 08FEB21; v.4.0 26JUL21

PROTOCOL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Chief Investigator:

[redacted]

Sponsor Signatory:

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Version**	**Date**
Original Protocol	Version 1.0	20NOV20
Protocol v.2.0 (safety information added [redacted]	Version 2.0	07DEC20
Protocol v.3.0 (exclusion criteria [redacted] clarified [redacted]; spirometry requirements clarified in [redacted] clarified the conditions for continuing diaries post treatment in [redacted]	Version 3.0	08FEB21

DOCUMENT HISTORY		
Document	**Version**	**Date**
Protocol v.4.0 (changes in relation to [redacted] Dose Finding Phase: [redacted] minor clarifications to [redacted] exclusion criteria; [redacted]; new safety data added; [redacted] other minor clarifications)	Version 4.0	26JUL21
Protocol v. 5.0 Changes in relation to [redacted] Part 1 and [redacted] specifying bronchodilator dose and requirement for using it with a spacer device	Version 5.0	18NOV21

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1 Study Synopsis

Title	Community participants with COPD or bronchiectasis and at risk of Respiratory Viral Infections including SARS-CoV-2: An open-label, multicentre feasibility study of an inhaled nitric oxide generating solution (RESP301)
Short title	**CO**mmunity patients at **R**isk of **V**iral **I**nfections including **S**ARS-CoV-2 (CORVIS)
Protocol number	RESP301-005
IRAS ID	290709
EudraCT number	2020-004951-34
Phase	Phase 2
Sponsor	Thirty Respiratory Limited
Chief Investigator	Professor Anthony De Soyza, Newcastle Hospitals, UK
Rationale	Nitric Oxide (NO) is a potent antimicrobial produced naturally in the human body and is a key component of our defence against microbial infection in the lung. Gaseous NO is an approved product for treatment of pulmonary hypertension in neonates and has already been delivered as a potential pulmonary vasodilator in COPD. RESP301 readily produces NO and has distinct advantages over gaseous NO by delivering a more targeted and localised delivery. RESP301 is a formulation consisting of 3 agents already used in clinical practice: mannitol, sodium nitrite and citric acid. RESP301 is administered as nebulised fine particle droplets via a handheld nebuliser. *In vitro*, RESP301 has been shown to be highly effective against a range of respiratory viruses, including SARS-CoV-2 and influenza strains, and multiple types of bacteria. RESP301 is currently being used as treatment for hospitalised COVID-19 patients in an ongoing randomised controlled trial. Community patients with pre-existing respiratory disease are at higher risk of adverse outcomes such as hospitalisation and/or death due to exacerbations caused by SARS-CoV-2 or other respiratory infections. This study will first determine the maximum tolerated dose of RESP301 in patients with COPD or bronchiectasis, and will then assess the feasibility of recruiting and retaining these patients and treating them with RESP301 in the community at onset of viral infection symptoms. Additionally, we will collect safety, tolerability and disease symptom data.
Objectives	**Primary objectives:**

	• To determine the maximum tolerable dose (MTD) and recommended therapeutic dose (RTD) of single agent RESP301 in patients with mild to moderate COPD or bronchiectasis • To assess the feasibility of administering RESP301 safely at the MTD with the co-administration of a short acting bronchodilator • To assess the feasibility of recruiting and retaining patients with COPD or bronchiectasis who have viral infection symptoms and treating these patients with RESP301 in a community setting. **Secondary objectives:** The following secondary objectives will be considered for the cohort as a whole, and in addition for a sub-cohort of those who have confirmed SARS-CoV-2 infection: • To assess the safety and tolerability of single doses of RESP301 in patients with COPD or bronchiectasis, who are at high risk of SARS-CoV-2 and other acute respiratory pathogens. • To assess the safety and tolerability of RESP301 and a pre-dose short acting bronchodilator (two inhalations of Ventolin [redacted]) in patients with COPD or bronchiectasis. • To collect preliminary data on the efficacy of RESP301 in treating exacerbations in patients with COPD or bronchiectasis.
Intervention/treatment	RESP301 is delivered by vibrating mesh nebuliser at least 4 hours apart. Each dose of RESP301 is an admixture of [redacted] sodium nitrite, [redacted] mannitol and [redacted] citric acid, buffered at pH [redacted] **Part 1(a): Dose Finding Phase** The MTD of RESP301 will be determined in order to obtain the RTD for the Expansion Phase. **Part 1(b): Concomitant Medication Expansion Phase** Up to 8 patients with COPD or bronchiectasis will be enrolled into a cohort to receive a short acting inhaled broncholdilator through a spacer device 10 minutes before receiving a single test dose of RESP301 at the MTD

	Part 2: Expansion Phase A test dose of RESP301 at RTD will be administered during the baseline visit under clinical supervision in a minimum of 50 patients. Patients who tolerate the test dose will progress to the Dormant Period to which a further 100 participants will also be recruited with or without a test dose (depending on review of safety data after the first 50 patients). Participants in the Dormant Period will inform the clinical team if symptoms develop indicative of a possible respiratory infection (exacerbation) and will then progress to the Treatment Period, in which eligible participants receive RESP301 by courier or at a subsequent clinic visit for treatment by self-administration at home. During the Treatment Period, RESP301 is taken at the RTD three times a day at least 4 hours apart for 7 days alongside normal Standard of Care (SOC) (treatment period may extend into Day 8 depending on time of commencing on Day 1). During the Treatment Period participants may use rescue medication as required.
Comparator	Not applicable
Study design	This is a single arm, non-randomised, open-label study. **Part 1(a): Dose Finding Phase** Up to 48 eligible participants will be administered single ascending doses of RESP301 under clinical supervision to determine the MTD, according to the following schedule: • 8 participants to receive RESP301 at a dose of 1 ml • 8 participants to receive RESP301 at a dose of 2 ml • 8 participants to receive RESP301 at a dose of 3 ml • 8 participants to receive RESP301 at a dose of 4 ml • 8 participants to receive RESP301 at a dose of 5 ml • 8 participants to receive RESP301 at a dose of 6 ml Safety data will be reviewed by the PIs and Sponsor after each dose before proceeding to the next higher dose. Safety data will include: • Treatment-related Adverses Events including troublesome cough, chest pain or tightness, bronchospasm or dyspnoea the patients finds intolerable • Changes in FEV1 • Changes in methaemoglobin level

	Provided that individual stopping criteria are not met in ≥ three participants, and there are no serious adverse events that are at least possibly related to RESP301, the next dose cohort can be enrolled. Subjects can be enrolled into more than one dose cohort provided they did not meet individual stopping criteria from any given prior dose. A Safety Advisory Committee will review the data from the 8 participants in Part 1(a) and determine a Maximum Tolerated Dose(MTD) and Recommended Therapeutic Dose (RTD). **Part 1(b): Concomitant Medication Expansion Phase** Up to 8 eligible participants will be administered a single dose of RESP301 at the MTD under clinical supervision to assess the effect (if any) of a short acting bronchodilator upon symptomatic or asymptomatic bronchial hyper-reactivity associated with nebulised RESP301. Administration will be according to the following schedule: • 8 participants to receive RESP301 at the determined MTD after pre-dosing with a short acting inhaled bronchodilator (2 inhalations of Ventolin - [redacted] per inhalation) through a spacer device 10 minutes before administration of RESP301. Once the Maximum Tolerated Dose (MTD) has been determined in Part 1(a), a cohort of 8 patients who are not experiencing an exacerbation will be recruited and RESP301 administered at the MTD but will in addition receive a single dose of a short acting bronchodilator (2 inhalations of Ventolin - [redacted] per inhalation) through a spacer device 10 minutes preceding administration of RESP301. The following parameters will be measured: • Assess response to RESP301 (incl. recording any AEs, FEV1 pre- and post dose and monitoring up to 1 hour post dose). Part 1 (b) will be conducted after an MTD and RTD have been determined in Part 1(a) but will not delay initiation of Part 2. A Safety Advisory Committee will review the data from the 8 participants in Part 1(b). Participants from cohorts 1(a) and 1(b) may also enter the Dormant and Treatment Phase of the study, as long as they meet eligibility criteria.

