Short title:
RAS and coagulation in COVID-19

Title:
Investigating the relationship between the renin angiotensin system and the coagulopathy associated with COVID-19

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Protocol authorised by:

<table>
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<tr>
<th>Name &amp; Role</th>
<th>Date</th>
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<tbody>
<tr>
<td>David Owen</td>
<td>16 Mar 2021</td>
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</tbody>
</table>
Study Management Group

Chief Investigators: David Owen
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Study Management: Lisa Hurley

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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This protocol provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.
Table of Contents

1. INTRODUCTION
2. STUDY OBJECTIVES
3. STUDY DESIGN
4. PARTICIPANT ENTRY
5. ADVERSE EVENTS
6. ASSESSMENT AND FOLLOW-UP
7. STATISTICS AND DATA ANALYSIS
8. REGULATORY ISSUES
9. STUDY MANAGEMENT
10. PUBLICATION POLICY
11. REFERENCES
STUDY SUMMARY

TITLE  Investigating the relationship between the renin angiotensin system and the coagulopathy associated with COVID-19

DESIGN  Double blind randomised placebo-controlled trial

AIMS  To determine whether RAS inhibition modulates coagulopathy in COVID-19

OUTCOME MEASURES  D-dimer

POPULATION  Inpatients with COVID-19

ELIGIBILITY  Hospitalised, aged 18 or over

DURATION  Each subject will be in the study for 30 days. The study is expected to take 6 months
1. INTRODUCTION

1.1 BACKGROUND

Several clinical trials testing blockade of Angiotensin II (AngII) in COVID-19 using angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) are underway (e.g. NCT04330300, NCT04335786 and NCT0435936). The rationale for these trials is based on the two predicates. First, SARS-CoV2 will lead to internalisation and inactivation of ACE2 (the enzyme that metabolises AngII to Ang(1-7)) and cause AngII accumulation, as occurred with SARS-CoV1 (Kuba, Lo, Gralinski, Wang). Second, that COVID-19 has many features which are strikingly similar to the effects of excessive exposure to AngII (Tang (a), Tang (b), Whitaker, Gavras (a), Gavras (b)). However, this approach may fail to yield net benefit, because it overlooks the role of Ang(1-7) and the impact of these drugs on Ang(1-7). Ang(1-7) is the product of ACE2 mediated AngII metabolism, and hence the inactivation of ACE2 induced by COVID-19 will lead not only to AngII accumulation, but also to Ang(1-7) depletion. Because this is due specifically to ACE2 inactivation, it does not occur in more classical conditions featuring renin-angiotensin axis activation, such as heart failure. Ang(1-7) functionally antagonises AngII through its agonist action at the MAS receptor, and may also potentially act as a biased agonist at the AngII receptor (AT1R) (Bader, Galandrin, Montezano, Teixeira, Touyz). Indeed, animal models show that Ang(1-7) depletion causes pathology which aligns with that seen in COVID-19 patients, including lung injury, lung inflammation, myocardial microinfarcts, characteristic glomerular thrombosis and coagulopathy. (Bihi, Bossi, Diggin, Fraga Silva, Hao, Klein, Supe, Xue, Yang (a), Yang (b), Zhang K, Zhang X).

The coagulopathy is particularly noteworthy given an early increase in D-dimer has very high positive predictor value for death in COVID-19, and D-dimer concentrations are unusually high in COVID-19, over and above what would be expected for an acute phase response in an unwell patient (Tang (a), Tang (b)). Given the pleiotropic effects of AngII and Ang(1-7) on the components of the coagulation system, overactivation of the renin angiotensin system may partly drive dysregulation of coagulation. We therefore hypothesise that the coagulopathy associated with COVID-19 is partly explained by both AngII accumulation and Ang(1-7) deficiency. Importantly, whilst ACEI and ARB treatment will antagonise AngII accumulation, they not only fail to address Ang(1-7) deficiency, but would in fact worsen it. This is because ACEI will further deplete Ang(1-7) production, over and above that caused by ACE2 internalization (Luque), and whilst an ARB will not further deplete Ang(1-7), it will prevent it from binding AT1R and hence block its beneficial actions via this receptor. Hence neither ACEI nor ARBs are appropriate tools to address this hypothesis in the context of COVID-19 infection.

