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Safety assessment of inhaled RESP301 in patients with pulmonary tuberculosis

Submission date
29/12/2022

Recruitment status
Stopped

Registration date
30/12/2022

Overall study status
Stopped

Last Edited
03/03/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Nitric oxide (NO) is a naturally produced gas in the human body and is an important part of our protection against infection in the lungs. However, some types of infection can overwhelm nitric oxide production, and certain organisms, notably viruses, can 'switch off' the enzymes that produce this vital protective mechanism.
RESP301 is designed to deliver extra nitric oxide to the lungs, to support the body's normal shield against infection and supply more of the gas, if needed. In the laboratory, RESP301 has been shown to be highly effective against Mycobacterium tuberculosis – the organism that causes tuberculosis. It has shown activity against antibiotic-sensitive as well as antibiotic-resistant bacteria.
The purpose of the study is to see whether the activity we have seen with RESP301 in the laboratory can be reproduced in the human body. The aim of this study is to test RESP301 alongside standard of care treatment (SOC) in patients who have antibiotic-sensitive or multidrug-resistant pulmonary tuberculosis (MDR-TB). The question we are asking is: can RESP301 be used as an effective treatment for TB on its own or alongside standard antibiotics? The drug has been tested in previous clinical trials as a treatment for patients with chronic obstructive pulmonary disease (COPD) and for hospitalised COVID-19 patients. The drug is also currently being tested as a treatment for chronic infection in patients with cystic fibrosis, and to prevent postoperative pulmonary in patients undergoing surgery.

Who can participate?
Patients aged 18 years or over with antibiotic-sensitive or multidrug-resistant pulmonary tuberculosis (MDR-TB)

What does the study involve?
The study investigates a new inhaled treatment called RESP301 that you breathe in from an easy-to-use, hand-held, and approved nebuliser device. Clinical staff will assess participants at the research site, A&E or clinic to make sure they are eligible to participate in the study. If they are eligible and agree to be in the study, participants will receive the study drug RESP301 alongside the normal treatment prescribed by their clinical team. Treatment with RESP301 shall continue while participants are in the hospital with a maximum treatment period of 7 days. Participants will be monitored for up to 12 weeks and receive calls from research staff alongside being

treated as normal by their GP/primary care centre. A list of procedures that will be performed during the study are detailed below.

The total study duration for a participant from screening to last follow-up will be a maximum of 90 days or as per continuation phase appointment under routine care.
The study will be divided into the following periods:
1. Screening Period: Day -1 (24 hours) before the start of treatment on Day 1
2. Treatment Period: Days 1 to Day 7 (or to day-of-discharge if less than 7 days)
3. Safety Follow-Up (clinic or on the phone)

Screening Visit:
Before any study procedures take place, the study team will discuss the study with participants and they will have an opportunity to ask any questions they might have. The following procedures will take place:
1. Participants will be asked to sign the Informed Consent Form
2. A note will be taken about their age, sex and ethnicity and their weight will be measured
3. Participants will be asked about their medical history, medication history and about any medications they are currently taking
4. The study doctor shall perform a physical examination (such as check their heart or lungs)
5. Breathing capacity and rate, blood pressure, heart rate and temperature will be measured
6. Participants will be asked to provide a sputum sample at the Screening visit to confirm their TB diagnosis
7. As part of eligibility screening, methaemoglobin levels will be measured using a non-invasive fingertip monitor and should be confirmed to be not greater than 3% in order to enter the study
8. Pulse oximetry measurements of oxygen in the body will be done using a non-invasive fingertip monitor
9. Participants will have an ECG which stands for an electrocardiogram which is a non-invasive, non-painful, recording of the electrical activity of the heart
10. A small amount of blood (about 5-9 ml, about two teaspoons) will be collected from a vein in the arm for some tests
11. Women of childbearing potential will take a urine pregnancy test
12. If eligible to be included in the trial participants will be given their first dose called a Test dose, under the supervision of a study team member to make sure they can tolerate both the nebuliser and RESP301
13. A member of the research team will provide training on using the nebuliser and study drug
14. Participants will be asked about how they are feeling and any medications you are taking
15. If during or after the first dose of study intervention, participants do not tolerate the treatment, they will not be allowed to continue
If participants do tolerate the Test dose they will enter the study (if they still wish to participate) and continue to Baseline

Baseline Visit:
1. Participants will be asked to provide a sputum sample at the Screening visit to confirm their TB diagnosis.
2. Breathing rate, blood pressure, heart rate and temperature will be measured.
3. Pulse oximetry measurements of oxygen in the body will be done using a non-invasive fingertip monitor
4. A small amount of blood (about 5-9 ml, about two teaspoons) will be collected from a vein in the arm for some tests
5. Receive the study drug via nebuliser – See Treatment Period Day -1/1 – 7 below
6. Participants will be asked about how they are feeling and any medications they are taking.

