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Vascular leak and inflammation: a study to understand underlying mechanisms and identify novel treatment options

Submission date 27/06/2023	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol
Registration date 20/07/2023	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 18/06/2025	**Condition category** Other	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
Acute Respiratory Distress Syndrome (ARDS) is a severe type of lung injury that affects 10% of patients admitted to Intensive Care Units worldwide, with an unacceptably high death rate of up to 48% in those with the most severe form of the condition. It is a complex and poorly understood syndrome that results in progressive failure of the lungs. Crucially, the inflamed lungs allow fluid to leak from the circulation into the airspace, so that patients' lungs fill with fluid - "drowning from the inside". As this condition progresses, the patient typically requires increasing amounts of oxygen and eventually, support from a ventilator. To date, there are no effective treatments for ARDS that can limit, stop or repair this process.
This study is aiming to look at a naturally occurring substance produced by blood vessels, C-type natriuretic peptide (CNP). The investigators have evidence suggesting that CNP plays a role in maintaining the barrier provided by blood vessels that stops fluid leaking out into tissues. This is based on various studies done on CNP by the investigators' research group that have established its widespread role in maintaining cells that line blood vessels and play a vital role in the lungs' barrier function: the endothelium.
CNP is broken down in part by an enzyme called neutral endopeptidase and therefore, drugs that inhibit this enzyme would result in increased CNP concentration and activity. If CNP does in fact strengthen the lungs' endothelial barrier, then this class of drug may benefit patients with ARDS. The aim of this study is to assess the effect of using the licensed NEP inhibitor racecadotril in a well-established, safe model of inflammation-induced skin blisters in healthy human volunteers to determine primarily whether the fluid accumulation (i.e. leak) in these blisters is reduced by treatment with this drug.

Who can participate?
Healthy volunteers aged 18-45 years

What does the study involve?
Participants will be screened and recruited (Day 0) and on Day 1 a blister will be created on one arm. After 24 hours the blister volume will be measured and the blister fluid collected for analysis. 7 days later participants will be randomly allocated to either placebo (dummy drug) or

racecadotril (100 mg, three times daily; licensed dose) for 3 days then an identical blister will be created on their other arm. 24 hours later the blister volume will be measured and the blister fluid collected for analysis.

What are the possible benefits and risks of participating?
This study will not benefit participants directly. However, in the future, the results from this study may benefit patients with various inflammatory conditions, especially an inflammatory condition affecting the lungs called ARDS.
Cantharidin may cause some mild discomfort whilst the blister is forming. Participants may also have mild discomfort and/or bruising after blood-taking.
Racecadotril is widely available as a generic drug and has an established safety record. When used for its licensed indication the most common adverse effects are headache, nausea or constipation. Participants will be counselled thoroughly on these and provided with advice on how to manage any adverse effects that may occur.

Where is the study run from?
William Harvey Research Institute, Queen Mary University of London (UK)

When is the study starting and how long is it expected to run for?
August 2020 to June 2025

Who is funding the study?
Medical Research Council (MRC) (UK)

Who is the main contact?
Dr Aemun Salam, aemun.salam@qmul.ac.uk

Contact information

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Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
288749

ClinicalTrials.gov number
NCT05600062

Secondary identifying numbers
IRAS 288749

Study information

Scientific Title

Assessment of the effect of neutral endopeptidase inhibition on vascular leak and leukocyte accumulation in a human cantharidin blister model

Acronym
NEPi-INFLAMMATION

Study objectives
The neutral endopeptidase (NEP) inhibitor racecadotril leads to a reduction in cantharidin-induced blister fluid volume and inflammatory infiltrate compared to placebo.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 15/08/2022, London - South East Research Ethics Committee (Equinox House, Nottingham, NG2 4LA, United Kingdom; +44 (0)2071048263; londonsoutheast.rec@hra.nhs.uk), ref: 22/LO/0496

Study design
Double-blind randomized placebo-controlled single-centre parallel-study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
University/medical school/dental school

Study type(s)
Other

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Evaluating the role of CNP in fluid movement and inflammatory cell infiltration, and its relationship to inflammation in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

Interventions
Healthy volunteers (equal numbers of males and females, with stratification according to sex) will be screened and recruited (Day 0) and on Day 1 a blister (10µl of 0.1% cantharidin; Dormer Labs) will be created on one arm. After 24 hours the blister volume will be measured and the blister fluid collected for analysis including quantification of leukocyte numbers, cytokine concentrations and profiling of pro-inflammatory and anti-inflammatory/pro-resolving mediators. 7 days later volunteers will be randomised to either placebo or racecadotril (100 mg,

tid; licensed dose) for 3 days then an identical blister will be created in the contralateral arm. 24 hours later the blister volume will be measured and the blister fluid collected for analysis as above.

Method of randomisation
Block randomisation, 1:1 group allocation in blocks of 6, using Random Numbers Calculator on Graphpad (https://www.graphpad.com/quickcalcs/randMenu/).

Intervention Type
Drug

Pharmaceutical study type(s)
Mechanistic

Phase
Not Applicable

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

Primary outcome measure
Blister fluid volume measured by weight at study visits 3 and 5

Secondary outcome measures
1. Concentration of blister fluid cytokines, specifically interleukin (IL) -1β, IL-6, IL-8, IL-10, CXCL1, CXCL2, CCL5 and CCL2, measured using enzyme-linked immunosorbent assay/bead array, on study visits 3 and 5
2. Blister fluid leukocyte count measured using microscopy and flow cytometry at study visits 3 and 5
3. Pro and anti-inflammatory mediators from blister fluid, measured using enzyme-linked immunosorbent assay/bead array on study visits 3 and 5
4. Plasma cGMP measured using enzyme immunoassay at study visits 3 and 5

Overall study start date
01/08/2020

Completion date
01/06/2026

Eligibility

Key inclusion criteria
1. Healthy male and female volunteers
2. BMI 18-40 kg/m²
3. Aged 18-45 years
4. Volunteers who are willing to sign the consent form

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
45 Years

Sex
Both

Target number of participants
48

Key exclusion criteria
1. Healthy subjects unwilling to consent
2. Smokers
3. Known sensitivity to racecadotril
4. History of any serious illnesses, including recent infections or trauma
5. A personal history of keloid scarring, or a family history of keloid scarring in a first-degree relative with similar skin pigmentation
6. Subjects taking systemic medication (other than the oral contraceptive pill)
7. Subjects who are pregnant or any possibility that a subject may be pregnant, unless in the latter case a pregnancy test is performed with a negative result
8. Women who are breastfeeding
9. Subjects with recent or current antibiotic use
10. Subjects with a history of skins conditions
11. Subjects with a history of allergic reaction to any topical application or history of angioedema
12. Subjects with any history of a blood-borne infectious disease such as hepatitis B or C virus, or HIV

Date of first enrolment
01/08/2023

Date of final enrolment
01/05/2026

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Queen Mary University
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Sponsor type
University/education

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ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal and presentation at relevant meetings
The type of data that will be shared: raw data from CRFs
Whether consent from participants was required and obtained: included in the consent form for the study
Comments on data anonymization: no personally identifiable information will be shared
Any ethical or legal restrictions: data sharing will be in line with GCP and ethics approvals

Intention to publish date
15/06/2026

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current stud will be available upon request from Dr Aemun Salam (aemun.salam@qmul.ac.uk)

IPD sharing plan summary
Available on request