	Part 2: Expansion Phase Once the Recommended Therapeutic Dose has been determined in Part 1 (a), a minimum of 150 patients will be enrolled in to the Expansion Phase, which is split into 3 periods. For participants taking part in the Dose Finding Phase (Part 1), eligibility criteria will be reassessed prior to entering Part 2 of the trial. 1) Baseline visit In a minimum of 50 participants the following will be performed: • Administration of a test dose of RESP301, at the RTD • Assesses response to RESP301 (incl. recording any AEs, FEV1 pre- and post dose and monitoring methaemoglobin levels pre-, during and post- administration, using fingertip sensor; methaemoglobin level should be <=2% before, <=5% during, and <=3% at 30-60 mins post dose (i.e. if still >3% at 30 mins, check again at 60mins post dose). During the visit participants who satisfactorily tolerate the test dose will then be enrolled into the "dormant period" of the study for 12 months. An independent Data Monitoring Committee will review the data from the 50 participants that received the RTD. Based on the data from these participants, it will be decided whether test doses should be administered to further participants before enrolling them into the Dormant Period. 2) Dormant Period Dormant period patients are requested at the baseline visit, and monthly follow-up calls, to inform the study team if they develop exacerbation symptoms indicative of a respiratory infection. There will be no other study procedures or data collection during the "dormant study phase" unless the participant experiences exacerbation symptoms. 3) Treatment Period A patient who experiences exacerbation symptoms for at least 24 hours should contact the study team as soon as practicable to allow a study interaction to be undertaken remotely (via video link, if possible), within 72 hours of onset of at least one of the following: fever (>38.0°C), systemic malaise, increased cough or wheeze, increased sputum volume or increased purulence. During the remote visit the patient's symptoms will be discussed and if

	the patient is willing to continue in the study, they will have a rapid delivery of a study pack containing study IMP and nebuliser and other equipment for the trial. Note that if COVID-19 is suspected, the patient will be advised to follow the prevailing NHS guidance on testing for COVID-19 taking into account any specific recommendations for patients with COPD or bronchiectasis. Where serial SARS-CoV-2 swabs are undertaken, data will be collected for analysis. During the treatment period, lasting 7 days, at home/ community setting, patients will be asked to: • Administer RESP301 three times daily at the RTD • Take daily temperature measurements • Complete a daily diary to record treatment doses • Attend a daily call with study coordinator to check compliance, assist with issues with product, and report any AEs and changes to medications or medical history, including COVID-19 test results, if available Each participant will receive a maximum of one course of treatment of RESP301 during the study. Remote follow up visit will be carried out approximately 14 and 28 days following end of treatment to record any AEs and changes to medications or medical history, including COVID-19 test results, if available. Additionally, participants whose symptoms had not returned to baseline by the end of treatment period, will be followed up with a phone call 2 weeks post end of treatment.

Endpoints	**Primary endpoint:**
	• Proportion of patients tolerating RESP301 at each dose level in Part 1 (according to pre-defined criteria)
	• Feasibility of self-administering RESP301 treatment with nebuliser in terms of:
	  ○ percentage of patients who, having experienced and correctly reported an exacerbation, commence self-administeration of the treatment on the day the treatment is delivered
	  ○ compliance with RESP301 administration schedule over the treatment period: for those participants commencing treatment, the percentage of total doses taken
	Secondary endpoints:

	To be evaluated on the full cohort, and separately in the sub-cohort of those who test positive for SARS-CoV-2:
	• Safety and tolerability of RESP301 in terms of:
	  o % of participants able to tolerate the test dose in Parts 1(a), 1 (b) and 2
	  o Total counts and cumulative incidence of:
	  ▪ Adverse Events (AEs)
	  ▪ Serious Adverse Events (SAEs)
	  ▪ Suspected Unexpected Serious Adverse Reactions (SUSARs)
	  ▪ Severe AEs
	  ▪ Treatment-related AEs/SAEs
	• Feasibility in terms of percentage of patients who, having experienced and correctly reported an exacerbation, receive the treatment within 48 hours of reporting their exacerbation
	• Efficacy of RESP301 in terms of:
	  o % of participants recovered by Day 7 and Day 14 post starting treatment
	  o time to recovery (days until patient feels all their symptoms are back to their usual baseline (all VAS = 0))
	  o preventing exacerbation-related hospitalisation and/or death
	  o change in CCQ score

Duration of participation in the study	The overall study duration for each participant will be at most approximately 60 weeks, including one or more visits at a study centre in Parts 1/2, monthly follow-up calls, and, for those who experience an exacerbation, one week of treatment and additional monitoring calls at the beginning, during and following the treatment period.
Study population	Participants will be adult patients with spirometry-confirmed COPD or computerised tomography (CT) proven bronchiectasis, recruited from secondary and primary care sites in the UK.
Sample size	Part 1(a): We aim to recruit up to 48 participants. All participants who complete Part 1a, will also be eligible to enter Part 2 of the trial. Part 1(b): We aim to recruit 8 participants who are not experiencing an exacerbation. These participants will receive a short acting

	inhaled bronchodilator 10 minutes before receiving a single dose of RESP301 at the MTD. Participants from Part 1b may also enter Part 2 of the study if they fullfill eligibity criteria. Part 2: We aim to recruit 150 patients from secondary care and primary care sites in the UK (includes eligible participants from Part 1 of the study). A minimum of 50 consented participants will receive an initial test dose of RESP301. We estimate that over 12 months, a minimum of 30 of the enrolled participants will exacerbate. These participants will commence self-administered RESP301 treatment. Non-exacerbating participants will receive no further study interventions.
Inclusion criteria	1. Female of non-childbearing potential or male ≥35 years of age, at the time of signing the informed consent 2. Able and willing to provide informed consent 3. Spirometry-confirmed diagnosis of COPD (FEV1/FVC<0.7 post-bronchodilator at screen 1, or from historical data) or computerised tomography (CT) proven bronchiectasis 4. Part 1 only: FEV1 ≥50% predicted at screen 1 (i.e. FEV1 prior to any in-clinic administered short acting bronchodilator)
Exclusion criteria	1. Unable to safely use a nebuliser as required by the study according to Investigator's opinion 2. Severe COPD or bronchiectasis defined as FEV1 % predicted <20% or requiring non-invasive ventilation 3. History of methaemoglobinaemia 4. Baseline methaemoglobin concentration (using fingertip sensor) > 2% 5. Uncontrolled or severe asthma or history of severe bronchospasm 6. Presence of tracheostomy/inability to provide spirometry or contraindication for performing spirometry 7. Allergy to any of the components of the study intervention 8. Participation in other clinical investigations utilising investigational treatment within the last 30 days / 5 half-lives whichever is longer 9. Deemed unlikely to be able to adhere to protocol in view of investigator 10. Any subject who in the opinion of the investigator would not be best served by participating in this clinical trial

	11. Any unstable, uncontrolled or severe medical condition which in the opinion of the investigator would make the patient unsuitable for the trial 12. Participant lives at home with no other adults in the household (Part 2 only) 13. On long-term non-invasive ventilation and/or at higher risk of bronchospasm 14. Prescribed Nitric Oxide donating agent 15. Female of childbearing potential 16. Clinical diagnosis of COPD but Screening Visit spirometry at study centre excludes COPD (i.e. FEV1/FVC post bronchodilator ratio is not <0.7)
Study centres	The study will be conducted at two sites, Newcastle Hospitals, the NIHR National Patient Recruitment Centre, Newcastle, and the Medicines Evaluation Unit (MEU) Ltd.
Statistical planning	The primary objective is to determine the MTD of RESP301 and to assess the feasibility of recruiting and retaining patients with COPD or bronchiectasis who have viral infection symptoms and treating these patients with RESP301 in a community setting. No formal statistical planning has been carried out.