TRV027 is a similar peptide to Ang(1-7) but is a much more potent biased agonist at AT1R than Ang(1-7), potently and selectively recruiting β-arrestin to the AT1R while antagonizing Ang II-stimulated Gq activation (Violin). This β-arrestin bias of the ligand translates into unique downstream signaling, including extracellular signal-regulated kinases 1 and 2 (ERK1/2) phosphorylation and AT1R internalization. Recruitment of β-arrestin by TRV027 stimulates the activation of endothelial cell nitric oxide synthase (eNOS) and prostacyclin production (Violin). The combination of inhibition of Ang-II-mediated G-protein activation and activation of eNOS and prostacyclin production may contribute to the in vivo vasodilatory properties of TRV027 (Violin). In summary, TRV027, a biased agonist at AT1R, would be expected to oppose the effects of AngII accumulation, and functionally correct the Ang(1-7) deficiency. Hence it is an appropriate tool to examine the link between RAS activation and coagulopathy in the context of COVID-19 infection.
1.2 HYPOTHESIS

Inhibition of RAS activation by biased agonism of AT1R with TRV027 improves coagulopathy in COVID-19 infection.

1.3. SUMMARY OF RISK MANAGEMENT

TRV027

Non-Clinical Safety

Nonclinical safety pharmacology and toxicology studies have shown that TRV027 is compatible with blood, non-genotoxic, and that continuous IV infusions up to 14 days duration are well tolerated. The no observed adverse effect level (NOAEL) in 2-week continuous IV infusion studies in rats and dogs was 500 μg/kg/min, the highest dose tested. Measured TRV027 plasma concentrations at the NOAEL dose in rats and dogs were approximately 20-times higher than extrapolated steady-state plasma concentrations in humans administered the highest Phase 2 clinical dose of 25 mg/hr.

Clinical Safety

TRV027 has been studied in healthy volunteers (n=20) and in three studies in patients with heart failure. In the FTIH study (NCT01514578), a dose range of 0.01 to 20 μg/kg/min for 4 hours (2.4 to 4800 μg/kg) was studied in 20 healthy subjects; the highest dose was expected to be approximately 20-fold higher than the efficacious dose in acute decompensated heart failure (ADHF) patients. All AEs reported were mild and transient. There were three AEs, in two subjects, that were considered possibly related to study drug: mild fatigue, and mild dizziness and paresthesia. All resolved within 2 hours without medical intervention. There were no deaths, no SAEs, and no AEs that led to discontinuation from the study. There were no clinically significant changes in laboratory findings, vital signs (Heart Rate, Blood pressure, Oxygen saturation, respiratory rate and temperature), ECGs or physical examinations.

Study CP120027.1002 enrolled 17 patients with HF and renal dysfunction. Each patient received both placebo and a dose (1.25-31.25 mg/hr) of TRV027 as a 6.5 hr continuous infusion (NCT01444872). All AEs reported in this study were mild or moderate in nature. There were no serious adverse events or clinically significant adverse events reported.

In CP120027.2001, 33 patients with NYHA class 3-4 heart failure and a clinical indication for right-heart catheterization received either a dose regimen of TRV027 or volume-matched placebo (NCT01187836). The doses studied were as follows:

- Cohort 1: 0.1, 0.2, 0.4, 0.7 μg/kg/min each for 1 hour over hours 1-4, followed by 1 μg/kg/min for 10 hours
- Cohorts 2 and 4: 0.3, 0.6, 1.2, 2.4 μg/kg/min each for 1 hour over hours 1-4, followed by 3 μg/kg/min for 10 hours
- Cohort 3: 1, 2, 4, 8 μg/kg/min each for 1 hr over hours 1-4, followed by 10 μg/kg/min for 10 hours.
There were no serious adverse events attributed to TRV027 treatment. In the first cohort, one subject experienced hypotension necessitating dose reduction and then discontinuation of the study drug infusion. No other TRV027-related clinically significant adverse events were reported.

In the CP120027.2002 study (n= 621 patients with ADHF) which used doses ranging from 1-25 mg/hr for 48-96 hours, no safety issues were identified that affected the safety of trial subjects (NCT01966601). There was no difference from placebo in non-serious and serious treatment-emergent adverse events, events leading to discontinuation, or deaths.