Day -1/1 – 7 Treatment Period:
Participants will take RESP 301 twice a day for up 7 days, i.e. a maximum of 14 doses in total, including the Test dose at the Screening Visit. If their stay in hospital is shorter than 7 days, treatment with RESP301 will stop on the day of discharge from hospital.

Taking the study treatment will involve inhaling with a nebuliser. Inhalation should start within 5 minutes of mixing the solutions and typically lasts 8-10 minutes. If you want to pause the nebuliser at any time this is easy to do by pressing the On/Off button and pressing again to restart. Temporary pausing does not affect the activity of RESP301, but participants should try to complete the inhalation process within 20 minutes if possible. A member of the study team will show how to do this.
Treatment is taken twice a day, leaving at least 8 hours between the doses. Treatment will start on Day -1/1 and complete on Day 7 unless stopped sooner because you have been discharged from hospital before the 7-day treatment period is completed.
During the treatment period the following procedures will be performed:
1. The study doctor shall perform a physical examination (such as check the heart or lungs)
2. Breathing rate, blood pressure, heart rate and temperature will be measured
3. Participants will be asked to provide a sputum sample
4. Methaemoglobin levels will be measured using a non-invasive fingertip monitor
5. Pulse oximetry measurements of oxygen in the body will be done using a non-invasive fingertip monitor
6. A small amount of blood (about 5-9 ml, about two teaspoons) will be collected from a vein in the arm for some tests
7. Participants will be asked about how they are feeling and any medications they are taking
After leaving hospital, all participants will receive regular phone calls from one of the clinical team to check on any symptoms, changes to medical history or medications or discuss any issues that may have arisen as a result of the treatment.

End of Treatment – Day 7 (or day of discharge if earlier):
On the last day of the treatment period (Day 7) or day of discharge (if earlier) the following procedures will be performed:
1. Physical examination
2. Weight measurement
3. Breathing rate, blood pressure, heart rate and temperature measurement
4. Sputum sample
5. Methaemoglobin level measured using a non-invasive fingertip monitor
6. Pulse oximetry measurements of oxygen in the body using a non-invasive fingertip monitor
7. A small amount of blood (about 5-9 ml, about two teaspoons) will be collected from a vein in the arm for some tests
8. Participants will be asked about how they are feeling and any medications they are taking

Follow-up Period (from 4 to 12 weeks post end of treatment) - days 28 to day 90:
1. Breathing rate, blood pressure, heart rate and temperature will be measured
2. Sputum sample
3. Methaemoglobin levels will be measured using a non-invasive fingertip monitor
4. Pulse oximetry measurements of oxygen in the body using a non-invasive fingertip monitor
5. Participants will be asked if there has been any change to their medical history, medication history and other medicines they are currently taking
6. Participants will be asked about any side effects

Follow-up Call(s):
A phone call with the study coordinator to report any side effects and any changes to medical history or medications

What are the possible benefits and risks of participating?
It is hoped that RESP301 will help participants with their condition. The researchers are testing RESP301 alongside standard-of-care treatment (SOC) to see if it can be an effective treatment for patients with antibiotic-sensitive or multi-drug-resistant pulmonary tuberculosis (MDR-TB). However, participants may not get any direct benefit from taking part in this study but the information from the study may be of help to others in the future.
As with all research studies, the study medication and study procedures may involve unknown risks. Any medication can have temporary and permanent side effects and can cause unforeseen side effects.
Before entering the trial, participants will receive a Test dose under the supervision of the study team and will be monitored for up to 1 hour following the Test dose. Participants taking RESP301 in other studies have experienced a mild cough associated with the inhalation. Some patients have also experienced a cough during and after the study treatment has finished. However, patients have recovered well, and the medicine is deemed to be tolerated.
There are general risks of nebulisation such as temporary chesty cough and temporary difficulty with breathing. The study doctor will monitor participants closely when they are given the study medication to minimise all risks.
Collecting a blood sample from a vein may cause pain, bruising, light-headedness, fainting, and very rarely, infection at the site of the needle insertion.
There is a very low risk of developing a condition called methaemoglobinaemia during or immediately after the nebulisation. This condition is caused when an excess of nitrite or nitric oxide displaces oxygen from haemoglobin in the blood and, as a result, less oxygen is delivered to cells. At higher levels of methaemoglobinaemia, which are unlikely with RESP301, the symptoms include headaches, dizziness shortness of breath, nausea, blue-coloured skin (cyanosis) and muscle weakness. In severe cases it can cause heart arrhythmia and seizures. However, the levels of all the constituents in RESP301 have been carefully calculated to minimise the risk of methaemoglobinaemia and no evidence of it has yet been seen in any patients in other trials with RESP301.
If participants or their partners become pregnant there may be unknown risks to the baby. The effects of RESP301 on sperm, a pregnancy, a foetus, or a breastfeeding infant are not known because it has not yet been specifically tested during pregnancy. Therefore, as a precaution, participants must use reliable contraception during treatment with RESP301 and notify the study doctor immediately if they or their partner become pregnant.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
December 2022 to December 2023