2 Abbreviations

AE	adverse event
CCQ	Clinical COPD Questionnaire
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRO	contract research organisation
CT	computerised tomography
DMC	Data Monitoring Committee
DRE	disease-related events
ECG	Electrocardiogram
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
mHb	Methaemoglobin
NHS	National Health Service
NO	Nitric oxide
NO_2	Nitrogen dioxide
NOx	Oxide of nitrogen
PEoT	Post End of Treatment
PP	Per protocol
RTD	Recommended therapeutic dose
SAC	Safety Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
SoA	Schedule of activities
SOC	Standard of care
SP	Safety population
SpO_2	Oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
TID	Three times daily
VAS	Visual Analogue Scale

3 Introduction

3.1 Background

Chronic obstructive pulmonary disease (COPD) and bronchiectasis are chronic lung conditions mainly affecting middle-aged or older adults. A Global Burden of Disease report in 2020 estimates COPD as being the 6th largest cause of wordwide disease burden (and the 3rd largest for those 75 years and older)(GBD 2019 Diseases and Injuries Collaborators, 2020). Bronchiectasis is less common but around 1,000 people die each year from the disease in England and Wales (Roberts and Hubbard, 2010).

COPD is characterised by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. COPD patients are prone to worsening of symptoms and lung function due to infection; these episodes are known as exacerbations. The frequency of exacerbations tends to increase in line with the severity of the undelying COPD. Furthermore, exacerbations contribute to the progression of the condition, being associated with a rapid decline in lung function and increased mortality.

One in eight emergency admissions in the UK is due to a COPD exacerbation, making it the second most common cause; 31% of patients were re-admitted to hospital within 30 days (British Thoracic Society, 2012; Devon LPC and Mediapharm, 2014). Exacerbations of COPD patients are most often caused by respiratory viruses, which tend to lead to more severe symptoms and hospitalisation; other triggers are bacterial infections, air pollutants and ambient temperature.

The occurrence of COPD exacerbations is linked to the stage of the disease, as seen in the ECLIPSE study in which the exacerbation rates were 0.85 per person for patients with moderate disease (GOLD stage 2) and 2.00 for those with very severe disease (GOLD stage 4; Hurst et al, 2010). Other factors for exacerbations were seasonal effects or inhalation of harmful substances, and epidemic peaks in exacerbations of COPD were noted in the autumn and winter months (Johnston & Sears, 2006). As with COPD, infections can also cause severe symptoms in patients with bronchiectasis who are particularly vulnerable to recurrent acute chest infections (Chalmers et al, 2018).

Of particular concern at the present time is the appearance of a new and potent coronavirus which has caused the global COVID-19 pandemic. The appearance of this deadly virus is of major concern for those patients with underlying lung conditions. Viral-detected exacerbations showed a larger decline in lung function and longer recovery time than non-viral exacerbations (Seemungal et al, 2001; Bafadhel et al, 2011). A critical factor is the tendency of viral infections to provoke secondary bacterial infections. Viral and sequential bacterial infections may be associated with severe respiratory symptoms (van der Molen et al, 2003

van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the clinical COPD questionnaire. Health Qual Life Outcomes. 2003; 28:1–13.

Wilkinson et al, 2006; Harper et al, 2009; Mallia et al, 2012).

A critical early component of innate host defence 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). The airway epithelium has highly efficient nitric oxide (NO) synthetic machinery which is amplified in viral infection. Healthy human airway epithelium has abundant expression of the endothelial enzyme NOS II due to continuous transcriptional activation of the gene in vivo. Loss of NO synthesis in lung diseases predisposes individuals to increased virus/microbe infection (Xu et al, 2006).

The physiological roles of NO and the enzymatic pathways for its synthesis via NO synthase have been clearly established for many years (Tucker et al, 2007). In particular, NO has been demonstrated to have potent anti-microbial properties against a wide range of pathogens. An alternative non-enzymatic synthetic pathway for NO synthesis has been developed, which generates NO and related higher oxides of nitrogen (NOx) via the chemical reactions of acidified nitrite (Hardwick et al, 2001, Tucker et al, 1999). A solution of co-mixed NO/NOx and ascorbic acid (RespiNOS), delivered by nebuliser, was found to be safe and well tolerated in healthy volunteers (Tucker et al, 2007). Spectral investigations further confirmed that there were no potentially harmful moieties present in the solution. The study concluded that RespiNOS had potential for use as a broad-spectrum anti-microbial agent in patients with chronic bronchial sepsis such as bronchiectasis, COPD, and cystic fibrosis.

Thirty Respiratory Limited has developed a NO-generating liquid designed to release NO in situ in the upper airways and deep in the alveolar spaces (RESP301). RESP301 is an admixture solution of two precursor solutions mixed together at point of care for immediate inhaled administration via a CE-marked handheld nebuliser and has specific advantages [redacted] over inhaled NO gas in treating a range of respiratory viruses, including SARS-CoV-2 in laboratory testing. RESP301 has also demonstrated potent activity against various influenza virus strains, rhinovirus and coronavirus. It has also shown high in vitro activity against respiratory pathogens, both viral and bacterial.

Key advantages of RESP301 over inhaled NO gas are:

- RESP301 demonstrates powerful evidence in vitro as a broad-spectrum anti-microbial;
- Treatment is quick, easy and portable using a standard handheld nebuliser;

- The formulation is nebulised and forms a fine particle mist that settles on the lung surface, at the point of infection, and is therefore a more targeted approach;
- NO production continues in-situ post treatment;
- Because of the design of the formulation, production of NO_2 is negligible by virtue of the NO_2 being rapidly converted to a NO donor species.

The novel concept for RESP301 is that it will restore the levels of NO in the lungs with a dual action of both killing virus and bacteria and boosting the host response against these pathogenic microbes.

RESP301 delivers NO in a specifically focused way and with a unique mode of action. It is an important evolutionary step in delivering NO that is more physiological and overcomes the technical difficulties and efficacy limitations of current NO gas therapy. [redacted] RESP301 has at least 3 distinct mechanisms of action in fighting virus infection [redacted] two of which are common to many viruses and one is very specific to coronaviruses, such as SARS-CoV-2:

- First it has a direct kill effect on the virus in the extracellular space. Nitric oxide-mediated nitrosylation of viral and host macromolecules appears to block viral replication and this has been demonstrated for several viruses (Saura et al, 1999; Basu et al, 1999). Enzymes, such as proteases (reverse transcriptases, and ribonucleotide reductase) which are vital for the life-cycle of the virus, are targets for nitric oxide nitrosylation (Benz et al, 2002; Chalmers et al, 2018
- Chalmers JD, Chang AB, Chotirmall SH, Dhar R, McShane PJ. Bronchiectasis. Nat Rev Dis Primers. 2018; 4:45.
- Colasanti et al, 1999).
- Second, in coronaviruses, like SARS-CoV-2, it specifically prevents membrane fusion of the S-protein (the spike protein that gives the virus its characteristic crown-like appearance) to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell.
- A third mechanism of action attacks the virus indirectly. Since viruses are non-living entities and do not have their own metabolism, they hijack the host cell's metabolic processes, and derive their energy and specific cellular substrates from the host cell.

Nitric oxide suppresses the virus-induced hyperactivity in the host cell and thereby deprives the virus of its crucial supply-chain.

[redacted]

As NO is naturally produced in most tissues and organs in the body, it is a well-tolerated and non-toxic compound. The exogenous supply of NO is therefore considered safe for human use, [redacted], RESP301 could be used as a prophylaxis against virus infection and in asymptomatic patients, as well as those with overt disease.

