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Inhibition of bradykinin in SARS-CoV-2 infection: a randomised, double-blind trial of icatibant compared with placebo (ICASARS)

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ABSTRACT

SARS-CoV-2 binds to ACE2 receptors and enters cells. The symptoms are cough, breathlessness, loss of taste/smell and X-ray evidence of infiltrates on chest imaging initially caused by oedema, and subsequently by a lymphocytic pneumonitis. Coagulopathy, thrombosis and hypotension occur. Worse disease occurs with age, obesity, ischaemic heart disease, hypertension and diabetes.

These features may be due to abnormal activation of the contact system. This triggers coagulation and the kallikrein-kinin system, leading to accumulation of bradykinin and its derivatives, which act on receptors B1R and B2R. Receptor activation causes cough, hypotension, oedema and release of the cytokine interleukin-6 (IL-6) which recruits lymphocytes. These effects are core features seen in early SARS CoV-2 infection.

Methods and analysis In this study, hypoxic patients with COVID-19 with symptom onset ≤7 days will be randomised to either a bradykinin inhibitor (icatibant) or placebo. Patients and investigators will be blinded. The primary outcome will be blood oxygenation, measured by arterial blood sampling. The secondary outcome will be cardiovascular status. Retinal imaging will be performed to assess vessel size. Blood samples will be taken for measurement of inflammatory analyses including IL-6. As a separate substudy, we will also take comparator blood inflammatory samples from a COVID-19-negative cohort.

Ethics and dissemination The study has received the following approvals: West Midlands–Edgbaston Research Ethics Committee. Medicines and Healthcare products Regulatory Agency has issued a clinical trial authorisation. Belfast Health and Social Care Trust is the study sponsor. Results will be made available to participants upon request and findings will be presented and published.

Trial registration number NCT05407597

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The first study to investigate the effect of icatibant on the alveolar arterial gradient in patients with early COVID-19.
⇒ Prospective, randomised, double-blind trial of treatment versus placebo.
⇒ Retinal imaging is a novel investigation in COVID-19 and in the assessment of the effect of icatibant.
⇒ Findings may be translatable to other disease states such as acute respiratory distress syndrome and sepsis, which have many features in common with severe COVID-19 infection.
⇒ The target recruitment number is small.

INTRODUCTION

SARS-CoV-2 causes a spectrum from asymptomatic infection to severe respiratory failure and death. SARS-CoV-2 enters cells by binding to the ACE2 receptor, which is expressed in many tissues including the upper airway, kidneys, adipose tissue, small intestine, heart and lungs.[1 2] The principal effects of the resultant infection are cough, breathlessness, loss of taste/smell and infiltrates on the chest radiograph or CT. These infiltrates are alveolar filling defects caused by oedema. Patients may also develop coagulopathy, abnormal thrombosis, hypotension[3 4] and acute renal impairment.[5] People who progress to more symptomatic disease often have an underlying condition such as obesity, ischaemic heart disease, hypertension, diabetes or lung disease, particularly chronic obstructive pulmonary disease.[6–8]

There are four phases in the evolution of COVID-19 illness. The first is from exposure to virus shedding. Many people do not progress beyond this stage and remain asymptomatic.[9] The second phase is the start of symptoms. The third phase is the development of hypoxia and generally requires hospitalisation. There are well-defined temporal radiological features seen in hospitalised patients with COVID-19. Within the first 7 days of symptoms, ground glass opacities are the main finding on chest imaging.[10] After 7 days, changes become more widespread and consolidation increases, which may lead to respiratory failure. This is the fourth phase of the illness, occurring in a proportion of

admitted patients. In addition to imaging patterns, blood results can be characteristic and reflect disease stage. Lymphopenia occurs in approximately two-thirds of people with COVID-19.[11] Lymphocyte counts reach their lowest point after 7 days from symptom onset,[10] reflecting recruitment to affected lung tissue. Interleukin-6 (IL-6) is released, with levels peaking at 7–10 days.[12]