Pharmacokinetics of TRV027

The pharmacokinetics of TRV027 has been studied in healthy volunteers, in patients with stable mild/moderate heart failure, patients with stable NYHA class III/IV CHF, and in 621 adults with acute decompensated heart failure. The clearance of TRV 027 is rapid (ranging between 51.3-127 L/hr) and exhibits a short half-life (4.2-15.8 minutes). Heart failure, sex, or renal dysfunction had no significant effect on the clearance of TRV027. TRV027 is not metabolized by, nor does it inhibit any of the CYP450 enzymes. The plasma protein binding of TRV027 is low at 53.4%.
2. STUDY OBJECTIVES

Primary

To determine whether the coagulopathy associated with COVID-19 infection is driven by over activation of the renin angiotensin system (RAS)

Secondary objective

To investigate whether dysregulation of other systems associated with COVID-19 infection is driven by over activation of the renin angiotensin system (RAS)

3. STUDY DESIGN

The proposed study will be run as a double-blind, randomized controlled experimental medicine study in male and female hospitalised patients (n=60) aged 18 or over, with confirmed COVID-19 infection. Patients who are admitted with confirmed COVID-19 infection will be screened with a routine medical assessment (see Table 1) and enrolled if they meet the eligibility criteria. Subjects will be block randomised based on age to continuous intravenous infusion of placebo or TRV027 for 7 days.

Day 1 procedures can occur on the same day of screening and include a venous blood test prior to commencing an intravenous infusion of either placebo (250ml sodium chloride 0.9%) or TRV027 in 250ml sodium chloride 0.9% at 12mg/hr. The infusions will continue for 7 days. Venous blood tests will be repeated at days 3, 5 and 8 amounting to approximately 120mLs of blood in total over the 8-day period.

Once the infusion has finished, the subjects will remain in hospital for a further 24 hours for vital signs and adverse event monitoring. If the infusion is stopped before the 7-day dosing period finishes, they will be advised to remain in hospital for a 24-hour period for monitoring during which time the study assessments will continue. If discharge is planned for day 6 or 7 the day 8 blood tests can be taken on the day of discharge. They will also be followed up at Day 30 either by telephone call or through examination of medical records.
## Table 1: Schedule of Study Events

<table>
<thead>
<tr>
<th>Study Day</th>
<th>&quot;Screening&quot;</th>
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*Screening and day 1 can be combined
All concomitant medications will be reviewed at baseline but only those which affect eligibility or are associated with AEs will be recorded for subsequent days in the Ecrf. ACEI and aldosterone antagonists will be recorded.

Dose Rationale

TRV027 has been studied in patients with acute heart failure in doses ranging from 1.25 – 31.25 mg/hr. Using in vitro-derived AT1R receptor binding data as well as population PK data in healthy volunteers, simulations were performed to explore a range of doses of TRV027 which might be expected to result in at least 80% receptor occupancy, correcting for protein binding. The results (Figure 1) suggest that 12 mg/hr will result in median receptor occupancy well in excess of 80%. This dose is in the mid-range of what has been studied clinically and is expected to be well tolerated.

Figure 1: Estimation of the median AT1R receptor occupancy resulting from TRV027 given at a dose of 12 mg/hr for 96 hours

3.1 STUDY OUTCOME MEASURES

Primary Endpoint
- Mean change from baseline D-dimer at day 1 to day 3 post randomisation

Exploratory Endpoints
- Assessed on days 1, 3, 5, and 8
  - Markers of dysregulation of coagulation system, e.g.
    - D-dimer, Coagulation profile
  - Markers of dysregulation of RAS, e.g.
    - Renin mass and activity (Day 1 only)
  - Markers of dysregulation of other systems, e.g.
    - SOFA score ((Pa/Sa02)/FiO2, GCS, Total bilirubin, platelets, creatinine, BP and inotrope requirement).
4. PARTICIPANT ENTRY

4.1 INCLUSION CRITERIA

A subject will be eligible for inclusion in this study only if all of the following criteria apply at the time of screening:

1. Hospitalised with confirmed COVID-19 infection.
2. Screened within 96 hours of SARs-CoV-2 positive PCR.
3. Age 18 or over
4. Systolic blood pressure between 100 and 180

4.2 EXCLUSION CRITERIA

A subject will not be eligible for inclusion in this study if any of the following criteria apply at the time of screening:

1. Any unrelated clinical condition, which, in the opinion of the investigator, may affect D-dimer during the course of the study, independent of COVID-19 infection, e.g. a subset of cancers and coagulopathies.
2. Concomitant medications which inhibit the action of TRV027 (ARB's).
3. Any clinically significant medical conditions that in the opinion of the investigator would compromise subjects' safety or compliance with study procedures.
4. Any clinical condition which in the opinion of the investigator would compromise the scientific integrity of the study
5. Unwillingness or inability to follow the procedures outlined in the protocol.
6. Subject is pregnant or breastfeeding

4.3 CONSENT OR AGREEMENT FROM CONSULTEE

Patients with Capacity
Consent will be obtained from participants who have capacity. After reading the information and having an opportunity to ask questions, they will be asked to sign the consent form. Once the consent form has been signed, a digital copy will be created using the NHS approved PANDO
app, and the original will be destroyed for infection control purposes. At the time of taking consent, patients will be informed of the possibility that they may lose capacity during the study, and they will be asked to record their wishes on the consent form should this happen.