RESP301 has an additional advantage particularly in the context of COPD exacerbations where superimposed bacterial infection is a major cause of morbidity and mortality. RESP301 has been shown to be very active against [redacted]

RESP301 is therefore very well-positioned to be an effective agent against respiratory viruses and other microbial pathogens that cause exacerbations in COPD and justify its use in clinical trials. [redacted]

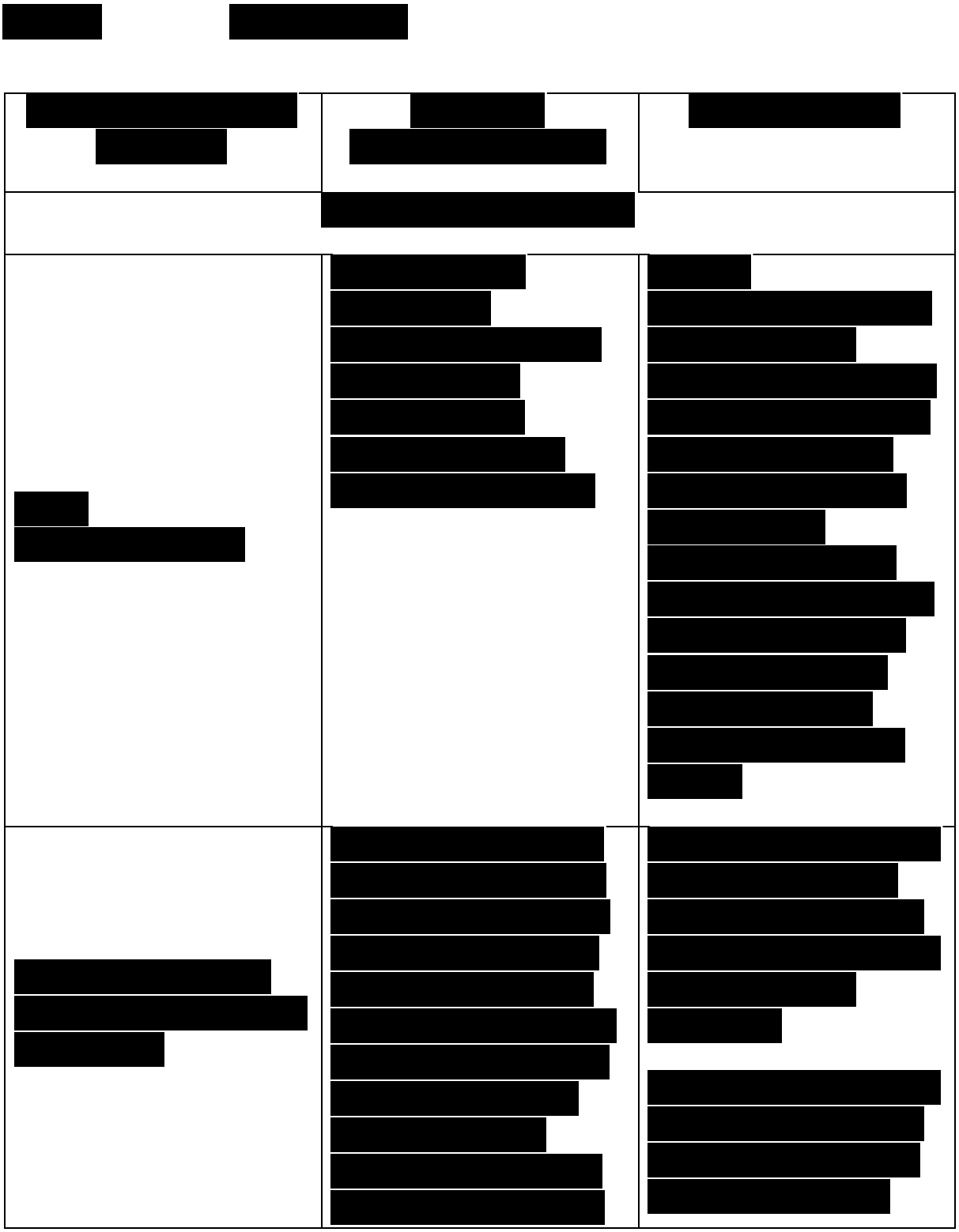
The proposed clinical trial will be an open-label, multicentre, feasibility study of an inhaled nitric oxide generating solution (RESP 301) in participants with COPD or bronchiectasis who are at risk of Respiratory Viral Infections, including SARS-CoV-2.

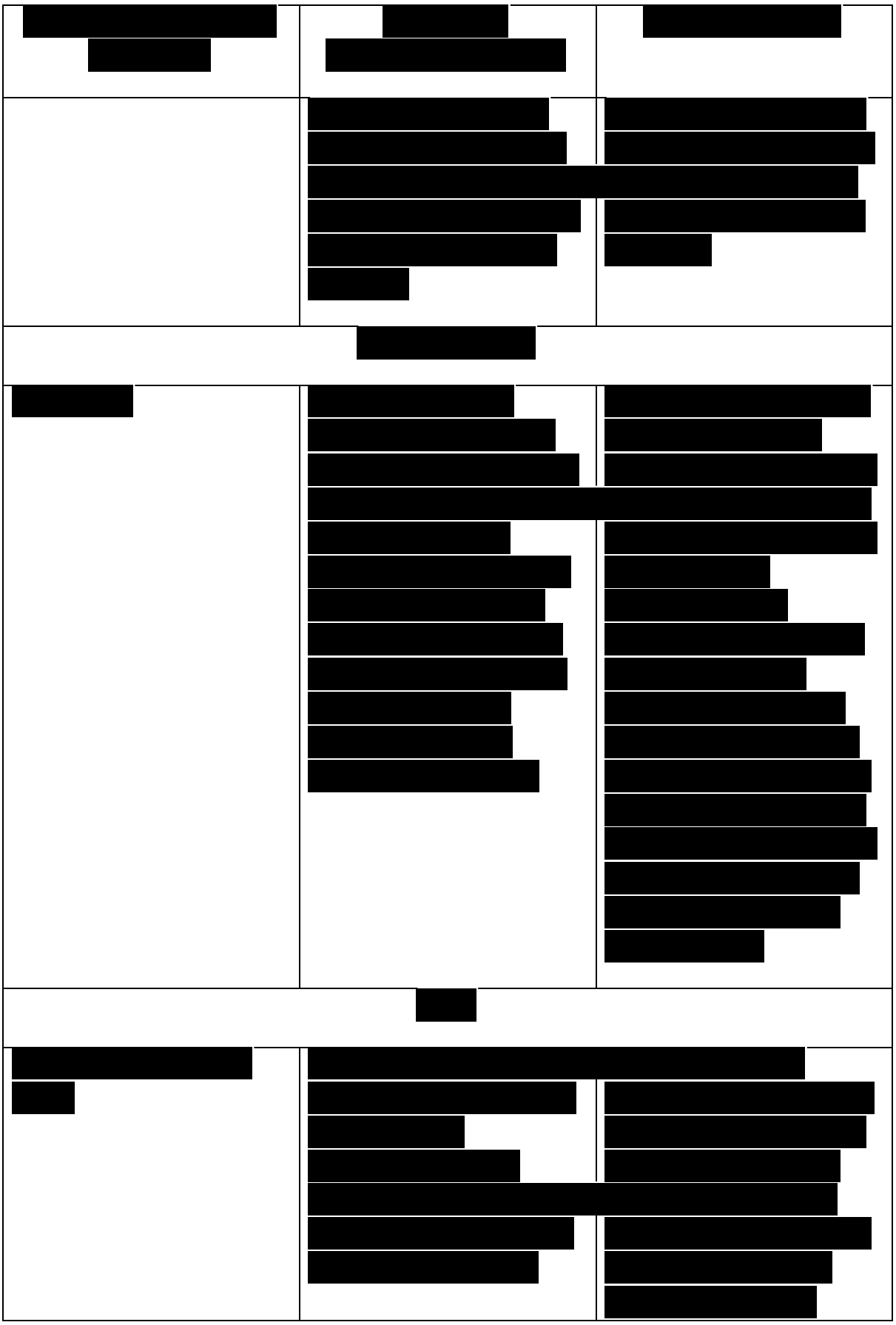
Patients in the community with pre-existing respiratory disease are at a higher risk of adverse outcomes such as hospitalisation and/or death due to exacerbations caused by SARS-CoV-2 or other respiratory infections. This study will assess the safety, tolerability and feasibility of recruiting and retaining these patients and treating them with RESP 301 in the community at onset of viral symptoms.

3.2 Benefit/Risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of RESP301 may be found in the Investigator's Brochure.

3.2.1 Risk assessment





Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	patient may increase risk of spread of disease	minimise the risk of spread of disease.

3.2.2 Benefit assessment

Patients with an underlying respiratory illness (e.g. COPD, bronchiectasis) are at higher risk of adverse outcomes due to exacerbations caused by SARS-CoV-2 or other respiratory infections. To date, no treatment of COVID-19 has demonstrated clinical efficacy. Patients and their physicians are critically in need of treatments that decrease the risk of severe levels of disease, particularly the rate of intubation or other ventilatory support as they significantly lead to fatal outcomes. Considering the current pandemic, even a limited improvement in the rate of progression to severe stage of the disease would provide sizable benefits for patients and society.