The diverse features of COVID-19 may potentially be accounted for by dysregulation of the kallikrein-kinin system (KKS) and the contact system. The KKS is a host response mechanism that is triggered following activation of the contact system in response to inflammatory processes. Ultimately, this leads to the release of kinins which act at bradykinin receptors to induce vasodilatation, enhance microvascular permeability, activate endothelial cells and modulate the release of numerous proinflammatory cytokines such as IL-6 and tumour necrosis factor-alpha.[13 14] The effects of excess bradykinin can be demonstrated by the side effects of ACE inhibitor drugs, which are widely used to treat hypertension, heart failure and diabetic nephropathy. ACE inhibition causes accumulation of bradykinin. Between 7% and 25% of people develop a dry cough.[15 16] A lymphocytic alveolitis can also occur.[17]

Bradykinin receptor activation may explain the features of COVID-19 in terms of symptoms, radiological oedema and cytokine release. The use of a receptor antagonist at an early stage of infection may interrupt this pathway and prevent progression to secondary damage, as defined by inflammatory cell infiltrates, thrombosis and vascular injury. There may be also wider implications for lung injury and sepsis as a study of bradykinin inhibition in patients with systemic inflammatory response syndrome due to gram-negative sepsis showed an improvement in the 28-day risk-adjusted survival.[18]

Icatibant is a bradykinin B2 receptor antagonist that has been used since 2008 for the treatment of oedema caused by hereditary angioedema. It has a rapid onset of action, with median time of 2–2.5 hours to symptom relief following a single dose.[19 20] Published data are available from four trials of icatibant in hypoxic patients with COVID-19. A case–control study described a reduction in oxygen requirements in patients receiving icatibant versus standard care.[21] An open-label trial with three treatment arms; icatibant, C1-esterase inhibitor or standard care found no differences in outcomes between the groups.[22] Another open-label trial of icatibant versus standard care found no significant differences between groups in terms of primary outcome (WHO ordinal status at day 10); however, patients treated with icatibant had a significantly shorter inpatient admission, maintenance of clinical response at 28 days and lower mortality.[23] A platform study investigated icatibant in critically ill patients with COVID-19 but did not find a large signal for improved recovery time/mortality.[24] Importantly, there have been no safety concerns regarding icatibant use in COVID-19.

In this study, hypoxic patients with COVID-19 within 7 days of symptom onset will be randomised to receive either icatibant or placebo. Patients and investigators will be blinded to intervention allocation. Oxygenation and cardiovascular status will be measured before and after treatment. Retinal imaging will be carried out to assess vessel size. Blood samples will be taken for measurement of IL-6 and future use. Blood samples for IL-6 and future use will also be taken from a COVID-19-negative cohort.

STUDY AIMS AND OBJECTIVES

Study hypothesis

There is excess accumulation of bradykinin during symptomatic SARS-CoV-2 lung infection. Bradykinin causes oedema in the lung, with reduced oxygen. It also causes vasodilation, hypotension and cytokine release.

Study aim

To block bradykinin at an early stage in symptomatic patients with COVID-19 with hypoxia. We will inhibit the effect of bradykinin with a B2 receptor antagonist, icatibant. This will be compared with placebo.

Study objectives

Primary objective: To assess the effect of icatibant on blood oxygenation.

Secondary objective: To assess the effect of icatibant on heart rate, blood pressure and mean arterial pressure (MAP).

Exploratory objectives: We will image the retina to assess the vessel size. We will document ward measurements of oxygen saturations and oxygen requirements 24 hours after intervention. A blood sample will be taken for the measurement of IL-6 and storage for future use. We will also recruit a comparison cohort of non-COVID-19 subjects. Participants will have a blood sample for the measurement of IL-6 and storage for future use.

STUDY DESIGN

Patients with COVID-19 with hypoxia will be invited to take part in a randomised, double-blind trial comparing a single dose of icatibant with single-dose placebo. We will recruit up to 32 patients, with the aim to have a minimum of 28 completed.

The choice of 28 randomised to treatment or usual care is based on the icatibant ACE inhibitor oedema study which used this number of patients to inhibit bradykinin effects from ACE inhibitors treatment.[25]

Following consent, baseline observations will be carried out. The study drug group will then receive icatibant 30 mg subcutaneously and the placebo group will receive a subcutaneous injection of 0.9% sodium chloride. The half life of icatibant is 1.48±0.35 hours.[26] The repeat measurements will therefore be taken at 3 hours, after treatment (see table 1).