Who is funding this study?
Thirty Respiratory Limited (UK)

Who is the main study contact?
Prof. Onn Min Kon, onn.kon@nhs.net

Contact information

Type(s)
Principal investigator

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Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
1006631

Protocol serial number
RESP301

Study information

Scientific Title
An open-label non-randomised trial designed to evaluate the safety and tolerability of RESP301 alongside standard of care in the treatment of fully sensitive and multidrug-resistant pulmonary tuberculosis

Acronym
RESCU

Study objectives
The study has been designed to evaluate the safety and tolerability of RESP301 alongside standard of care (SOC) in the treatment of multidrug-resistant pulmonary tuberculosis (MDR-TB).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, South Central - Oxford B Research Ethics Committee, ref: 23/SC/0103

Primary study design
Interventional

Study design
Single-centre open-label interventional trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Fully sensitive multidrug-resistant tuberculosis

Interventions
Inhaled RESP301 (via a nebuliser)

The total study duration for a participant from screening to the last follow-up will be a maximum of 90 days or as per continuation phase appointment under routine care.

The study will be divided into the following periods:
1. Screening Period: Day -1 (24 hours) prior to the start of Treatment on Day 1
2. Treatment Period: Days 1 to Day 7 (or to day-of-discharge if less than 7 days)
3. Safety Follow-Up (clinic or on the phone)

Single treatment arm: RESP301 will be given twice daily in conjunction with standard-of-care antibiotics in hospitalised patients with pulmonary tuberculosis. RESP301 is an investigational medicinal product therefore no generic name is available. Antibiotics will vary from patient to patient depending on their standard of care.

Dosage Level(s): 6 ml inhalation (with a handheld device) BD (12 hourly) with a minimum of 8 hours between two consecutive doses.

Dosing Instructions: A vibrating mesh nebuliser will be used to administer the RESP301. Treatment is to commence within 5 minutes of RESP301 preparation.

The treatment will be taken BD for up to 7 days alongside normal Standard of Care (SOC). All participants will receive the first test dose of RESP301 under the supervision of the study team. If any concerns arise, the participant will not be allowed to continue in the study.

Study intervention will be provided as two separate vials: $NaNO_2$/mannitol (3 ml) and citric acid buffered to pH 5.4 (3 ml), which will be labelled as required per country requirement.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
RESP301

Primary outcome(s)
Safety and tolerability of RESP301 in terms of total counts and cumulative incidence and relatedness of:
1. Adverse Events (AEs)
2. Serious Adverse Events (SAEs)
3. Suspected Unexpected Serious Adverse Reactions (SUSARs)
4. Severe AEs
AEs recorded for the duration of the study): at Screening (Day -1) to Day 90 (or at early termination)

Key secondary outcome(s)
Efficacy of RESP301 in terms of changes in the colony count of Mycobacterium tuberculosis in the sputum following administration of RESP301; measured using a sputum sample at Screening (Day -1), Baseline (Day 1), Day 2 and Day 7 (end of treatment/or early withdrawal if earlier)

Completion date
31/12/2023

Reason abandoned (if study stopped)
Lack of staff/facilities/resources

Eligibility

Key inclusion criteria
Hospitalised patients with:
1. Smear, culture or DNA probe-proven pulmonary tuberculosis
2. On approved guideline-based treatment (subject to drug sensitivity)
3. Age ≥18 years of age
4. Able to give written informed consent
5. Able to understand instructions
6. Able to operate and maintain nebuliser, as assessed by the Investigator

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Concomitant severe respiratory disease such as severe asthma and severe COPD with predicted FEV1 <40%
2. Any current or previous condition/circumstance that, in the opinion of the investigator, may put the individual at risk
3. Unable to tolerate the use of a nebuliser for approximately 8-10 minutes as required by the study, according to the Investigator's opinion
4. Any unstable, uncontrolled, or severe medical condition that in the opinion of the investigator would make the participant unsuitable for the trial
5. Participation in other clinical investigations utilising investigational treatment within the last 30 days / 5 half-lives, whichever is longer
6. Known allergy/hypersensitivity to, or relevant drug-drug interaction with, the study drug /components of the study drug
7. History of methaemoglobinaemia
8. Any subject who in the opinion of the investigator would not be best served by participating in this clinical trial
9. Prescribed nitric oxide donating agents (e.g. nitroprusside, isosorbide dinitrate, isosorbide mononitrate, naproxcinod, molsidomine and linsidomine)

Date of first enrolment
31/05/2023

Date of final enrolment
01/10/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Imperial College London Imperial Clinical Respiratory Research Unit (ICRRU)
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Sponsor information

Organisation
Thirty Respiratory Limited

Funder(s)

Funder type
Industry

Funder Name
Thirty Respiratory Limited

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Stored in publicly available repository, Data sharing statement to be made available at a later date