ISRCTN16086655 https://doi.org/10.1186/ISRCTN16086655

Investigating potential treatments for human lung injury in healthy volunteers

Submission date	**Recruitment status**	[X] Prospectively registered
28/12/2023	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
26/04/2024	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
18/11/2024	Respiratory	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
ARDS is a very serious condition that affects people who are in the hospital's intensive care unit. It happens when someone has another illness like an infection in their body. In ARDS, the immune system, which usually helps protect our bodies, causes an exaggerated inflammatory response and harms the lungs instead. This causes the lungs to become damaged and filled with fluid making it hard to breathe and get enough oxygen. Inflammation is a normal process which occurs in response to illness or injury. Normally it allows immune cells to target specific areas, but when this is dysregulated it causes harm to normal tissue.
When someone gets ARDS, there's a 40% chance they could die from it. There isn't a specific medicine to treat ARDS. Severe COVID-19, which has some similarities to ARDS, responded to treatment with a drug called baricitinib, and we want to explore how it could be used to treat people with ARDS. To do this we want to test how the drug works in the lungs of healthy people.

Who can participate?
Healthy non-smoking adults aged 18-45 years old

What does the study involve?
Some of the volunteers will get the baricitinib and others won't get any medicine. To see how the medicine affects the lungs, the volunteers will breathe in a special particle called lipopolysaccharide (LPS) which causes an inflammatory response which is similar to that which we see in ARDS but to a small degree and for a shorter period. The amount of LPS that we give is similar to that which people would be exposed to if they smoked 5 cigarettes.

We will do a test using a small camera called a bronchoscope. It's a thin tube with a camera at the end that goes into the lungs through the mouth. This lets the scientists look at the lungs and take samples. We will compare the responses in the lungs between the group that got the baricitinib medicine and the group that did not. By doing this, we hope to find out if baricitinib can help reduce the inflammatory response in the lungs of people with ARDS. If it works well, it could be used as a treatment for ARDS in the future.

What are the possible benefits and risks of participating?
Participants will be compensated for taking part in the study, but will otherwise not directly

benefit from treatment administered. Outcomes from this study will however be used to help inform future clinical trials for patients who have acute respiratory distress syndrome.

Baricitinib is a reversible well tolerated JAK 1 and 2 inhibitor. It is commonly used in treating rheumatoid arthritis. Previous healthy volunteer studies have demonstrated that plasma concentration peaks within 1.5 hours post-dose and subsequently declines in a bi-exponential fashion, with minimal systemic accumulation over repeated dosing.

In healthy volunteer studies where baricitinib has been given for a short duration no serious infections or adverse effects were noted.

In chronic treatment studies in rheumatoid arthritis patients baricitinib has been associated with an increased risk of upper respiratory tract infection, increase in blood cholesterol count, abnormal liver blood tests, anaemia, low white cell counts, high platelets, risk of pneumonia, urinary tract infections and gastroenteritis. There is also a risk of reactivation of tuberculosis (TB), hepatitis B and C, and varicella zoster. This can occur in 1 in 100. Uncommon side effects with chronic use include risk of deep vein thrombosis, pulmonary embolism and diverticulitis (1 in 1000 risk). It has been associated with an increased risk of non-melanoma skin cancers in those receiving chronic treatment.

These adverse effects have not been demonstrated to occur in COVID-19 patients treated with baricitinib for up to 10 days.

Participants will be screened: for medical history, clinical examination and safety bloods to exclude those at increased risk of complications from participating in the study. Baricitinib is only being used for 3 days. This is to allow the drug to reach a steady state without prolonged exposure to the drug. Baricitinib is cleared with minimal systemic accumulation and is expected to be cleared within 48 hours of the last dose.

Inhaled LPS challenge is a safe healthy volunteer model of ARDS. The dose of LPS administered is equivalent to that obtained from 5-6 cigarettes. It causes a short-lived reaction which lasts for up to 24 hours and is associated with a mild flu-like illness which can be treated with paracetamol. This procedure will be carried out using a calibrated dosimeter by experienced staff in an appropriate clinical setting.

Bronchoscopy and broncho-alveolar lavage is a safe procedure which is carried out under conscious sedation and local anaesthetic. This procedure will be carried out in a suitable clinical area with experienced clinical staff under the supervision of an experienced respiratory physician. This procedure is normally well tolerated but some can experience a flu-like illness in the 24 hours post-procedure.