End of study

The trial will end when all of the participants have completed the study and database closure occurs for the

Table 1 Schedule of assessments

	Screening	Baseline data	3-hour data	24-hour data	28 days
Inclusion/exclusion criteria	X				
Pregnancy test (if necessary)	X				
Informed consent	X				
Demographic data	X				
Randomisation/registration	X				
Oxygen requirements and oxygen saturations		X	X	X	
FiO_2 measurement		X	X		
Retinal imaging		X	X		
Haemodynamic measurements		X	X		
Blood sample		X	X		
Drug administration		X			
Adverse events (up to 28 days)		X	X	X	X

final study analysis. The trial will be stopped prematurely if:

- Mandated by the research ethics committee (REC).
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA).
- Mandated by the sponsor (eg, following recommendations from the Data Monitoring and Ethics Committee (DMEC)).
- Funding for the trial ceases.
- The COVID-19 admissions cease during the funding period.

The REC that originally gave a favourable opinion of the trial and the MHRA who issued the clinical trial authorisation (CTA) will be notified in writing once the trial has been concluded or if terminated early.

PATIENT SELECTION CRITERIA

Study setting

This study will take place in the Mater Hospital, Belfast. Patients attending hospital with low oxygen levels due to COVID-19 will be considered for recruitment.

Inclusion criteria

- Age ≥18 years.
- Documented evidence of COVID-19 and symptom onset of 7 days or less.
- Acute hypoxia which will be defined as either low resting saturations ≤94% or supplementary oxygen to maintain oxygen saturations at ≥94%.

Exclusion criteria

- Patients known to be pregnant or breast feeding.
- Patients with unstable ischaemic heart disease or acute stroke.
- Patients enrolled in other clinical trials of an investigational medicine within the previous 28-day period.
- Patients who refuse to have blood samples taken.
- Known hypersensitivity to icatibant.
- Patients who at time of consent are likely to require imminent non-invasive/invasive ventilatory support or patients already on acute non-invasive/invasive ventilation.
- Patients with chronic heart or lung disease whose oxygen levels are reduced but are unchanged from baseline.

Screening procedure

Eligible subjects will be identified and screened by members of the care team based on the inclusion/exclusion criteria as specified. Medical notes and/or electronic health records will be reviewed as necessary for confirmation of eligibility. Women of childbearing age will be asked to undergo a pregnancy test. Eligible subjects will receive REC-approved written study information sheets. A screening log will be kept.

Informed consent

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki. An appropriately trained doctor or nurse may take consent. Signatures and dates must be obtained on the informed consent documentation prior to collection of trial data and administration of the trial drug. If no consent is obtained a patient cannot be randomised into the trial. If the patient decides to enter the trial, they will be asked to sign the patient consent form (see online supplemental material), which will be countersigned by the responsible doctor or designee. The patient will retain a copy of the signed consent form. A copy of the consent form will be placed in the patient's medical records, while the original will be retained in the investigator site file.

Withdrawal of consent

Patients may withdraw from the trial at any time. Data recorded up to the point of withdrawal will be included in the analysis. If a patient requests termination before the drug is administered, no further data will be obtained.

If withdrawal of consent is after the dose of medicine is administered, then no further data will be recorded.

RANDOMISATION

Randomisation procedure

Eligible participants will be randomly allocated using a 1:1 ratio to receive either icatibant or placebo. After informed consent has been obtained and eligibility has been confirmed, the researcher will contact the designated pharmacist who will assign a unique trial identifier in accordance with the randomisation schedule and confirm the study drug to be dispensed or placebo.

Blinding

Icatibant and sodium chloride 0.9% injections to be administered in this study are marketed products and differ in appearance. To maintain blinding, the injections will be dispensed by the site pharmacy and will be prepared and administered by an unblinded member of the research team who will not undertake any other study-related activity.

The investigator or treating physician may unblind a participant's treatment assignment in the case of an emergency. Should a treating clinician require emergency unblinding, they should contact the site pharmacy department available on a 24-hour basis.

Coenrolment guidelines

Patients who are already enrolled in observational studies will be eligible for coenrolment with the ICASARS study. Participants who have been enrolled in other investigational medicinal product (IMP) trials within the last 28 days will not be eligible for coenrolment in ICASARS.

STUDY DRUG

Study medication

The following are regarded as IMPs for the purposes of this study:

- Icatibant 30 mg solution for injection in prefilled syringe.
- Sodium chloride 0.9% solution for injection.