Patients who are physically unable to sign a consent form (due to the severity of their illness) may consent for themselves provided they can understand the information and verbally express their wishes. Their verbal consent will be witnessed by an observer who is independent of the study and the witness will countersign the consent form.

Patients will be informed that they may lose capacity during the study and will be asked to record their advance wishes regarding continuing enrolment on the consent form.

**Patients who lack Capacity**
If the patient lacks capacity to give consent due to the severity of their medical condition, then they may be enrolled on the advice of a partner, friend or relative acting as the patient’s personal consultee. Consent will then be sought with the patient if and when they recover capacity.

Patients who lack capacity to consent and for whom a personal consultee is not immediately available, may be enrolled on the study provided a nominated consultee can be appointed to advise on their behalf. A nominated consultee may be a treating clinician or professional carer (must be independent of the study). Further advice will be obtained from the patient’s personal consultee (or consent will be taken directly from the patient if they recover promptly) at the earliest opportunity.

**4.4 WITHDRAWAL CRITERIA**

Based on current outcome statistics, many subjects are likely to progress to end organ failure resulting in Intensive Therapy Unit (ITU) admission or death. Admission to ITU is therefore expected and will not result in withdrawal of the subject. Provision for informed consent of participants lacking capacity are specified in sections 4.3 and 8.2.

Subjects may withdraw from the study at any point, without giving a reason. If the subject loses capacity, the clinician in charge of their care can elect to withdraw the subject if they deem it clinically appropriate to do so.

**5 SAFETY REPORTING**

**5.1 DEFINITIONS**

**Adverse Event (AE):** any untoward medical occurrence in a patient or clinical study subject that falls within the criteria specified in section 5.2.

**Serious Adverse Event (SAE):** any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject 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
- Requires prolongation of existing inpatients’ hospitalisation
- Results in persistent or significant disability or incapacity
• Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 RECORDING AND REPORTING OF ADVERSE EVENTS

Any adverse events will be reviewed by clinicians and recorded from the point of consent to the end of infusion plus 24 hours. Any serious adverse events should be reported as indicated in section 5.3.

We will record any new grade 3 or 4 laboratory abnormalities (CTCAE) in Haemoglobin, Neutrophil count, Alanine aminotransferase (ALT), Potassium, Sodium, as adverse events in addition to any clinically significant untoward medical occurrence. Lymphopaenia is well reported in COVID-19 infection and therefore will not be recorded1 (Table 2).

We will also specifically record any incidence of deep vein thrombosis or myocardial infarction.

Routine observations, D-dimer, Platelets, aPTT, Fibrinogen, INR, Plasma Renin Mass, Bilirubin, LDH, Haptoglobin, Creatinine, BNP, Ferritin, Troponin, Pro-calcitonin and Glucose will all be recorded as study endpoints and therefore not recorded separately as adverse events.

Medical judgement will be used to determine clinical significance and the need to record other events as AEs. Other non-serious events below CTCAE grade 3-4 or other known symptoms of COVID-19 would not normally be considered clinically significant for the purposes of AE reporting in this study.

Table 2.

<table>
<thead>
<tr>
<th>CTCAE Term</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>Male (225 – 900), Female (170 – 680) if baseline was normal; &gt;5.0 - 20.0 x baseline, if baseline was abnormal</td>
<td>Male (&gt;900), Female (&gt;680) if baseline was normal; &gt;20.0 x baseline if baseline was abnormal</td>
</tr>
<tr>
<td>Male 0-45 unit/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female 0-34 unit/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia (Hgb)</td>
<td>Hgb &lt;80 g/L; transfusion indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Male 130-168 g/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female 114-150 g/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin increased</td>
<td>Increase in &gt;40 g/L</td>
<td>-</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>&lt;1.0 - 0.5 x 10⁹ /L</td>
<td>&lt;0.5 x 10⁹ /L</td>
</tr>
<tr>
<td>2.0-7.1 x10⁹/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia 3.5-5.3 mmol/L</td>
<td>&gt;6.0 - 7.0 mmol/L; hospitalisation indicated</td>
<td>&gt;7.0 mmol/L; life-threatening consequences</td>
</tr>
<tr>
<td>Hypokalemia 3.5-5.3 mmol/L</td>
<td>&lt;3.0 - 2.5 mmol/L; hospitalisation indicated</td>
<td>&lt;2.5 mmol/L; life-threatening consequences</td>
</tr>
<tr>
<td>Hypernatremia 133-146 mmol/L</td>
<td>&gt;155 - 160 mmol/L; hospitalisation indicated</td>
<td>&gt;160 mmol/L; life-threatening consequences</td>
</tr>
<tr>
<td>Hyponatremia 133-146 mmol/L</td>
<td>125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms</td>
<td>&lt;120 mmol/L; life-threatening consequences</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Any adverse events should be recorded in the CRF. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