Where is the study run from?
Queen's University Belfast

When is the study starting and how long is it expected to run for?
December 2023 to August 2025

Who is funding the study?
Belfast Health and Social Care Trust, Belfast Trust Charitable Funds

Who is the main contact?
Prof Danny McAuley, d.f.mcauley@qub.ac.uk

Contact information

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1006421

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
23017DMcA/UC, IRAS 1006421

Study information

Scientific Title
Inhaled lipopolysaccharide challenge as a human model to investigate potential therapies in Acute Respiratory Distress Syndrome

Study objectives
Primary objectives:
The primary outcome of this trial is the number of neutrophils in bronchoalveolar lavage fluid. Tissue damage in acute respiratory distress syndrome is mediated by immune cells called neutrophils. These cells are involved in the first line of protection against bacteria and viruses. To that end neutrophils produce a number of enzymes which cause tissue damage, as well as signals which attract other immune cells to areas of injury. In ARDS this immune response leads to respiratory failure and multi-organ failure as the response becomes uncontrolled. In an animal model of COVID 19 lung injury which shares some features with ARDS baricitinib reduced the BAL neutrophil count by 50% with corresponding reduction in histological changes of severe lung injury. ARDS is common and has a mortality of 40%. It does not have a treatment. Data from this study will inform a clinical trial of baricitinib in ARDS patients.

Secondary objectives:
To understand how JAK STAT inhibition works within lung tissue cells and immune cells which are resident in the lung, by allowing for direct assessment of inflammatory response by measuring cell signalling proteins (cytokines) and tissue destruction enzymes (proteases) in both the bronchoalveolar lavage fluid and the blood stream. It has been shown in animal models and in COVID 19 studies that the JAK STAT inhibitor Baricitinib can reduce the amount of cytokines and proteases produced by cells present in the lungs (both lung cells and immune cells). In clinical trials this has been shown in COVID 19 lung injury to significantly reduce mortality. COVID lung injury shares some similarities with ARDS and as such this trial hopes to provide a scientific basis for the development of a clinical trial in ARDS patients.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 27/03/2024, London- London Bridge Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 1048387; londonbridge.rec@hra.nhs.uk), ref: 24/LO/0081

2. approved 28/03/2024, Medicines and Healthcare products Regulatory Agency (MHRA) (10 South Colonnade, Canary Wharf, London , E14 4PU, United Kingdom; +44 (0)20 3080 6000; info@mhra.gov.uk), ref: CTA 32485/0044/001-0001

Study design
Interventional PROBE (prospective randomized open blinded end-point) controlled trial

Primary study design
Interventional

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Acute Respiratory Distress Syndrome (ARDS)

Interventions
Participants will be randomised to intervention or comparator by computer programme.

The intervention will be Baricitinib (Olumiant) 4 mg orally, once daily for 3 days.

Comparator is no intervention.

Participants and clinicians will be unblinded to intervention. Laboratory staff undertaking the analysis will be blinded.

Day 4 of study period: the participant will be brought back the day after they have completed all study interventions i.e.: completed treatment period of 3 days and undergone LPS challenge, and bronchoalveolar lavage for safety screening.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Olumiant [Baricitinib]

Primary outcome(s)
Broncho-alveolar lavage neutrophil count during bronchoscopy at day 4

Key secondary outcome(s))
Broncho-alveolar lavage fluid/Plasma/Urine: cytokines including but not limited to Il-6, IL-10, IL-18, CXCL8, IL-1b, markers of epithelial and endothelial injury including but not limited to RAGE, SP-D, Ang2, single-cell RNA sequencing, plasma differential white cell count, BAL differential white cell count, plasma C-reactive protein

Completion date
06/08/2025

Eligibility

Key inclusion criteria
Healthy non-smoking adults aged 18-45 years old

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit

45 years

Sex
All

Key exclusion criteria
1. Age <18 years
2. Age >45 years
3. BMI >30 kg/m²
4. On concomitant medications including over-the-counter medications excluding hormonal contraception and paracetamol
5. Previous adverse reactions to LPS, lignocaine or sedative agents
6. Pregnant or breast-feeding
7. Participation in a clinical trial of an investigational medicinal product within 30 days
8. Consent declined
9. History of asthma or other respiratory conditions
10. Smoking or e-cigarette use
11. Marijuana use or other inhaled products (with or without nicotine) in the last 3 months
12. Alcohol abuse, as defined by the Alcohol Use Disorders Identification Test (AUDIT)
13. Subjects with history of prior conventional cigarette (> 100 cigarettes lifetime and smoking within 6 months) or electronic cigarette use.
14. Live vaccine with in preceeding 4 weeks
15. Abnormal blood count, renal function or liver function tests identified at screening
16. History of shingles
17. History of Hepatitis B/C
18. Allergy to Baricitinib

Date of first enrolment
01/10/2024

Date of final enrolment
01/11/2025

Locations

Countries of recruitment
United Kingdom

Northern Ireland

Study participating centre
Mater Hospital
45-54 Crumlin Rd
Belfast
United Kingdom
BT14 6AB

Sponsor information

Organisation
Belfast Health and Social Care Trust

ROR
https://ror.org/02tdmfk69

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Belfast Health and Social Care Trust, Belfast Trust Charitable Funds

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Published as a supplement to the results publication