Patients will be randomised to receive icatibant 30 mg to be given subcutaneously (once) or 3 mL 0.9% sodium chloride to be given subcutaneously (once).

Study drug termination criteria and compliance

As this is a single-dose treatment study there will be no additional requirements for termination criteria after the drug is given. Similarly, compliance will be achieved after drug administration.

Concomitant therapy

Patients will be allowed to continue their usual therapy for other conditions. Icatibant is not known to interact with other medications. Patients will receive all treatments used as standard care for patients with COVID-19, including but not limited to dexamethasone, remdesivir, tocilizumab and antibiotics.

STUDY ASSESSMENTS

Oxygenation assessments

The outcome for oxygenation is the alveolar/arterial gradient. Approximately 10 mL of arterial blood will be taken. The alveolar/arterial gradient will be calculated from 1 to 2 mL. The remaining blood will be stored for future use.

We will also record the number of litres of oxygen by nasal prongs (if this is the primary source of oxygen), the measured concentration of oxygen by mask, respiratory rate and oxygen saturations.

In order to measure the FiO_2, a face mask will be used to maintain the oxygen saturations and the preinspiratory FiO_2 will be measured inside the mask (if oxygen administered).

Cardiovascular assessments

Blood pressure will be recorded as the mean of three reproducible measurements at baseline and on study completion. The outcomes recorded will be the mean between measurements. The MAP will be taken as displayed on the automated blood pressure monitor. If a manual pressure is taken, the same averaging of three systolic and three diastolic recordings will be made. MAP will be calculated as (systolic pressure+diastolic pressure+-diastolic pressure)/3. Heart rate will be measured using finger probe or manually.

Exploratory retinal assessments

Bradykinin dilates arterioles and constricts venules, leading to increased capillary pressure and oedema, which may be visible around the retinal vessels. Patients will have a retinal photograph taken before and after treatment. Vascular diameter in the retinal vessels will be measured.

Exploratory blood samples

Blood will be divided for analysis of IL-6 and storage for future use.

Exploratory 24-hour oxygen saturation and oxygen requirement

We will document oxygen requirement and saturations as taken by ward staff. The value recorded will be taken from observations at approximately 24 hours after administration of study drug.

Exploratory control samples

We will recruit a group of COVID-19-negative participants. They will be eligible if they have no COVID-19 symptoms and have not had a COVID-19 infection in the past 4 weeks. Participants will have a COVID-19 PCR swab carried out. They will have approximately 10 mL of blood taken for the measurement of IL-6 and storage for future use. If a participant tests positive on PCR, the blood

sample will be disposed of and they will be informed of the result.

DATA MANAGEMENT

Data collection and management

The chief investigator (CI) or designee will collect participant study data and record it in the case report form (CRF). Patient identification in the CRF will be through their unique trial identifier and initials. Data will be collected from the time the patient is consented for entry into the trial through to the end of treatment with follow-up phase. Data will be stored on a secure Excel database. Data queries will be generated as required to clarify data or request missing information. The designated staff will be required to respond to any queries and correct them. Any amended information shall then be entered onto the database.

Data storage

All documentation and trial records will be stored in conformance with the applicable regulatory requirements. Access to stored information will be restricted to authorised personnel. The trial master file (TMF) will be managed according to sponsor SOP.

Data archiving

Trial documentation and data will be archived after completion of the trial in keeping with the applicable regulatory requirements.

ADVERSE EVENT INFORMATION

The CI or designee will record all directly observed adverse events (AEs) and all AEs spontaneously reported by the patient. In addition, the patient will be asked about AEs at each of the data collection points following the signing of informed consent.

AE reporting period

AEs will be recorded up to 28 days from the signing of informed consent. All AEs assessed as possibly, probably or definitely related to the study drug and all serious adverse events (SAEs) that occur during this time will be followed until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

AE/SAE reporting

COVID-19 infection causes numerous, well-described multisystem effects and it is expected that many patients will experience undesirable effects. Examples of such events include lymphopenia, thrombocytopenia, coagulopathy, arrhythmias, hypoxia, pneumothoraces, pneumomediastinum, secondary infections and respiratory failure. Such events will not be considered AEs. Similarly, AEs associated with a patient's pre-existing medical condition should not be reported. All SAEs will be reported within 24 hours.