### 5.3 SERIOUS ADVERSE EVENTS

All such events, whether expected or not, should be recorded.

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to Covid19, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the London South East Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- ‘related’, i.e. resulted from the administration of any of the research procedures; and
- ‘unexpected’, i.e. an event that is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

### 5.4 DATA SAFETY MONITORING COMMITTEE (DSMC)

A trial Data Safety Monitoring Committee (DSMC) will be formed to review the study after every 12 patients recruited to assess the progress, the safety data and the endpoints and to recommend to the sponsor whether to continue, modify or end the study.

Contact details for reporting SAEs
jrco@imperial.ac.uk
CI email (and contact details below)
d.owen@imperial.ac.uk

Please send SAE forms to: London South East Research Ethics Committee
Tel: 0207 104 8085 (Mon to Fri 09.00 – 17.00)

### 6. ASSESSMENT AND FOLLOW-UP

Incidental findings will be reviewed by the PI or designee and reported to the clinical team in charge of the patient if deemed clinically significant. The subject will be followed up for 24 hours after the dosing period has finished, and at day 30 at which point the subject will finish the study. There will be no further follow up. The definition of the end of trial is the last visit day of the last subject (Day 30).
7. STATISTICS AND DATA ANALYSIS

This sample size (30 each group) provides 80% power (alpha 0.05) to detect a 30% change in D-dimer. Subjects will be block randomised based on age (<60, 60-69, >69 years) using a code generated by the trial statistician.

Mean change from baseline D-dimer at day 1-3 post randomisation (and exploratory variables) will be compared using paired or unpaired non-parametric methods as appropriate. The relationship between change from baseline and pre-treatment plasma renin will be investigated, on the basis that subjects with low renin (and hence greater RAS activation) would be predicted to have the greater response.

The aim of this study is to understand the relationship between the RAS, coagulopathy, and COVID-19. The results of this study have potential implications for studies which are currently being planned using RAS modulators (including TRV027) in COVID-19. Design decisions for these study need to be taken before this study will fully recruit. Hence, unblinded aggregate data, for those patients who have completed the dosing period, will be reviewed by the study team to help guide the design of these studies. Individual unblinded data will not be reviewed.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the London South East Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an approved participant information sheet provided and time allowed for consideration. Signed participant consent should be obtained before initiating any study procedures in patients that are capable of giving consent (refer to section 4.3 for further details). The right of the participant to refuse to participate without giving reasons must be respected. Participants that lack capacity may also be enrolled on the advice of a consultee (see section 4.3).

After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis.

All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

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8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

The study is funded by Imperial College London COVID-19 Fund, the British Heart Foundation and Trevena. Trevena is providing TRV027 and additional funds for pathology investigations, pharmacy costs, and study personnel support.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

8.8 COMPENSATION

Participants will not receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research.

No individual researchers will receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated by the study project manager.

10. PUBLICATION POLICY

Data will be prepared for publication (open access) as soon as is practically possible at the end of the study. This could be through peer reviewed journals, internal reports and/or conference presentations.
11. REFERENCES

- Gavras et al. (b) Acute renal failure, tubular necrosis, and myocardial infarction induced in the rabbit by intravenous angiotensin II. Lancet 1971 July 3;2(7714):19-22.
- Violin et al. Selectively Engaging β-Arrestins at the Angiotensin II Type 1 Receptor Reduces Blood Pressure and Increases Cardiac Performance. J Pharmacol Exp Ther. December 2010, 335 (3) 572-579
- Yang et al. Endogenous activated angiotensin-(1-7) plays a protective effect against atherosclerotic plaques.... Int J Cardiol 2015 April 1;184:645-52.
- Zhang et al. Cellular basis of angiotensin-(1-7)-induced augmentation of left ventricular functional performance in heart failure. Int J Cardiol 2017 June 1;236:405-12.