[redacted]

[redacted]

3.2.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants in this study, the potential risks identified in association with RESP301 are justified by the anticipated benefits that may be afforded to participants at high risk of adverse outcomes due to exacerbations caused by SARS-CoV-2 or other respiratory infections.

4 Objectives and endpoints

Table 4-1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the maximum tolerable dose (MTD) and recommended therapeutic dose (RTD) of RESP301 in patients with mild to moderate COPD or bronchiectasis • To assess the feasibility of recruiting and retaining patients with COPD or bronchiectasis who have viral infection symptoms and treating these patients with RESP301 in a community setting.	• Proportion of patients tolerating RESP301 at each dose level in Part 1 (according to pre-defined criteria) • Feasibility of self-administering RESP301 treatment with nebuliser [redacted]
Secondary	
The following secondary objectives will be considered for the cohort as a whole, and in addition for a sub-cohort of those who have confirmed SARS-CoV-2 infection: 1) To assess the safety and tolerability of RESP301 in patients with COPD or bronchiectasis, who are at high risk of SARS-CoV-2 and other acute respiratory pathogens.	To be evaluated on the full cohort, and separately in the sub-cohort of those who test positive for SARS-CoV-2: 1) Safety and tolerability of RESP301 [redacted]

Objectives	Endpoints
2) To collect preliminary data on the efficacy of RESP301 in treating exacerbations in patients with COPD or bronchiectasis.	○ [redacted] • Total counts and cumulative incidence of: • Adverse Events (AEs) • Serious Adverse Events (SAEs) • Suspected Unexpected Serious Adverse Reaction (SUSARs) • Severe AEs • Treatment-related AEs/SAEs Feasibility in terms of percentage of patients who, having experienced and correctly reported an exacerbation, receive the treatment within [redacted] of reporting their exacerbation 2) Efficacy of RESP301 [redacted]

5 Study design

5.1 Overall design

This is an open-label, single arm, multicentre study to investigate the feasibility, safety and tolerability of RESP301 in patients with pre-existing respiratory disease who are at higher risk of adverse outcomes such as hospitalisation and/or death due to exacerbations caused by SARS-CoV-2 or other respiratory infections. The study is conducted in a clinical setting in Part 1 [redacted] Part 2 of the study will assess the feasibility of recruiting and retaining these patients in a community setting [redacted]

Part 1(a): Dose Finding Phase

In Part 1(a), [redacted] subjects with COPD will be enrolled in separate cohorts to receive a single dose of [redacted] or [redacted] of RESP301. Each cohort will comprise [redacted] subjects. This part of the study will consist of one visit in which subjects receive a single dose of RESP301 in the clinic on Day 1, with a follow up safety phone call being conducted on the morning of Day 2 to check for any adverse events. Enrollment to these cohorts will be sequential and subsequent cohorts will only be enrolled after safety review of the previous cohort. The safety reviews will be conducted by the safety advisory committee (SAC), comprising the site Principal Investigators (or delegates) and the Sponsor's Executive Medical Officer as a minimum.

[redacted]

Subjects can receive more than one dose level as long as they did not meet individual stopping criteria from any given prior dose.

Part 1(b): Concomitant Medication Expansion Phase

In part 1(b) up to [redacted] patients with COPD or bronchiectasis will be enrolled into a cohort to receive a short-acting inhaled broncholdilator (2 inhalations of Ventolin - [redacted] per inhalation) through a spacer device 10 minutes before receiving a single dose of RESP301 at the MTD determined in part 1(a). Subjects will continue Standard of Care medication prior to receiving RESP301 apart from their usual short acting bronchodilators which will be withheld for [redacted] before dosing with RESP301. Pre-dose short acting bronchodilator will then be administered in clinic.

Subjects from Part 1a may also enter Part 1b (if deemed eligibile).

This part of the study will operate under the same oversight, monitoring and follow up criteria as Part 1(a)

Part 2: Expansion Phase

Baseline Visit

Once the RTD has been established in Part 1, [redacted]

- [redacted]

During the visit participants who satisfactorily tolerate the test dose will be enrolled into the "dormant period".

All patients including those receiving the test dose will undergo the following procedures

- Informed consent
- Inclusion and exclusion criteria
- Any medical assessments (e.g. heart or lung examination) which in the PI's opinion are required to assess whether the patient is suitable for the trial
- Demographic information
- Medical history and concurrent medications
- Height and weight
- Vital signs
- Pulmonary function tests (FEV1, FVC and % predicted), if required

Subjects that participate in Part 1 and do not meet any of the individual stopping criteria can enrol in Part 2. Eligibility criteria will be reassessed prior to entering Part 2 of the trial. Participants who have not satisfied inclusion/exclusion criteria will be excluded from continuing in the study.

An independent Data Monitoring Committee will review the data from the [redacted] participants that received RTD. Based on the data from these participants, it will be decided whether test doses should be administered to further participants for the remaining duration of the study.

Dormant period

A minimum of [redacted] patients will be enrolled into the dormant period and it is expected that approximately [redacted] patients will go on to receive treatment in the treatment period of the trial. The duration of the dormant period is from Day 1 of Part 2 of the trial, until the first exacerbation or end of study at week 52. During this period, monthly calls will be conducted.

Treatment period

A patient entered into the dormant period who experiences exacerbation symptoms for at least [redacted] will be eligible to enter the Treatment period. Patients will be instructed to contact the study team as soon as practicable to allow a study interaction to be undertaken remotely (via video link, if possible), within [redacted] of onset of at least one of the following:

- Fever (>38.0°C),
- Systemic malaise,
- Increased cough or wheeze,
- Increased sputum volume or increased purulence.

During the remote visit the patient's symptoms will be discussed and if the patient is willing to continue in the study, [redacted]

Note that if COVID-19 is suspected, the patient will be advised to follow the prevailing NHS guidance on testing for COVID-19 taking into account any specific recommendations for patients with COPD or bronchiectasis. Where serial SARS-CoV-2 swabs are undertaken, data will be collected for analysis.

During the treatment period, [redacted], at home/ community setting, patients will be asked to:

- Administer RESP301 [redacted] at the dose determined in Part 1 of the study (RTD).
- Take daily temperature measurements
- Complete a daily diary to record treatment doses

- Attend a daily call with study coordinator to check compliance, assist with issues with product, and report any AEs and changes to medications or medical history, including COVID-19 test results, if available.

[redacted]

[redacted]

[redacted]

In summary, the Part 2 of the study will involve the following visits/calls and study phases:

- Screening/Baseline Visit (Day 0), including test dose if required
- Dormant period (from Day 1, until the first exacerbation or end of study at week 52)
  - During this phase, monthly calls will be conducted
- Remote study visit ([redacted])
- Treatment period ([redacted])
  - During this phase, daily monitoring calls will be conducted; additionally, a call to collect [redacted] data will be conducted 1 day PEoT
- Follow-up period ([redacted]
  - Patients who still experience exacerbations symptoms at the end of the [redacted] treatment period will be asked to continue the study diary until symptoms return to baseline level (i.e. VAS score = 0), or until [redacted] after the end of treatment, whichever is sooner.
  - All patients will receive a follow-up call [redacted]
  - All patients will receive a final follow-up call [redacted]

The maximum total study duration from screening to last follow up will be [redacted] unless the participant experiences an exacerbation at the end of the [redacted] dormant period, in which case the study duration will be up to [redacted]

[redacted]

[redacted]

[redacted]

5.4 End of Study Definition

[redacted]

End of the study is defined as the last participant's last follow up call.

6 Study Population and Recruitment

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The study population will consist of male and female patients with [redacted] Participants must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria. [redacted] Participants can also be recruited through advertising on social media, newsletters, websites etc. using materials approved by the Research Ethics Committee.

6.1 Study Rationale

This is a single arm, non-randomised, multicentre, open-label study to determine [redacted].

Considering [redacted] the current public health emergency resulting from the COVID-19 pandemic, a Phase 2 study of RESP301 is considered reasonable in order to generate efficacy data in patients at risk of adverse outcomes such as hospitalisation and/or death due to exacerbations caused by SARS-CoV-2 or other respiratory infections.

6.2 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant is a female of non-childbearing potential or male [redacted] at the time of signing the informed consent.