Suspected unexpected serious adverse reaction reporting

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are considered to be related to icatibant and are unexpected. The reference safety information is the summary of product characteristics for icatibant. All SUSARs will be the subject of expedited reporting.

Recording and reporting of urgent safety measures

If the CI becomes aware of information that necessitates an immediate change in study procedure to protect clinical trial participants from any immediate hazard, they can implement this immediately prior to approval by REC or MHRA. The CI should phone the clinical trials unit at the MHRA and discuss the issue with a medical assessor once an urgent safety measure is taken. Urgent safety measures should be reported to the sponsor immediately.

STATISTICAL CONSIDERATIONS

Sample size

As this is a proof-of-concept study, it is based on studies used to inhibit bradykinin in other circumstances. In the study of Baş *et al*, patients with ACE inhibitor angioedema were randomised to either icatibant or standard care.[25] There were 27 patients (13 and 14 in active treatment vs placebos). In the van de Veerdonk study there was a reduction in oxygen requirements after 24 hours in 100% of patients with COVID-19 treated with icatibant (n=9) compared with 44% in usual treatment (n=18).[21]

Statistical analysis

All statistical tests will be at the two-sided p value of 0.05. For normally distributed outcomes, differences between groups will be tested using parametric testing such as unpaired t-testing. For non-normal distributions non-parametric tests will be used.

Missing data

Every effort will be made to minimise missing baseline and outcome data. Standard approaches will be used to detect patterns in missing data. The level and pattern of the missing data in the baseline variables and outcomes will be established and the likely causes of any missing data will be investigated. This information will be used to determine whether the missing data have the potential to introduce bias into the analysis results, or substantially reduce the precision of estimates related to treatment effects.

STUDY MONITORING

Data access

The agreement with the CI or designee will include permission for trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data and trial-related documentation. Consent from patients for direct access to data will also be obtained. The patients' confidentiality will be

maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Monitoring arrangements

Monitoring will be an ongoing activity from the time of initiation until study close-out and will comply with the principles of Good Clinical Practice (GCP) and European Union (EU) Directive 2001/20/EC. The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial sponsor.

TRIAL COMMITTEES

Trial Management Group

Trial Management Group (TMG) will be established and chaired by the CI. This group will have responsibility for the day-to-day operational management of the trial, and regular meetings of the TMG will be held to address problems and monitor progress.

Data Monitoring and Ethics Committee

A DMEC will be appointed with responsibility for safeguarding the interests of trial patients, they will monitor the main outcome measures including safety and efficacy. The DMEC will include two clinicians and a statistician who are independent of the trial. The DMEC will discuss trial progress as and when required, but at least every 3 months.

The DMEC will function primarily as a check for safety reviewing AEs and will specifically review the incidence of AEs, SAEs and SUSARs and produce a recommendation following each meeting. The DMEC will report any issues pertaining to safety to the CI. It will be the responsibility of the CI to inform the sponsor who will take appropriate action to halt the trial if concerns exist about participant safety.

Patient and public involvement

Patient and public involvement will be integrated during the study through working closely with patients who have had COVID-19. The study design was discussed with a panel of patients with COVID-19 who were in the Mater Hospital. The measurements were taken and use of a subcutaneous treatment was felt to be reasonable. At the end of the trial, study subjects will be receiving a thank you letter for their participation and provided with a summary of the trial findings. Further details about the trial may be obtained on request.

REGULATIONS, ETHICS AND GOVERNANCE

Sponsorship

The Belfast Health and Social Care Trust (BHSCT) will act as sponsor for the study and the CI will take overall responsibility for the conduct of the trial.

Regulatory and ethical approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by an REC. The trial will be conducted in accordance with the EU Directive 2001/20/EC and adhere to the appropriate regulatory requirements. A CTA will be obtained from the MHRA before the start of the trial.

Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation GCP guidelines (www.ich.org). All members of the trial team will complete GCP training.

Protocol compliance

The CI or designee will conduct the study in compliance with the protocol given approval/favourable opinion by the ethics committee and the appropriate regulatory authority. Changes to the protocol may require competent authority/ethics committee approval/favourable opinion prior to implementation, except when modification is needed to eliminate an immediate hazard(s) to patients. The CI in collaboration with the sponsor will submit all protocol modifications to the competent authority/RECs for review in accordance with the governing regulations. Any deviations from the protocol will be fully documented on the protocol deviation form in the CRF.