Informed Consent

2. Participant is capable of giving signed informed consent as described in Section 11.2 [redacted]

Type of Participant and Disease Characteristics

3. Spirometry-confirmed diagnosis of COPD ([redacted] a) or CT proven bronchiectasis
4. [redacted]

6.3 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Unable to safely use a nebuliser as required by the study according to Investigator's opinion
2. Severe COPD or bronchiectasis defined [redacted]
3. History of methaemoglobinaemia
4. [redacted]
5. Uncontrolled or severe asthma or history of severe bronchospasm
6. Presence of tracheostomy/inability to provide spirometry or contraindication for performing spirometry
7. Any unstable, uncontrolled or severe medical condition which in the opinion of the investigator would make the patient unsuitable for the trial
8. On long-term non-invasive ventilation and/or at higher risk of bronchospasm
9. [redacted]

Prior/Concurrent Clinical Study Experience

10. Participation in other clinical investigations utilising investigational treatment within the last 30 days / 5 half-lives whichever is longer, excluding participation in Part 1 of this study

Other exclusions

11. Allergy to any of the components of the study intervention
12. Deemed unlikely to be able to adhere to protocol in view of investigator
13. Any subject who in the opinion of the investigator would not be best served by participating in this clinical trial
14. Participant lives at home with no other adults in the household (Part 2 only)
15. [redacted]
16. Female of childbearing potential [redacted]

6.4 Lifestyle Considerations

No restrictions are required.

6.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not subsequently meet all of the inclusion criteria or meet one or more of the exclusion criteria [redacted]

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6.6 Screening and Enrollment Log and Participant Identification Numbers

The participant's enrollment will be recorded in the Screening and Enrollment Log.

Upon enrollment, each participant will receive a unique participant identification number. Participant numbers must not be re-used for different participants.

7 Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1 Study Intervention Administered

Table 7-1 Study Intervention(s) Administered

Study Treatment	[redacted]
Intervention Name:	RESP301
Type:	Drug
Dosage Formulation:	Admixture for inhalation
Unit Dose Strength(s):	[redacted]
Dosage Level(s):	[redacted]
Route of Administration:	Inhalation
IMP and NIMP:	IMP
Sourcing:	RESP301 provided centrally by the Sponsor.
Dosing Instructions:	[redacted]
Packaging and Labeling:	[redacted]

7.1.1 Medical Devices

1. Medical device [redacted] provided for use in this study will be an FDA-approved and CE-marked [redacted] nebuliser.
2. Instructions for medical device use will be provided in the participant instruction manual which will be provided at the first study visit and with the device.

7.1.2 Device Training

Training will be provided to ensure all study staff are familiar with the device, [redacted] cleaning the device.

7.2 Preparation, Handling, Storage, and Accountability

7.2.1 Preparation of Study Intervention Product

RESP301 is prepared by mixing [redacted] in the nebuliser. The solution is to be nebulised within 5 minutes post mixing as per the instructions given in the SoA [redacted]

RESP301 is mixed in the nebuliser chamber before use following the steps below [redacted]

[redacted]

purpose of the aerosol is to deliver NO to the participant. [redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
	[redacted]		[redacted]

7.2.2 Storage and Accountability of Study Intervention at site

The Investigator or designee must document whether appropriate temperature conditions [redacted] have been maintained during storage for all study intervention received and any discrepancies are reported and resolved before use of the study intervention. [redacted]

Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer the test dose at site. All RESP301 kept at site(s) must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records) for RESP301 stored at site.

Further guidance and information for the final disposition of unused study intervention are provided in the Investigator Manual.

7.2.3 Storage of Study Intervention at home

All RESP301 delivered to the study participants must be stored securely at [redacted]

7.3 Measures to Minimise Bias: Randomisation and Blinding

This is an open-label, non-randomised single arm study. Potential bias will be reduced by keeping the eligibility criteria as broad as possible, and by enrolling participants through both primary and secondary care sites. All participants included in the study are at high risk of adverse outcomes due to exacerbations caused by SARS-CoV-2 or other respiratory infections [redacted]

7.4 Study Intervention Compliance

Participants will receive the first study intervention dose directly from the Investigator or designee, under clinical supervision. [redacted]

[redacted]

7.5 Concomitant Therapy

During the study, participants will receive SOC for the treatment of respiratory infection and underlying conditions. [redacted] The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. [redacted]

[redacted]

- [redacted]

7.5.1 Rescue Medication

Not applicable. [redacted]

7.6 Intervention After the End of the Study

After the end of the study, participants may continue their SOC (if any). [redacted]

7.7 Stopping Criteria for Dose Finding Phase (Part 1a &1b)

7.7.1 Dose Finding

[redacted]

7.7.2 Individual Stopping Criteria

[redacted]

Subjects can be enrolled in more than one dose cohort provided they did not meet individual stopping criteria from any given prior dose.

7.7.3 Cohort Stopping Criteria

If a stopping criterion is determined to have been met at any point during Part 1, including during any SAC review, the party aware of the stopping criterion being met will notify the Sponsor via e-mail or phone call as soon as possible, and no more than [redacted] from the time of becoming aware of the criterion being met.

[redacted]

[redacted]

7.7.4 Study Stopping Criteria

The Sponsor and the Investigator reserves the right to discontinue this study or the participation of any subject at any time for any reason. Certain circumstances may require the premature termination of the study, if the Investigator or the Sponsor feel that the type, number, relatedness, and/or severity of AEs justify discontinuation of the trial.

[redacted]

7.8 Discontinuation of Study Intervention and Participant Discontinuation

7.8.1 Permanent Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety on [redacted]

[redacted]

[redacted]

7.8.2 Temporary Discontinuation of Study Intervention

Brief temporary discontinuation of study intervention is permitted during the test dose administration and treatment period, [redacted]

[redacted]

7.8.3 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, or administrative reasons. The participant will be definitively discontinued from both the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

[redacted]

[redacted]

7.8.4 Loss of Participants to Follow-Up

A participant will be considered lost to follow-up if he or she is unable to be contacted by the study site. [redacted]

- [redacted]

- [redacted]

7.9 RESP301 Safety

NOCOV$_2$ Study

NOCOV$_2$, is a first-in-human, phase 2/3 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 in the UK (NCT04460183)

At the time of writing the safety data have not been audited and are incomplete. [redacted]

CORVIS

At the time of writing 4 patients have been screened, which included each receiving a test dose of RESP301. [redacted]

- [redacted]

[redacted]

- [redacted]

At the time of writing the safety data have not been audited and are incomplete, as the trial is currently temporarily suspended to allow for a substantial amendment to be submitted.

8 Study Assessments and Procedures

[redacted]

Table 8-1 Schedule of Activities (SoA)

	Part 1 (a & b)			Part 2								
Procedure	**Screen 1**	**Screen 2/Dosing Visit (Day 1) [a]**	**Follow-up Phone Call (Day 2)**	**Screen 1**	**Screen 2 / Baseline Visit[b]**	**Dormant period (monthly call)**	**Pre-treatment call (within 24 - 72 hrs of exacerbation onset)**	**Treatment Period (daily monitoring call for 8 days)**	**Post-treatment Follow-up call (Day 14 (± 3) PEoT**	**Post-treatment Follow-up call (Day 28 (± 3) PEoT)**	**Early withdrawal (Days 0, 14 and 28 (± 3) post withdrawal)**	**Notes**
Informed consent	X			X	X							
Inclusion and exclusion criteria	X	X		X	X							
Demographics	X			X	X							
Medical history	X			X								
Medication history and concomitant medications	X			X								
Height, weight, BMI	X			X								
Physical examinations	(X)	(X)		(X)	(X)							Any examinations which in the PI's opinion are required in order to assess suitability

Pulmonary function tests	(X)[c]	X		(X)	X							In Part 1 and Part 2 Screen 1, post bronchodilator if not recorded in medical record. Pre bronchodilator should be assessed at a screen visit (prior to test dose) In Part 2, first 50 participants only: FEV1 % predicted measured pre and post test dose.
Vital signs	X	X		X	X							Body temperature, pulse, respiration rate, blood pressure