Patient confidentiality

Due care will be taken to ensure data safety, integrity and compliance with the Data Protection Act. The patient's trial identifier, name, address and other contact details will be kept separate. The CI or coinvestigator will keep these details in a locked filing cabinet. All documentation regarding the study will identify the patients by the assigned unique trial identifier. Computers where information will be stored will be password protected. Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Record retention

On completion of the trial, the TMF and study data will be archived by the sponsor according to the applicable regulatory requirements.

Indemnity

The BHSCT will provide indemnity for any negligent harm caused to through the Clinical Negligence Fund in Northern Ireland.

Finance

The study is funded by the Health and Social Care Research and Development Division. Belfast Health and Social Care will manage the grant.

DISSEMINATION/PUBLICATIONS

The intention is to publish results in high-quality peer-reviewed scientific journal(s). The TMG (and where appropriate collaborators) will take an active part in

preparing and reviewing of all manuscripts and reports generated during/on completion of the study. Any papers reporting the study outcome will be provided to collaborators and/or the sponsors for advisory review and comment prior to submission for publication. The trial will be reported in accordance with the Consolidated Standards of Reporting Trials guidelines.

Definition of authorship

An author is considered to be someone who has made substantive intellectual contribution to a study. All investigators will potentially be coauthors and collaborators will be acknowledged. Honorary or guest authorship is not acceptable.

Dissemination policy

In addition to the provision of annual and final reports, study findings will be presented at national and international meetings. It is anticipated that the study outcomes will be published in open access journals.

WHO trial registration data set

Primary registration	ClinicalTrials.gov: NCT05407597
Date of registration	7 June 2022
Secondary identifying numbers	Protocol number: 21036JK-AS
Source of monetary or material support	R&D
Primary sponsor	Belfast Health and Social Care Trust
Secondary sponsor	N/A
Contact for public queries	Dr Joe Kidney Mater Hospital, Belfast Joe.kidney@belfasttrust.hscni.net 028 9074 1211
Contact for scientific queries	As above
Public title	Icatibant in SARS-CoV-2
Scientific title	Icatibant inhibition of bradykinin in SARS-CoV-2 infection
Countries of recruitment	Northern Ireland Single site (Mater Infirmorum Hospital, Belfast)
Health conditions being studied	Patients attending hospital with reduced oxygen levels due to COVID-19
Interventions	Icatibant Solution for injection, 30 mg (3 mL) administered as a single subcutaneous injection or Placebo (sodium chloride 0.9%) Solution for injection (3 mL) administered as a single subcutaneous injection
Inclusion criteria	Age >18 Presence of COVID-19 and symptom onset of 7 days or less Acute hypoxia which will be defined as either low resting saturations ≤94% or supplementary oxygen to maintain oxygen saturations at ≥94%
Exclusion criteria	Patients known to be pregnant or breast feeding Patients with unstable ischaemic heart disease or acute stroke Patients enrolled in other clinical trials of an investigational medicine within the previous 28-day period Patients who refuse to have blood samples taken Known hypersensitivity to icatibant Patients who at time of consent are likely to require imminent non-invasive/invasive ventilatory support or patients already on acute non-invasive/invasive ventilation Patients with chronic heart or lung disease whose oxygen levels are reduced but are unchanged from baseline
Study type	Prospective, randomised, double-blind trial of icatibant compared with placebo Phase IIB
Date of first enrolment	16 May 2022
Sample size	32 (to have 28 completed)
Recruitment status	Recruiting
Primary outcome	Change in oxygen levels Time points: baseline and 3 hours after study drug/placebo Measured by alveolar arterial gradient
Secondary outcomes	Change in blood pressure and heart rate Time points: baseline and 3 hours after study drug/placebo Measured by mm Hg, systolic, diastolic, mean arterial pressure and pulse (beats per minute)
Ethics review	Approved West Midlands–Edgbaston Research Ethics Committee Reference number: 22/WM/0014 14 February 2022
Completion date	31 December 2023
Summary results	N/A
IPD sharing statement	Plan to share IPD: No

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Contributors MB and DL: protocol design and trial recruitment. HGP: laboratory assays. DFM: protocol design. OE and TP: protocol design and retinal imaging analysis. CT: protocol design and laboratory assays. JK: grant application, protocol design, trial recruitment.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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