	Part 1 (a & b)			Part 2								
Procedure	**Screen 1**	**Screen 2/Dosing Visit (Day 1) [a]**	**Follow-up Phone Call (Day 2)**	**Screen 1**	**Screen 2 / Baseline Visit[b]**	**Dormant period (monthly call)**	**Pre-treatment call (within 24 - 72 hrs of exacerbation onset)**	**Treatment Period (daily monitoring call for 8 days)**	**Post-treatment Follow-up call (Day 14 (± 3) PEoT**	**Post-treatment Follow-up call (Day 28 (± 3) PEoT)**	**Early withdrawal (Days 0, 14 and 28 (± 3) post withdrawal)**	**Notes**
Methaemoglobin level	X	X		X	X							Pre-, during and post-test dose
Short acting bronchodilator before single dose administration of RESP301		X (Part 1(b) only)										2 puffs of 100cg Ventolin through a spacer 10 mins before test dose
Test dose administration of RESP301 and assessing response		X			X							In Part 2, for the first 50 participants at minimum.
CCQ					X			X (days 1 and 7)	X			

	Part 1 (a & b)			Part 2								
Procedure	**Screen 1**	**Screen 2/Dosing Visit (Day 1) [a]**	**Follow-up Phone Call (Day 2)**	**Screen 1**	**Screen 2 / Baseline Visit[b]**	**Dormant period (monthly call)**	**Pre-treatment call**	**Treatment Period**	**Post-treatment Follow-up**	**Post-treatment Follow-up**	**Early withdrawal**	**Notes**
Instructions to participants					X		X	(X)				
Follow-up			X			X						
Review of symptoms							X	X	X			
Study intervention, TID								X				

	Part 1 (a & b)			Part 2								
Procedure	**Screen 1**	**Screen 2/Dosing Visit (Day 1) [a]**	**Follow-up Phone Call (Day 2)**	**Screen 1**	**Screen 2 / Baseline Visit[b]**	**Dormant period (monthly call)**	**Pre-treatment call**	**Treatment Period**	**Post-treatment Follow-up**	**Post-treatment Follow-up**	**Early withdrawal**	**Notes**
AE/SAE review	X	X	X	X	X			X	X	X	(X)	
Medical history review							X	X	X	X	X	
Concomitant medication review			X		X		X	X	X	X	X	

	Part 1 (a & b)			Part 2								
Procedure	**Screen 1**	**Screen 2/Dosing Visit (Day 1) [a]**	**Follow-up Phone Call (Day 2)**	**Screen 1**	**Screen 2 / Baseline Visit[b]**	**Dormant period (monthly call)**	**Pre-treatment call**	**Treatment Period**	**Post-treatment Follow-up**	**Post-treatment Follow-up**	**Early withdrawal**	**Notes**
VAS								X	X			
Body temperature							X	X	X			
Treatment compliance								X				

[redacted]

[redacted]

[redacted]

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 8-1).

8.1 Screening Visits (Part 1 and Part 2)

[redacted]

8.1.1 Informed Consent

Informed consent must be documented according to Section 11.2.

8.1.2 Eligibility Criteria

All inclusion and exclusion criteria will be reviewed by the Investigator or designee to ensure that the participant qualifies for the study.

8.1.3 Demographics

Age, gender and ethnicity should be recorded in the eCRF.

8.1.4 Medical history and medications

A medical history will be obtained by the Investigator or qualified designee. [redacted]

The Investigator or qualified designee will review prior medication use and record prior medications taken by the participant within 3 months prior to screening.

Smoking status and history should also be recorded in the eCRF.

8.1.5 Examinations and tests

Physical examinations

Height and weight should be measured and recorded in the eCRF, along with BMI.

[redacted] For all participants in Part 1 and for the minimum of first 50 participants in Part 2, spirometry will be perfomed to [redacted] For all participants thereafter, these will be measured only if the Data Monitoring Committee recommends that post test dose assessments should be continued. [redacted]

No other physical examinations are required for the study. However, the Principal Investigators should use their clinical judgement to assess the patients' suitability for the trial, and as part of this assessment, may decide to perform some physical examinations. Any abnormal physical examination findings should be recorded in the eCRF and medical records.

Vital signs

Vital signs to be collected include [redacted] signs should be taken while the patient is supine.

[redacted]

[redacted]

Methaemoglobin level

As part of eligibility screening, methaemoglobin level will be measured using a non-invasive fingertip monitor [redacted]

8.1.6 RESP301 tolerability

In Part 1 of the study, RESP301 tolerability will be assessed in all participants at each dose cohort against the individual stopping criteria (Section 7.7.2). In Part 2 of the study, a minimum of 50 consented participants who passed the eligibility criteria will receive a test dose of RESP301 to assess tolerability. [redacted]

In Part 1, participants who do not meet any of the Individual Stopping Criteria (Section 7.7.2), and are suitable in the Investigator's opinion to proceed, can proceed to the next cohort (subject to SAC review).

In Part 2, participants who satisfactorily tolerate the test dose based on the above assessments, and are suitable in the Investigator's opinion to proceed, will be enrolled into the dormant period of the study.

Participants who completed the Screening visit and test dose but were not suitable to continue to the dormant period, should be followed up with a phone call 7[redacted].

8.1.7 The Clinical COPD Questionnaire (CCQ) (Part 2 only)

The Clinical COPD Questionnaire (CCQ) is a validated, self-administered 10-item questionnaire which measures health status and can be used to assess health-related quality of life (van der Molen et al, 2003). It has three domains: symptoms (4 items), functional status (4 items) and mental state (2 items), graded on a 7-point Likert scale from 0 to 6 (0 = no impairment). The final score is the sum of all items divided by 10; separate scores for all three domains can be calculated. Higher scores indicate a worse health status.

8.1.8 Instructions to participants (Part 2 only)

Participants who satisfactorily tolerate the test dose in Part 2, or are not required to take the test dose (subject to DMC recommendations), will be trained in preparation, administration and transport of the drug product, and the care and cleaning of the nebuliser.

[redacted]

[redacted]

[redacted]

8.1.9 AE/SAE

Any Adverse Events observed during the visit should be recorded in the eCRF. [redacted]

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up until the AE has resolved, has stabilised or is otherwise explained, is no longer of clinical concern, or the patient is lost to follow-up [redacted]

8.2 Dormant period

During the dormant period, the participants will receive monthly follow-up calls to remind them to contact the study team if they start experiencing exacerbation symptoms.

8.3 Pre-treatment appointment

A participant who experiences symptoms for at least [redacted] should contact the study team as soon as practicable to allow a remote study appointment to be undertaken within [redacted]

[redacted]

[redacted]

[redacted]

Any changes to medical history or medications reported by the patient should be recorded in the eCRF.

8.4 Treatment period

During the treatment period at home/community setting, patients will be asked to:

- [redacted]

Each participant will only receive a maximum of one course of treatment of RESP301 during the study.

[redacted]

Participants should return the completed diaries and CCQ questionnaires to the study team [redacted]

8.5 Post-treatment Follow-up calls

For all participants enrolled into the treatment period, follow-up calls will be conducted [redacted] to discuss any AEs, changes to medications or medical history (including COVID-19 test results, if available).

Symptoms, AEs, and changes to medications or medical history (including COVID-19 test results, if available) will be recorded in eCRF.

The [redacted] follow-up call will be the end of study for participants enrolled into the treatment period, unless there are any unresolved AEs which should be followed up until resolved, stabilised or otherwise explained, no longer of clinical concern, or the patient is lost to follow-up [redacted]

8.6 Early Withdrawal

At the time of discontinuing from the study, if possible, an early discontinuation assessment should be conducted, as shown in the SoA (Table 8-1). [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

9 Pharmacovigilance

Further details are provided in Appendix 1: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

9.1 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Appendix 1: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up until the AE has resolved, has stabilised or is otherwise explained, is no longer of clinical concern, or the patient is lost to follow-up [redacted]

9.2 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from signing of informed consent until the last follow-up visit at the time points specified in the SoA (Table 8-1).

[redacted]

9.3 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 1: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

[redacted]

9.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution,

stabilisation, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section [redacted]

Further information on follow-up procedures is given in Appendix 1: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

9.5 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from the Sponsor will file it along with the Investigator's Brochure and will notify the local IRB/IEC, if appropriate according to local requirements..

9.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs (Not Applicable)

9.7 Adverse Events of Special Interest (Not Applicable)

No AEs of special interest are defined for this study.

9.8 Medical Device Deficiencies (Not Applicable)

The medical device to be used in this study is a [redacted] nebuliser that is FDA-approved and CE-marked and is to be used per the manufacturer's recommendations. Therefore, data on device deficiencies will not be collected in this study.

10 Statistical Considerations

10.1 Statistical Hypothesis

Since this is an open label non-randomised study where the primary objective is to assess feasibility, no formal statistical analysis will be performed.

10.2 Sample Size Determination

The primary objective of this study is to determine [redacted] and no formal sample size calculation was performed.

In Part 1, we aim to recruit [redacted] participants [redacted]

In Part 2, we aim to recruit 150 patients from secondary care and primary care sites in the UK into the dormant period. [redacted]

10.3 Populations for Analyses

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

Table 10-1 Populations for Analysis

Population (Analysis Set)	Description
Intent-To-Treat (ITT) Population	The ITT Population will include all participants enrolled into the treatment period. Participants who withdraw from treatment early will be followed for the assessment of the Day 7 primary endpoint. All efficacy analyses will be performed using the ITT Population.
Per Protocol (PP) Population	The 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.
Safety Population (SP)	The SP will include all participants who inhale any amount of study intervention.

The ITT Population will be the primary analysis set for all efficacy analyses and the PP Population will be used to demonstrate robustness of results for the efficacy endpoint.

10.4 Statistical Analyses

Below is a description of planned statistical analyses. Further details are presented in the Statistical Analysis Plan (SAP).

10.4.1 General Considerations

Data will be presented using appropriate summary statistics and patient data listings. In general, missing values will not be replaced unless otherwise stated. Baseline will be considered the latest assessment before first dose of study treatment.

A flow diagram of participant progress will be provided, including the number assessed for eligibility and reasons for exclusion, number enrolled, and participants with early withdrawal from the study, together with the primary reasons for discontinuations. Any recorded protocol deviations will be listed.

10.4.2 Primary Endpoint

In Part 1, the primary endpoint is the proportion of patients tolerating RESP301 at each dose level in (according to pre-defined criteria).

In Part 2, the primary endpoint is the feasibility of self-administering RESP301 treatment with nebuliser [redacted]

- [redacted]

10.4.3 Secondary Endpoint(s)

The secondary endpoints, which will be analysed on the full cohort and separately in the sub-cohort of those who test positive for SARS-CoV-2, are safety and tolerability and efficacy of RESP301. The endpoints are further defined below.

1) Safety and tolerability of RESP301 [redacted]

- [redacted]

All safety analyses will be performed on the Safety Population, ITT and PP,. Adverse Events will be coded using the MedDRA coding dictionary.

The number and percentage of participants with any AE, any related AE, any SAE, any related SAE, any severe AE, and related severe AE as well as the total number of events for each category will be summarised. The number of deaths due to an AE, hospitalisation due to an AE, and study discontinuation due to an AE will be summarised.

The number and percentage of participants with an AE, as well as the total number of AEs, will be summarised by SOC and preferred term. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, and related severe AEs.

All AEs will be provided in patient listings. Patient listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, related AEs, and severe AEs will be produced.

2) Efficacy of RESP301 [redacted]

- [redacted]

10.4.4 Other Analyses

Other analyses may be added to the SAP as applicable.

10.5 Interim Analyses

No formal statistical interim analysis is planned.

10.6 Data Monitoring Committee (DMC)

An IDMC will be responsible for closely reviewing the safety data and for providing their recommendations on continuation of the study. The detailed procedures and schedule of the meetings will be described in the DMC Charter.

11 Regulatory, Ethical, and Study Oversight Considerations

11.1 Regulatory and Ethical Considerations

- This study will be 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.

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
  - 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.

11.2 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the local regulations, ICH guidelines, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all participants subsequently enrolled in the study as well as those

currently enrolled in the study if they are affected by the revisions. A measured approach should be taken to determine which participants need to be reconsented.

11.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.4 Committees Structure

An IDMC will be responsible for closely reviewing the safety data and for providing their recommendations on continuation of the study (see Sections 10.5 and 10.6).

11.5 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategies (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organisations [CROs]).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 2 years after the last approval of a marketing application or 15 years from completion of the study, whichever is longer according to the relevant local laws and/or regulations. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- All data generated by the site personnel will be captured electronically at each study center using eCRFs. Once the eCRF clinical data have been submitted to the eCRF, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.
- If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail.
- The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

11.6 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

11.7 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is the first participant signing the informed consent form and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure (on site visit or remote closure) has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

11.8 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor at least one month before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.9 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the participant benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

11.10 Liability and Insurance

The study Sponsor holds a Clinical Trials Insurance for legal liabilities arising in relation to this trial. NHS bodies are legally liable for the negligent acts and omissions of their employees. If a patient is harmed whilst taking part in a clinical study as a result of negligence on the part of a member of the study team this liability cover would apply.

11.11 Access to Source Data

Access to source data is described in the Clinical Trial Agreement for each site.

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Appendix 1: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• 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. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's

condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are considered AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the clinical research organisation (CRO) in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the CRO/Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the CRO/Sponsor for review.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

- The CRF will be reconciled with the safety database during and at the end of the trial. Therefore, the sites should ensure that the data entered on any SAE forms and the data entered into the CRF are consistent.

Assessment of Intensity

The Investigator will make an assessment of the intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: 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 utilised for rating the intensity of an event; and both AE and SAE can be assessed as 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, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE on a 5-point scale (not related, unlikely, possible, probable, highly probable).
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report in the electronic CRF/EDC. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to electronic CRF/EDC.

- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAE

SAE Reporting

All SAEs will be recorded from signing of informed consent until the end of the study. Serious adverse events occurring after the end of the study and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally related to study intervention.

Other events which must be reported in the same manner as an SAE include:

- Overdose (any dose above that specified in the protocol, not necessarily intentional)
- Abuse or misuse
- Medication error (any unintentional error in the dispensing or administration of an IMP)
- Occupational exposure (to a person other than the patient, for example spilling of IMP on hands of nurse or splashing in the eye)
- STIAMP (suspected transmission of an infectious agent via a medicinal product)

- Any AE that could be related to the protocol procedures and which could modify the conduct of the trial.

The Investigator must report any SAEs to the Sponsor **within 24 hours** of becoming aware of the event by emailing an SAE form to the Sponsor's PV department.

The Sponsor's PV department will confirm receipt within one business day. The site should re-send any report where acknowledgement of receipt is not provided.

Each episode of an SAE must be recorded on a separate SAE form. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the PV department on a new SAE form.

Where an SAE has not been reported to the Sponsor within the specified timelines, a reason for lateness must be included with the SAE form.

All SAEs will be recorded from signing of informed consent until the end of the study. Serious adverse events occurring after the end of the study and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally related to study intervention.

- The primary mechanism for reporting an SAE will be using a paper SAE reporting form
- The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference document (Reference Safety Information section in the Investigator Brochure). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

Suspected Unexpected Serious Adverse Reactions (SUSARs)
Any AE that is a SUSAR has additional reporting requirements, as described below. • If the SUSAR is fatal or life-threatening, associated with study intervention, and unexpected, regulatory authorities and IECs will be notified within seven calendar days after the Sponsor learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total). • If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with study intervention, and unexpected, regulatory authorities and IECs will be notified within 15 calendar days after the Sponsor learns of the event. The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of participants. Follow-up information may be submitted if necessary. The Sponsor will also provide annual safety updates to the regulatory authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

Urgent Safety Measures (USM)
The sponsor/sponsor's designee or investigator may take appropriate urgent safety measures (USMs) in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect subjects from pandemics or infections that pose serious risk to human health. USMs may be taken without prior authorization from the competent authority. Should the site initiate a USM, the investigator must inform the sponsor or sponsor's designee immediately.

Investigator Agreement Page

Declaration of the Principal Investigator

Title: **Community participants with COPD or bronchiectasis and at risk of Respiratory Viral Infections including SARS-CoV-2: An open-label, multicentre feasibility study of an inhaled nitric oxide generating solution (RESP301)**

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the *Declaration of Helsinki* and the guidelines on Good Clinical Practice.

Principal Investigator

_____ _____

Signature Date

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Name (block letters)

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Title (block letters)

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Institution (block letters)